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Original Article

The 24-month course of manic symptoms in children

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Objectives: The Longitudinal Assessment of Manic Symptoms (LAMS) study was designed to investigate phenomenology and establish predictors of functional outcomes in children with elevated manic symptoms. The purpose of this series of analyses was to determine whether the participants demonstrated different trajectories of parent-reported manic and biphasic symptoms over the first 24 months of follow-up and to describe the clinical characteristics of the trajectories.

Methods: The 707 participants were initially aged 6–12 years and ascertained from outpatient clinics associated with the four university-affiliated LAMS sites. There were 621 children whose parents/guardians' ratings scored ≥ 12 on the Parent General Behavior Inventory–10-item Mania Form (PGBI-10M) and a matched random sample of 86 children whose parents/guardians' ratings scored ≤ 11 on the PGBI-10M. Participants were seen every six months after the baseline and their parents completed the PGBI-10M at each visit.

Results: For the whole sample, manic symptoms decreased over 24 months (linear effect $B = -1.15$, standard error = 0.32, $t = -3.66$, $p < 0.001$). Growth mixture modeling revealed four unique trajectories of manic symptoms. Approximately 85% of the cohort belonged to two classes in which manic symptoms decreased. The remaining ~15% formed two classes (*high and rising* and *unstable*) characterized by the highest rates of diagnostic conversion to a bipolar disorder (all p-values < 0.001).

Conclusions: Outcomes are not uniform among children with symptoms of mania or at high risk for mania. A substantial minority of clinically referred children shows unstable or steadily increasing manic symptoms, and these patterns have distinct clinical correlates.

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Youth receiving mental health services often experience numerous mania-like symptoms (1, 2). Furthermore, although symptoms of mania are, by definition, present in youth suffering from bipolar disorder, prior data have noted that many youth who experience manic symptomatology do not suffer from bipolar disorder (3–7). Whether or not a youth has suffered from a bipolar disorder, it has been noted that elevated symptoms of mania (ESM) are associated with substantial psychosocial impairments and notable degrees of psychopathology (7–9).

Despite these initial investigations of children who experience ESM, very little is known about the phenomenology or symptomatic course of ESM in youth. Data from a pilot study suggested that the presence of ESM in children with attention-deficit hyperactivity disorder (ADHD) may be associated with a poorer outcome (9, 10).

The National Institute of Mental Health-supported Longitudinal Assessment of Manic Symptoms (LAMS) study was designed to better understand the phenomenology and determinants of outcome (e.g., psychosocial functioning, diagnoses, medications, and service utilization) in children with ESM. LAMS used an epidemiological approach to assemble a cohort of 6–12-year-old children at their first outpatient mental health visit at university-affiliated clinics (11). The LAMS design used a low, sensitive threshold on a screening instrument for manic symptoms, both to capture a large portion of those already showing symptoms of bipolarity, and to include a substantial number of cases without bipolarity who were also experiencing similar emotional and behavioral dysregulation. Initial results have confirmed the finding that ESM in clinical mental health settings for youth are, in fact, common and that the majority of children with ESM indeed do not meet DSM-IV criteria for a bipolar spectrum disorder at baseline (5). The most common diagnoses are ADHD, oppositional defiant disorder, conduct disorder, and depression, often in various combinations (3, 5, 12).

A specific goal of the LAMS study was to examine the course of children's manic symptoms over time. To this end, we evaluated whether or not children who participated demonstrated different trajectories of parent-reported manic and biphasic symptoms over the first 24 months of follow-up. Based on prior longitudinal investigations of diagnostic status, combined with the choice of a low threshold of ESM to capture a heterogeneous group of youth in terms of clinical issues, we anticipated that there would be several distinct symptom trajectories, including at least one group that showed persistent symptoms of mania and at least one group that remitted. We also anticipated that a third group might show intermediate levels of mood symptoms, but whether this would be a stable pattern or whether manic symptoms would fluctuate was an empirical question. We next investigated what baseline determinants differentiated these distinct trajectories. Finally, we investigated what factors occur over the span of an initial 24-month observation period that could lead to categorization into these distinct classes.

Methods

Sample

The Institutional Review Boards at each of the four LAMS sites approved all procedures in the study protocol. Written informed consent and assent were obtained from participants and their parents/guardians before any study-related procedures were performed.

Study recruitment occurred between December 13, 2005 and December 18, 2008. To be eligible for screening, children had to: (i) be age six through 12 years; (ii) speak English and have an English-speaking parent/guardian; (iii) be new patients to LAMS outpatient clinics; and (iv) not live in the same household as another child previously screened. Parents/guardians of all eligible children were asked to complete the Parent General Behavior Inventory–10-item Mania Form (PGBI-10M) (13, 14) to screen for ESM and to answer questions about socio-demographic characteristics. The PGBI-10M comprises items that both describe hypomanic, manic, and biphasic symptomatology and discriminate bipolar disorder from other diagnoses in children and adolescents (13). Children whose parents/guardians' ratings scored ≥ 12 on the PGBI-10M (ESM+) were invited to participate in the longitudinal portion of the study. To broaden the variability of the sample, a smaller group of age-, race-, and socioeconomic status-matched children whose parents/guardians' ratings scored ≤ 11 (ESM−) were randomly selected to enroll in the longitudinal study as well. The rationale for the cutoff score of 12 on the PGBI-10M, participant ascertainment, and study design are described in greater detail in Horwitz et al. (11) and Findling et al. (5).

