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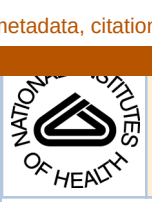

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Characteristics of children with elevated symptoms of mania: the Longitudinal Assessment of Manic Symptoms (LAMS) Study

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Abstract

Objective—To examine differences in psychiatric symptomatology, diagnoses, demographics, functioning, and psychotropic medication exposure in children with elevated symptoms of mania (ESM+) compared to youth without ESM (ESM−).

Method—Guardians of consecutively ascertained new outpatients 6 to 12 years of age were asked to complete the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M). Patients with scores ≥ 12 on the PGBI-10M (ESM+) and a matched sample of screen negatives (ESM−) were invited to participate.

Results—707 children [621 ESM+, 86 ESM−; mean age 9.4 (2.0) years] were evaluated. The ESM+ group, compared to the ESM− group, more frequently met DSM-IV criteria for a mood disorder ($p< 0.001$), bipolar spectrum disorders (BPSD, $p< 0.001$), and disruptive behavior disorders ($p<0.01$). Furthermore, they showed poorer overall functioning and more severe manic, depressive, attention deficit/hyperactivity, disruptive behavioral, and anxiety symptoms. Nevertheless, rates of BPSD were relatively low in the ESM+ group (25%), with almost half of these BPSD patients (12.1% of ESM+) meeting DSM-IV criteria for bipolar disorder not otherwise specified (BP-NOS). ESM+ children with BPSD had significantly more: current prescriptions for antipsychotics, mood stabilizers and anticonvulsants; psychiatric hospitalizations,

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and biological parents with elevated mood; and were lower functioning compared to ESM+ children without BPSD.

Conclusion—Although ESM+ was associated with higher rates of BPSD than ESM−, 75% of ESM+ children did not meet criteria for BSPD. Results suggest longitudinal assessment is needed to examine which factors are associated with diagnostic evolution to BPSD in children with ESM +.

Introduction

Evidence that Elevated Symptoms of Mania (ESM) are present in a substantial number of children seeking psychiatric care continues to build.[1–4] Although a portion of children with ESM may meet strict DSM-IV criteria for Bipolar Disorder Type 1 or 2 (BP1 or BP2), many do not. For example, a study of inpatient children found that a relatively high proportion (62.5%) experienced *DSM-III-R* symptoms of mania (defined as euphoria and/or irritability plus three of the remaining five symptoms on the mania symptom subscale from the Child Symptom Inventory (CAASI-4R)[5]). However, of those children with manic symptoms, only a small number met criteria for a bipolar disorder.[6]

Furthermore, the clinical implications of ESM in children are unclear because the presence of manic symptoms does not necessarily mean that a bipolar diagnosis is inevitable.[3, 7–9] In one sample of 9- to 13-year-old males meeting *DSM-III-R* criteria for ADHD and manic symptoms, no participants met criteria for a bipolar disorder at 6-year follow-up.[8] In one of the few published epidemiological studies, adolescents originally reporting some manic symptoms (defined as experiencing a distinct period of abnormally and persistently elevated, expansive, or irritable mood without meeting diagnostic criteria for a bipolar disorder) rarely developed a bipolar disorder in the 6- to 10-year follow-up period.[10]

Although relatively little is known about the phenomenology, course of illness, or symptom evolution of youth who experience ESM but do not meet DSM-IV criteria for a bipolar diagnosis, it appears that inpatient children with manic symptoms experience marked psychosocial dysfunction and a high degree of psychopathology regardless of bipolar diagnostic status.[3,6]

Though there is currently no clear means of distinguishing which children with ESM will eventually develop bipolar disorder, determination of a reliable method is a priority due to the important implications of assigning such a diagnosis to a child. For example, the diagnosis of bipolar disorder implies a lifelong, heritable condition, with psychological and social sequelae for both the child and his/her family. Youth who are assigned a bipolar diagnosis in error may receive inappropriate treatments for years, particularly unnecessary psychotropic medications that carry with them significant risks. On the other hand, failure to appropriately assign a BPSD diagnosis may result in a lack of appropriate treatment and prolonged suffering. Thus, making an accurate diagnosis regarding the presence or absence of bipolarity in a child manifesting EMS has important clinical implications. However, even in adults who have putatively more prototypic presentations of bipolar disorder, there are studies showing that many years typically elapse from the onset of mood symptoms until the correct BP diagnosis is made.[11, 12]