Of the 1124 children who screened ESM+, 1111 were eligible (IQ > 70 and no evidence of autistic disorder) and 621 agreed to participate. In addition, 86 ESM− children enrolled into the longitudinal study. After the initial screening visit, these 707 children completed a baseline assessment (5).

LAMS participants who continued to be eligible were seen by a highly trained study interviewer every six months after baseline for a total of up to five visits over the first 24 months. Interviewer training and inter-rater reliability are described in detail in Findling et al. (5).

Measures

Demographic characteristics. Parents/guardians provided demographic information, including child age, gender, race, ethnicity, and health insurance status, as well as family composition, socioeconomic status, parental education and employment, and medical history. Appropriate variables (e.g., insurance, employment, and medical history) were updated at each subsequent study visit.

Psychiatric diagnoses. To assess for current and past psychiatric disorders, children and their parent/guardian were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (K-SADS-PL) (15) with additional depression and manic symptom items derived from the Washington University in St. Louis Kiddie Schedule for Affective Disorders (WASH-U K-SADS) (16, 17). DSM-IV items screening for pervasive developmental disorders were also added to the K-SADS-PL. The resulting instrument, the K-SADS-PL-W, is a semi-structured interview that assesses current and lifetime psychiatric diagnoses and the time course of each illness. The presence/absence of mood disorder diagnoses was assessed at the baseline evaluation and every six months thereafter. The whole K-SADS-PL-W was repeated annually.

Unmodified DSM-IV diagnostic criteria were used in the LAMS study. The criteria for bipolar disorder not otherwise specified (BP-NOS) adopted for the LAMS study were the same as those used in the Course and Outcome of Bipolar Youth study (COBY) (18, 19). BP-NOS was operationalized as follows: (i) elated mood plus two associated symptoms of mania (e.g., grandiosity, decreased need for sleep, pressured speech, racing thoughts, increased goal-directed activity, etc.) or irritable mood plus three associated symptoms of mania; (ii) change in the participant's level of functioning (increase or decrease); (iii) symptoms had to have been present for a total of at least four hours within a 24-hour period; and (iv) the participant had to have had at least four episodes of four hours' duration each or a total of four days of the above-noted symptom intensity in his/her lifetime. All diagnoses were reviewed and confirmed by a licensed child psychiatrist or psychologist. Once a child met DSM-IV criteria for any bipolar disorder in the LAMS study, that diagnosis was always documented as a current diagnosis (although it could be listed as *in partial/full remission*).

Medication history. Each child's parent/guardian provided a complete history of the child's past and currently prescribed psychotropic medications during each interview using a modified version of the Service Assessment for Children and Adolescents (SACA) (20–22). For simplicity, lithium and anticonvulsants were both classified as *mood stabilizers*.

Functional assessment. Study interviewers completed the Children's Global Assessment Scale (CGAS) (23) to provide a severity rating of participants' current impairment, measuring overall functional capacity at home, at school, and with peers.

Symptomatic assessment. In addition to administration of the K-SADS-PL-W, which ascertained the presence or absence of manic and depressive symptoms specifically within the context of a mood episode (i.e., *filtered* ratings), *unfiltered* ratings of mood symptoms (regardless of the presence or absence of a syndromal mood disorder) were also assessed via both parental self-report and clinical rating scales at each of the five interview time points. Unfiltered mania ratings were obtained via parental self-report of their child's functioning on the PGBI-10M and via direct interview of parents and children using the Young Mania Rating Scale (YMRS) (24). Unfiltered depression ratings were obtained via direct interview of parents and children using the Children's Depression Rating Scale–Revised (CDRS-R) (25, 26).

At the baseline assessment and every 12 months thereafter, parents completed a 73-item General Behavior Inventory (27) which reflected their own symptoms of mania, hypomania, and depression. This self-report measure contains two subscales, *Hypomanic/biphasic* (mixed, 28 items) and *Depressive* (46 items). Items are rated from 0 ('Never or hardly ever') to 3 ('Very often or almost constantly'), with high scores indicating greater pathology.

Family factors. The Family History Screen (28) was obtained at the baseline assessment to collect information on 15 psychiatric disorders and suicidal behavior in biological parents, as well as first- and second-degree relatives. For the purposes of these analyses, the participant was considered positive for a family history of elevated mood if

one or both parents endorsed yes for the item questioning whether the parent had ever had a period of 'feeling extremely happy or high'.

Mental health services use. The SACA was completed with parents to document mental health services use for inpatient, outpatient, and school settings at six-month intervals, with detailed data on inpatient and outpatient services (20–22). At each interview, parents/guardians were asked about the most recent treatment their child had received, and to rate how well the most recent outpatient services matched their child's needs, and how much their child had benefited from the most recent treatment. Data on the type of treatment received (psychotherapy/medication) were collected as part of the SACA.

Statistical analyses

Analyses proceeded in three stages: (i) determining the overall trend of change in manic symptoms over time; (ii) identifying separate manic symptom trajectories for overall symptom scores (such as persistence, recovery, or worsening); and (iii) describing the correlates of identified trajectories. The first two steps addressed aim 1, and the third step addressed aims 2 and 3 of the present study. For the first two steps, the primary dependent variable was parent-reported manic symptoms (PGBI-10M) measured at baseline, six, 12, 18, and 24 months. For the third set of analyses, clinical characteristics (such as age and diagnoses), including baseline and longitudinal measurements (described below), were used to describe identified manic symptom trajectories.

A common growth model, also known as a linear mixed or hierarchical linear model (29–31), evaluated the overall linear and quadratic trends in manic symptoms across the five time points. The common growth model enabled us to fully benefit from repeatedly measured manic symptoms as it tolerates missing observations, a common occurrence in clinical observational studies. In this procedure, all available cases, including the ones with missing information, are included in the analyses. The inclusion of every subject who completed at least one assessment allowed for conservation of power and was also less likely to produce biased effect estimates. Random effects determined whether individual deviations from the overall trend were substantial and tested whether empirically estimating separate trends might help to explain the heterogeneity of manic symptoms over time.

Next, based on the observation of substantial individual deviations from the overall trend, growth mixture models (GMMs) were estimated. These evaluated the number and shape of separate trajectories and generated individual patient classifications into these trajectories. The number of separate trajectories was selected based on the Bayesian information criterion (BIC) (32) and the clinical plausibility and interpretability of trajectory classes. An initial GMM was estimated without baseline covariates. Next, GMMs were estimated with individual covariates in separate models (the inclusion of a large number of covariates simultaneously is impractical for model estimation). Finally, a multi-covariate GMM was conducted using a subset of baseline factors. This multi-covariate model provided a stringent test of model stability. Covariates in this model were chosen based on initial hypotheses about class composition and included: presence of any bipolar spectrum disorder (BPSD) diagnosis, any adjustment disorder diagnosis, any psychosocial therapy, mood stabilizer use, and total depression score on the CDRS-R. Initial hypotheses were that some classes would contain higher proportions of youth with bipolar disorder, some classes would differ in predominant mood presentation (mania versus depression), and other classes might represent less functionally impaired classes (where adjustment disorder diagnoses would be over-represented). Multi-covariate, uni-covariate, and no covariate GMMs all showed highly similar class solutions. For this reason, results presentation focused on the multi-covariate model. Interpretation of this model included evaluating relationships between covariates and the intercept (baseline manic symptom levels), linear slope (changes in manic symptoms over time), and class membership.

The final multi-covariate GMM included only a subset of potentially interesting baseline and longitudinal factors. To comprehensively describe baseline characteristics of empirically identified classes, several additional factors were examined using univariate analysis of variance and chi-square analyses. These included: age, gender, race/ethnicity, YMRS, CGAS, any family history of elevated mood, parental self-reports of mania and depression, antipsychotic agent use, antidepressant use, and stimulant use. The results are presented based on most likely class membership, after verifying that the pattern of findings was highly similar using class probabilities.

Finally, to explore the longitudinal differences between classes, we examined the relationship between class membership, bipolar disorder diagnostic conversion, and utilization of psychosocial, mood stabilizer, antipsychotic, antidepressant, and stimulant treatment over the two-year prospective

period. *Diagnostic progression* was defined as movement at any time point at least one step on a three-step diagnostic continuum from no bipolar diagnosis through BP-NOS/cyclothymia/bipolar II disorder (BP-II) to bipolar I disorder (BP-I). Diagnostic progression was classified into one of five categories: (i) no progression (no bipolar disorder at any time); (ii) no bipolar diagnosis at an earlier time point to any BPSD except BP-I (no bipolar disorder to BPSD); (iii) no bipolar diagnosis to BP-I (no bipolar disorder to BP-I); (iv) no bipolar diagnosis to any bipolar disorder (no bipolar disorder to any bipolar disorder); and (v) BPSD (e.g., BP-NOS/cyclothymia/BP-II) to BP-I (BPSD to BP-I).

Utilization of treatment was defined as the number of six-month intervals in which any form of psychosocial, mood stabilizer, antipsychotic, antidepressant, or stimulant treatment was reported.

Mplus (33) was used to estimate the common growth model and GMM analyses. SPSS (SPSS Inc., Chicago, IL, USA) was used to describe covariate relationships and longitudinal differences between classes. Class descriptive analyses were exploratory and, therefore, no *a priori* multiple comparison correction was applied to the baseline and 24-month follow-up covariate analyses.