Recent data from the National Ambulatory Medical Care Survey (1999–2003) indicated over 90% of youth who were given a diagnosis of bipolar disorder in office-based clinical settings received a psychotropic medication for this diagnosis.[13] However, data regarding medication treatment of children with ESM, regardless of diagnosis, are limited. Due to the presence of symptoms that might be construed as indicative of a bipolar diathesis, it is possible these children may receive medications indicated for patients with more narrowly

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defined bipolarity. According to treatment recommendations and practice parameters, children with a bipolar disorder may be prescribed atypical antipsychotics, frequently in combination with a mood stabilizer.[14, 15] Although these agents may be beneficial to some patients, they also may be associated with substantive risks.

The NIMH-supported Longitudinal Assessment of Manic Symptoms (LAMS) study was designed to prospectively follow an epidemiologically-ascertained cohort of children with ESM, as well as a comparison group of outpatient children without elevated manic symptoms, both to delineate the relationship between manic symptoms and bipolarity and to carefully define the characteristics of children with ESM. This paper describes the initial demographic information, diagnostic and symptom prevalence, and medication exposure for the LAMS cohort that will be followed longitudinally.

Method

Institutional Review Boards at each of the four university-affiliated LAMS sites (Case Western Reserve University, Cincinnati Children's Medical Center, the Ohio State University, and the University of Pittsburgh Medical Center/Western Psychiatric Institute and Clinic) reviewed and approved all procedures in the protocol. Written informed consent from parents/guardians and assent from participants were obtained before any study-related procedures were performed. Parents consented to complete the screening procedure described below; parents consented and children assented to participate in the longitudinal portion of the study.

Participant Ascertainment

Parents/guardians of all eligible children between the ages of 6 years, 0 months and 12 years, 11 months who were new patients to LAMS outpatient clinics (see inclusion/exclusion criteria below) were asked to complete the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M)[16, 17] to screen for ESM. The items that comprise the PGBI-10M describe hypomanic, manic, and biphasic symptomatology and have been reported to discriminate bipolar disorder in youth from other diagnoses.[17] Each item is scored from 0 (“never or hardly ever”) to 3 (“very often or almost constantly”); total scores range from 0 to 30 with higher scores indicative of greater symptomatology. Each patient whose parent/guardian rated the child at or above a score of 12 (ESM+) on the PGBI-10M was invited to participate in the longitudinal portion of the LAMS study. In addition, a smaller comparison group of patients who scored 11 or lower (ESM−) roughly matched in real time on age, sex, race, ethnicity, and Medicaid status was selected to enroll in the longitudinal portion of the study. More details concerning subject ascertainment and the rationale for the cut score of 12 on the PGBI-10M are described in detail in Horwitz et al.[4]

To be screened for the study, patients must: 1) not have received mental health treatment in the outpatient clinics where the LAMS study was being conducted within the past 12 months; 2) be between the ages of 6 years, 0 months and 12 years, 11 months; 3) speak English; 4) have an accompanying parent/guardian who speaks English, and; 5) not have a sibling or other child living in the same household who had already participated in screening for possible LAMS participation. See Horwitz et al.[4] for a detailed description of these screening and selection procedures.

Patients rated positively by their parents/guardians for ESM (scoring 12 or higher on the PGBI-10M; ESM+), and patients not presenting with ESM selected as the comparison group (ESM−), were invited to participate in the longitudinal portion of the study. Of the 1124 children who screened ESM+, 621 or 55% accepted the invitation. There were no sociodemographic differences between children/families agreeing to enroll in the

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longitudinal study and those who did not. ESM− children were sampled with replacement (those who were approached, but refused, were replaced by another demographically matched youth in the ESM− group) resulting in 86 children without ESM also being included in the longitudinal cohort[4] (see Figure 1).

Longitudinal Assessment and Follow-up

After the children and adolescents were assessed at baseline, participants who continued to be eligible were seen every six months for up to five years. Each of these study visits lasted approximately 2–4 hours.

Baseline Assessment

Demographics—Information including age, sex, race, ethnicity, and health insurance status was obtained from parents/guardians. In addition, a brief medical history was collected.

Diagnoses—Children and their guardians were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (K-SADS-PL)[18] with additional depression and manic symptom items derived from the Washington University in St. Louis Kiddie Schedule for Affective Disorders (WASH-U K-SADS).[19, 20] Items to assess nonverbal communication, the child's relationship with others, shared enjoyment, and social-emotional reciprocity according to DSM-IV criteria were added to the KSADS-PL to screen for pervasive developmental disorders (PDDs). The resulting instrument, the K-SADSPL-W, is a semi-structured interview that assesses current and lifetime psychiatric diagnoses and the time course of each illness.