Results

Participant characteristics

Table 1 presents the baseline demographic and clinical characteristics of the cohort. Previous reports have more fully described the clinically ascertained LAMS cohort (5, 11). The data presented herein do not include four individuals who were screened and recruited into LAMS but ended the study between screen and baseline and therefore did not have any baseline or follow-up PGBI-10M data. The majority of patients had PGBI-10M scores present at a minimum of two of the five time points (86.2%). Data capture remained high, even through the 24-month visit (missing: baseline 2.1%, six-month 24.2%, 12-month 26.4%, 18-month 32.7%, and 24-month 37.1%). As expected with only four individuals excluded, the remaining cohort was highly similar to the full LAMS cohort. The participants comprised a demographically and diagnostically heterogeneous cohort with a wide range of mood symptom levels and a minority of youth meeting criteria for bipolar diagnoses at baseline. Missing data analyses for follow-up PGBI-10M data found only one variable distinguishing those with missing data from other participants: a small trend (largest $r = 0.21$) for participants using Medicaid insurance to have missing data.

Table 1. Longitudinal Assessment of Manic Symptoms cohort baseline demographic and clinical characteristics (N = 703)

Baseline sample characteristics	
Age, years, mean (SD)	9.4 (1.9)
Male, n (%)	477 (67.9)
White, non-Hispanic, n (%)	437 (67.2)
Health insurance, n (%)	
Medicaid	366 (52.1)
Private	283 (40.2)
Private and Medicaid	44 (6.3)
Self-pay	10 (1.4)
Living with both biological parents, n (%)	223 (31.7)
History of psychiatric hospitalizations, n (%)	64 (9.1)
Any bipolar diagnosis, n (%)	162 (23.0)
BP-I	71 (10.1)
BP-II	3 (0.4)
BP-NOS	77 (11.0)
Cyclothymia	11 (1.6)
Any adjustment disorder diagnosis, n (%)	13 (1.8)
Mood symptom and functional measures, mean (SD)	
PGBI-10M	12.9 (7.2)
YMRS	16.8 (9.2)
CDRS-R	34.8 (10.7)
CGAS	54.6 (10.3)

BP-I = bipolar I disorder; BP-II = bipolar II disorder; BP-NOS = bipolar disorder not otherwise specified; CDRS-R = Children's Depression Rating Scale–Revised; CGAS = Children's Global Assessment Scale; PGBI-10M = Parent General Behavior Inventory–10 item mania form; YMRS = Young Mania Rating Scale.

Overall manic symptom severity over time

Figure 1 presents the estimated overall mean manic symptom trajectory from the common

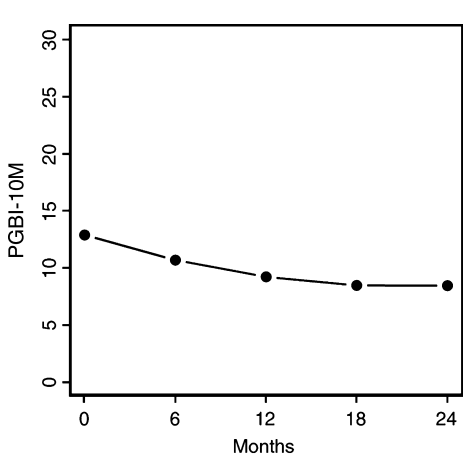

Fig. 1. Estimated overall growth trajectory of Parent General Behavior Inventory–10-item Mania Form (PGBI-10M).

growth model overall. Manic symptoms decreased over the two-year period, resulting in a 4.5-point decline in the PGBI score [$p < 0.001$; effect size = 0.68 based on the standard deviation (SD) of PGBI at 24 months]. The declines were more rapid for the first year (3.7-point decline; $p < 0.001$; effect size = 0.56 based on SD of PGBI at 12 months) than for the rate of decline during the second year (0.8-point decline; $p = 0.001$; effect size = 0.12 based on SD of PGBI at 24 months). Of note, after six months of follow-up, the mean score was below the threshold (12) used for selection of ESM+ participants; and by 18 months, the mean score was substantially lower than 12. Individual deviations from the overall trajectory were often substantial, supporting examination of potentially distinct trajectory shapes.

Manic symptom trajectories

The results of GMM analyses identified four unique trajectories of manic symptoms, as shown in Figure 2. The four-class solution was supported by model fit (BIC: one-class = 16605; two-class = 16579; three-class = 16558; four-class = 16550; five-class = 16557), where the difference in BIC estimates indicated support for the four-class solution (34). We also monitored the parametric bootstrapped likelihood ratio test (35), which preferred a five-class solution. The five-class solution splits one of the four classes (C3 in Fig. 2) in our four-class solution into two smaller trajectory classes (one class starting higher at baseline). The other three classes, including the 'unstable (C2)' class remained unchanged. Based on this observation, we selected the four-class solution instead of the five-class solution that further splits one of the trajectory classes. The four-class solution was also preferred based on the clinical plausibility and interpretability of trajectory classes (further discussed below). The solution was highly similar across the no covariate, single covariate, and multi-covariate models, indicating good model stability. Results are presented for the multi-covariate model.

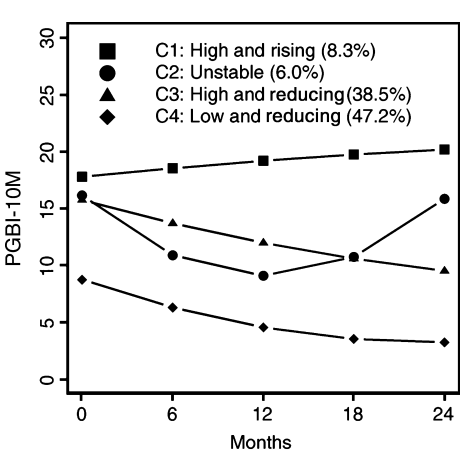

Fig. 2. Estimated Parent General Behavior Inventory–10-item Mania Form (PGBI-10M) growth trajectory classes in the presence of covariates (N = 703).

Figure 2 shows that, rather than simply identifying graded differences over time (i.e., consistent severity differences), the observed classes represent qualitatively distinct manic symptom trajectories (different shapes). Two classes comprised smaller proportions of participants and showed a less favorable course. Specifically, Class 1 (*high and rising*, 8.3%) began with high initial symptom levels that continued to increase over time. Class 2 (*unstable*, 6.0%) also began with high levels, followed by a sharp decrease, but then increased back to baseline levels by the 24-month follow-up.

The other two classes accounted for substantially larger proportions of the cohort and showed more clinically favorable manic symptom trajectories. Class 3 (*high and reducing*, 38.5%) began with high symptom levels but showed a consistent reduction over time. Class 4 (*low and reducing*, 47.2%) began with lower manic symptom levels and also showed reductions over time. These patterns indicate that a substantial minority of clinically referred youth experience ongoing or resurgent manic symptoms, but a larger proportion enjoys symptom reduction over time.

Differences in participant characteristics between the trajectory classes

Table 2 displays baseline demographic and clinical characteristics as well as diagnostic progression and treatment utilization at 24-month follow-up, separately by empirically derived classes. Tables 3 and 4 present multi-covariate GMM results which represent more precise estimates of covariate effects (but with a limited number of variables). For simplicity, the text focuses on descriptive analyses using class membership presented in Table 2. There were no significant differences between classes for age, gender, race/ethnicity, any ADHD diagnosis, and any antidepressant use at baseline or throughout the 24-month study. Features unique to the four classes are described below.

Class 1 had higher levels of caregiver manic and depressive symptoms based on the adults' reports about themselves than the other three classes. Class 1 was more likely than Classes 3 and 4 to receive both psychotherapy and antipsychotic medication over the course of the study.

Table 2. Demographic and clinical characteristics at baseline, diagnostic progression, and treatment utilization across the two-year study period, separately by empirical classifications

	Class 1[a]	Class 2[b]	Class 3[c]	Class 4[d]	χ^2/*F*, p-value
n (%)	58 (8.3%)	42 (6.0%)	271 (38.5%)	332 (47.2%)	
Baseline					
Age, years, mean (SD)	9.3 (1.9)	9.2 (2.1)	9.4 (1.9)	9.4 (1.9)	$F(3,699) = 0.38$, p = 0.767
Male, n (%)	34 (58.6)	27 (64.3)	178 (65.7)	238 (71.7)	$\chi^2(3) = 5.33$, p = 0.149
White, non-Hispanic, n (%)	36 (63.2)	29 (78.4)	151 (58.3)	221 (63.1)	$\chi^2(3) = 5.95$, p = 0.114
ESM screen, n (%)					$\chi^2(3) = 74.82$, p < 0.001
Negative (<12)	0 (0)[4]	2 (4.8)[4]	6 (2.2)[4]	78 (23.5)[1,2,3]	
Positive (≥12)	58 (100)[4]	40 (95.2)[4]	265 (97.8)[4]	254 (76.5)[1,2,3]	
Bipolar diagnoses, n (%)					$\chi^2(6) = 116.01$, p < 0.001
No bipolar disorder	30 (51.7)[4]	28 (66.7)[4]	169 (62.4)[4]	314 (94.6)[1,2,3]	
BP-I	11 (19.0)[4]	8 (19.0)[4]	45 (16.6)[4]	7 (2.1)[1,2,3]	
BPSD	17 (29.3)[4]	6 (14.3)[4]	57 (21.0)[4]	11 (3.3)[1,2,3]	
Any ADHD, n (%)	47 (81.0)	32 (76.2)	212 (78.2)	246 (74.1)	$\chi^2(3) = 2.17$, p = 0.538
YMRS score, mean (SD)	22.9 (9.4)[4]	20.6 (10.8)[4]	19.8 (9.1)[4]	12.9 (7.2)[1,2,3]	$F(3,699) = 49.03$, p < 0.001
CDRS-R score, mean (SD)	40.2 (10.8)[2,4]	33.9 (10.5)[1]	36.7 (10.3)	32.4 (10.4)[1]	$F(3,699) = 14.40$, p < 0.001
CGAS score, mean (SD)	52.9 (9.2)[4]	51.2 (12.0)[4]	52.7 (9.8)[4]	57.0 (10.2)[1,2,3]	$F(3,695) = 11.52$, p < 0.001
Family history of any elevated mood, n (%)	19 (36.5)[4]	8 (21.1)	72 (29.1)[4]	59 (19.2)[1,3]	$\chi^2(3) = 11.96$, p = 0.008
Caregiver self-reported mania on P-GBI, mean (SD)	24.5 (18.1)[2,3,4]	16.4 (13.4)[1]	18.2 (16.1)[1,4]	11.4 (11.9)[1,3]	$F(3,687) = 19.73$, p < 0.001
Caregiver self-reported depression on P-GBI, mean (SD)	48.2 (31.5)[2,3,4]	31.0 (22.9)[1]	36.8 (29.6)[1,4]	25.4 (23.8)[1,3]	$F(3,687) = 16.52$, p < 0.001
Any psychosocial therapy at baseline, n (%)	41 (71.9)[2]	9 (21.4)[1,3,4]	160 (60.4)[2]	193 (58.1)[2]	$\chi^2(3) = 28.20$, p < 0.001
Any mood stabilizer at baseline, n (%)	8 (13.8)[3]	15 (35.7)[3,4]	11 (4.1)[1,2]	17 (5.1)[2]	$\chi^2(3) = 11.96$, p = 0.008
Any antipsychotic agent at baseline, n (%)	19 (32.8)[4]	14 (33.3)[4]	77 (28.4)[4]	47 (14.2)[1,2,3]	$\chi^2(3) = 25.14$, p < 0.001
Any antidepressant at baseline, n (%)	4 (6.9)	6 (14.3)	35 (12.9)	40 (12.0)	$\chi^2(3) = 1.84$, p = 0.607
Any stimulant at baseline, n (%)	15 (25.9)[2,3]	23 (54.8)[1,4]	109 (40.2)[1]	129 (38.9)[2]	$\chi^2(3) = 8.73$, p = 0.033
24-month follow-up					
Diagnostic conversion at 24 months, n (%)					
No bipolar disorder to BPSD	8 (13.8)[3,4]	5 (11.9)[3,4]	12 (4.4)[1,2,4]	3 (0.9)[1,2,3]	$\chi^2(3) = 29.86$, p < 0.001
No bipolar disorder to BP-I	1 (1.7)	4 (9.5)[3,4]	6 (2.2)[2]	3 (0.9)[2]	$\chi^2(3) = 14.31$, p = 0.003
BPSD to BP-I	8 (13.8)[3,4]	2 (4.8)[4]	10 (3.7)[1,4]	2 (0.6)[1,2,3]	$\chi^2(3) = 29.40$, p < 0.001
No bipolar disorder to any bipolar disorder	9 (15.5)[3,4]	9 (21.4)[3,4]	18 (6.6)[1,2,4]	6 (1.8)[1,2,3]	$\chi^2(3) = 37.74$, p < 0.001
Any progression	17 (29.3)[3,4]	11 (26.2)[3,4]	28 (10.3)[1,2,4]	8 (2.4)[1,2,3]	$\chi^2(3) = 61.91$, p < 0.001
No. of time points receiving:, mean (SD)[e]					
Psychosocial therapy	2.9 (1.7)[3,4]	2.3 (1.6)	2.2 (1.7)[1]	2.0 (1.6)[1]	$F(3,696) = 5.02$, p = 0.002
Any mood stabilizer	0.7 (1.4)	1.2 (1.7)[3,4]	0.3 (0.9)[2]	0.2 (0.8)[2]	$F(3,687) = 12.97$, p < 0.001
Any antipsychotic agent	2.1 (2.0)[3,4]	1.9 (2.0)[4]	1.2 (1.8)[1,4]	0.8 (1.5)[1,2,3]	$F(3,699) = 14.99$, p < 0.001
Antidepressant	0.7 (1.2)	0.4 (0.9)	0.5 (0.9)	0.5 (1.1)	$F(3,699) = 0.93$, p = 0.425
Stimulant	1.9 (1.7)	2.6 (1.9)[3,4]	1.7 (1.9)[2]	1.7 (2.0)[2]	$F(3,699) = 3.25$, p = 0.022

ADHD = attention-deficit hyperactivity disorder; BP-I = bipolar I disorder; BPSD = bipolar spectrum disorder; CDRS-R = Children's Depression Rating Scale–Revised; ESM = elevated symptoms of mania; CGAS = Children's Global Assessment Scale; P-GBI-10M = Parent General Behavior Inventory–10-item mania form; SD = standard deviation; YMRS = Young Mania Rating Scale.

[a]High and rising.

[b]Unstable.

[c]High and reducing.

[d]Low and reducing.

[e]Maximum no. of time points: n = 5.

[1,2,3,4]Superscripts denote proportions or means that are statistically different (Bonferroni corrected) across classes. Superscripts correspond with the class number from which a value differs. Bonferroni correction was applied within each correlate for comparisons among classes.

Class 2 at baseline had significantly lower rates of psychosocial therapy use than the other three classes and less use of mood stabilizers than any class except Class 1. Class 2 was more likely than Classes 1 and 4 to use stimulants at baseline. Over follow-up, Class 2 was more likely to receive mood

Table 3. Four-class growth mixture analysis: mixed effects linear regression of baseline covariates and longitudinal P-GBI development within trajectory class

Parameter	Estimate	SE	p-value
Random intercept (initial P-GBI) regressed on covariates			
Intercept	12.996	1.359	0.000
Any bipolar diagnosis	1.738	0.714	0.015
Adjustment disorder diagnosis	−2.548	1.266	0.044
Any therapy	−0.127	0.293	0.666
CDRS-R total score	0.077	0.025	0.002
Random intercept residual variance	12.744	2.326	0.000
Random linear slope (linear decline) regressed on covariates			
Intercept	−5.641	1.519	0.000
Any bipolar diagnosis	−1.729	0.686	0.012
Adjustment disorder diagnosis	−0.252	1.016	0.804
Any therapy	−0.647	0.230	0.005
CDRS-R total score	−0.017	0.021	0.426
Random slope residual variance	0.597	0.189	0.002
Random intercept and slope covariance	−2.579	0.602	0.000
Quadratic slope (deceleration or acceleration of change) regressed on covariates			
Intercept	1.536	0.381	0.000
Any bipolar diagnosis	0.325	0.163	0.045
Adjustment disorder diagnosis	0.332	0.210	0.114
Any therapy	0.149	0.054	0.006
CDRS-R total score	0.001	0.005	0.837
Residual variance	Fixed at 0	–	–

CDRS-R = Children's Depression Rating Scale–Revised; P-GBI = Parent General Behavior Inventory–10-item Mania Form (PGBI-10M); SE = standard error.

Table 4. Four-class growth mixture analysis: multinomial logit regression of baseline covariates and trajectory class membership

Parameter	Estimate	SE	p-value
C1 versus C4			
Logit intercept	−3.993	0.672	0.000
Any bipolar diagnosis	2.485	0.575	0.000
Mood stabilizer	−0.135	0.659	0.838
Any therapy	0.504	0.172	0.003
CDRS-R total score	0.047	0.015	0.002
C2 versus C4			
Logit intercept	−1.963	0.739	0.008
Any bipolar diagnosis	1.434	0.717	0.046
Mood stabilizer	0.966	0.618	0.118
Any therapy	−0.924	0.538	0.086
CDRS-R total score	0.014	0.019	0.464
C3 versus C4			
Logit intercept	−1.791	0.447	0.000
Any bipolar diagnosis	2.169	0.495	0.000
Mood stabilizer	−1.014	0.677	0.134
Any therapy	0.353	0.159	0.027
CDRS-R total score	0.029	0.012	0.019
C1 versus C2			
Any bipolar diagnosis	1.051	0.779	0.177
Mood stabilizer	−1.101	0.835	0.187
Any therapy	1.428	0.559	0.011
CDRS-R total score	0.033	0.020	0.108
C2 versus C3			
Any bipolar diagnosis	−0.735	0.787	0.351
Mood stabilizer	1.980	0.847	0.019
Any therapy	−1.277	0.576	0.027
CDRS-R total score	−0.015	0.019	0.441

CDRS-R = Children's Depression Rating Scale–Revised; SE = standard error.

stabilizers and stimulants than Classes 3 and 4, and was more likely to receive antipsychotic agents than Class 4. Class 2 was similar to Class 1 in diagnostic progression over the course of the study and had higher conversion rates than Classes 3 and 4.

Class 3 differed from Classes 1 and 2 by having lower rates of mood stabilizer use at baseline and lower mood stabilizer use across the follow-up period (Class 2 only). Class 3 had higher rates of stimulant use at baseline relative to Class 1. Over follow-up, Class 3 was less likely to receive antipsychotic medication than Class 1 but more likely to do so than Class 4. Class 3 had moderate rates of diagnostic progression along the bipolar spectrum (lower levels than Classes 1 and 2 but higher than Class 4).

Class 4 differed from Classes 1–3 across almost all baseline variables. This class had the lowest proportion of bipolar diagnoses at baseline and was least likely to convert over 24 months. Class 4 had fewer manic symptoms, better functioning, a lower family history burden, the highest rate of ESM− participants, and the lowest level of antipsychotic agent utilization at baseline and across the study.

Diagnostic progression was least common in Class 4 compared to the other three classes [Class 1: relative risk (RR) = 15.70, 95% confidence interval (CI): 5.45–46.74; Class 2: RR = 16.82, 95% CI: 5.87–49.75; Class 3: RR = 6.19, 95% CI: 2.42–17.02]. Class 3 was less likely to experience diagnostic progression than Classes 1 and 2. There was a trend toward more progression from no bipolar disorder to BP-I in Class 2 relative to the Class 1 ($z = 1.77$, $p = 0.077$).

Of the 27 baseline and follow-up covariates examined, 21 were significant at $p < 0.05$. Of these 21, all survived false discovery rate correction and 15 of 21 survived a conservative Bonferroni correction ($p < 0.0019$). Thus, class descriptions across covariates were unlikely to have been strictly a result of type 1 error.

Discussion

The present study evaluated whether LAMS participants demonstrated different trajectories of parent-reported manic symptoms over the first 24 months of follow-up. This is the first study to explore longitudinally the progression of manic

symptoms in an ascertained cohort of children and adolescents. Based on prior longitudinal work looking at diagnostic changes, we anticipated that a GMM would identify multiple distinct trajectories. Findings confirmed the heterogeneity of symptom trajectory. In addition to profiles that followed patterns of recovery or progression to more severe mood disturbance, the analyses also revealed more granularity in the trajectories of a large portion of youth in the sample. The four latent classes of trajectory were unequal in size.

Of note, most LAMS participants belonged to one of two classes of patients that experienced a reduction in manic symptoms over time. The improvement in this large majority of patients is reassuring, reinforcing the point that what may appear to be manic symptoms at a given time point may reflect a variety of underlying diagnoses, and can follow several different longitudinal trajectories. Families are often concerned about prognosis, given the reports of poor outcomes and concerns about children with manic symptoms or bipolar disorder (7–9); findings indicate that there are likely to be multiple causes and outcomes for what many appear to be similar initial presentations (18, 36). However, approximately 15% of the sample was in one of two classes of patients that either experienced an increase in manic symptoms or an unstable pattern of symptoms over time, with high rates of diagnostic progression.

In addition to these global observations, interesting between-class differences were also found. Not surprisingly, the *low and reducing* class (Class 4) differed at baseline from the other three classes. More specifically, Class 4 demonstrated the fewest bipolar diagnoses, both at baseline and over the 24 months of the study, the highest functioning, and the lowest rate of antipsychotic agent use at baseline and throughout the study. These results are consistent with the fact that most of the ESM− recruits were in Class 4 and would not have been predicted to manifest a bipolar diagnosis. They are also internally consistent with a previous LAMS report that antipsychotic agent use is associated with more severe psychopathology and dysfunction (37).

By way of contrast, the *high and rising* class (Class 1) had the highest rates of parental self-reported symptoms of mania and depression. As this association is not necessarily reflective of causal relationships, it is possible that this association is simply a reflection of higher degrees of global symptomatic reporting. Additionally, it is possible that reports of child behavior problems and psychopathology are inflated by parents with mood symptoms, a phenomenon that has been explored in maternal depression (38–40). However, the possibility that higher degrees of parental self-reported affective symptoms may be associated with worse outcomes in their children is a consideration that seems plausible both genetically and environmentally, thus deserving further evaluation.

The *unstable* class (Class 2) had the lowest amount of psychosocial interventions and the highest rate of stimulant treatment, both at baseline and when considering all follow-up time points. As this result was surprising to us, these findings may simply reflect type I error.

As outlined in previous LAMS reports (5, 11, 37), the present study was primarily limited by the inability to generalize these findings to the general population of children due to the fact that participants were recruited from clinical settings. Although the data presented herein were collected from 703 LAMS participants, they do not reflect a PGBI-10M score for each of these participants at each of the five possible time points. Additionally, although a large portion of the data provided by the LAMS cohort are generated by carefully trained, reliable interviewers (5), many of the findings presented in this paper are based on data from the parent report. Finally, because this was the first study to use these statistical methods on prospective longitudinal data for manic symptoms, we did not have strong *a priori* hypotheses about the number of classes or their trajectories. Our findings were based on best practices of current statistical methods and are consonant with what we would expect based on studies of diagnostic change. They also provide a strong foundation for future prediction and replication in independent samples.

Despite its limitations, the present study found that elevated manic symptoms are heterogeneous and are characterized by distinct courses. The data indicate that what may appear to be manic symptoms can be associated with a variety of diagnoses and with multiple distinct trajectories over time. The findings complement recent work in adults with bipolar disorder that also empirically identified distinct classes based on summaries of patterns in mood symptoms. Our data may provide the ability to prognosticate outcome for children with elevated manic symptoms at the time of their initial assessment. Further, if the approximately 15% of children who do not experience a reduction in manic symptomatology over time can be identified at the start of treatment or at least early in the course of treatment, they may then be specifically targeted for more intensive therapeutic attention.

Conclusions

A unique finding from the present study is that the presence of four distinct classes demonstrates that outcomes are not uniform among youth with symptoms of mania. Most LAMS participants did well in respect to manic symptoms over time, compared to youth with bipolar disorder, who frequently struggle over the long term. Although the present study found several associations between manic symptom trajectory and clinical characteristics, subsequent research will be needed to determine whether these associations are indeed reflective of causal relationships and how much long-term prognostic value they have.

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