Unmodified DSM-IV diagnostic criteria were used in the LAMS study. The criteria for BP-NOS were clarified for the LAMS study to follow the same criteria used in the Course and Outcome of Bipolar Youth study (COBY).[21] BP-NOS was operationalized as follows: (a) 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; (b) change in the participant's level of functioning (increase or decrease); (c) symptoms must be present for a total of at least four hours within a 24-hour period; and (d) the participant must have had at least four episodes of four hours duration 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. It should be noted that once a child met criteria for a bipolar spectrum disorder (BPSD) 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 the interview. For simplicity, some medications have been grouped according to class (anticonvulsants, antidepressants, antipsychotics, stimulants, alpha-two agonists, benzodiazepines), whereas others are reported separately.

Functional Assessment—The Children's Global Assessment Scale (CGAS) was completed by study interviewers to provide a severity rating of participants' current impairment[22]. The CGAS is a clinical rating scale used to document children's overall functional capacity at home, school, and with peers over the past two weeks. Scores range from 1 (indicating a severely impaired child) to 100 (indicating a child with superior functioning).

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Symptomatic Assessment—In addition to administration of the K-SADS-PL-W, which ascertained presence or absence of manic and depressive symptoms specifically within the context of a mood episode (i.e., "filtered" ratings), "unfiltered" ratings of apparent mood symptoms were also assessed via both parental self-report and clinical rating scales. These unfiltered ratings did not require clinical judgment about the reasons for symptoms to be manifest. Because a key aspect of the LAMS study is the assessment of symptoms, regardless of etiology, over time, these unfiltered ratings were obtained to compliment those assessments of affective illness that were only manifest during the presence of a mood disorder.

Unfiltered mania ratings were obtained via parental self-report of their child's functioning over the past six months on the PGBI-10M and via direct interview of parents and children regarding the past two weeks using the Young Mania Rating Scale (YMRS)[23] via interview with both the child and parent. Total scores on this 11-item scale range from 0 (no manic symptoms) to 60. The YMRS has demonstrated good reliability[24] and good ability to discriminate bipolar spectrum disorders from attention deficit/hyperactivity disorders (ADHD).[25–27]

Unfiltered depression ratings were obtained via direct interview of parents and children regarding the past two weeks using the Children's Depression Rating Scale-Revised (CDRS-R).[28, 29] The CDRS-R is a 17-item scale administered as an interview with the child and parent. The instrument has demonstrated good validity and psychometric properties.[28, 29] CDRS-R scores range from 17 to 113, with higher scores being indicative of greater depressive symptomatology.

The Child and Adolescent Symptom Inventory-4R (CAASI-4R)[30] contains items reflecting DSM-IV criteria for emotional and behavioral disorders in children and adolescents. Parent-reported scores on the attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) subscales were examined. Frequency of symptoms and the frequency of symptom-related impairment over the past six months are scored on a scale of 0 (never) to 3 (very often). The CAASI-4R has demonstrated satisfactory internal consistency, test-retest reliability, and convergent/discriminant validity with corresponding scales of the Child Behavior Checklist and the Conners' Parent Rating Scale.[31]

The parent-completed Screen for Child Anxiety Related Emotional Disorders (SCARED)[32] quantified symptoms of anxiety over the past six months. The SCARED measures five aspects of anxiety: (1) panic/somatic; (2) generalized anxiety; (3) separation anxiety; (4) social phobia; and (5) school phobia. The 41 SCARED items are rated from 0 (not true or hardly ever true) to 2 (very true to often true). The SCARED has shown good internal consistency ($\alpha \sim 0.90$)[33] and excellent discriminant validity between children with anxiety disorders and children with non-anxiety psychiatric disorders (all $ps < 0.05$).[33]

The Family History Screen (FHS)[34] was obtained to collect information on 15 psychiatric disorders and suicidal behavior in biological parents. As family history will be described in more detail at a later time, this paper only examines presence or absence of elevated mood defined as ever have experienced a period of feeling extremely happy or high by the youth's biological mother or father.

Interviewer Training and Inter-rater Reliability

LAMS interviewers were trained in three parts: during a three-day start-up meeting; by rating along with taped interviews; and by leading administrations of the assessment instruments. To prevent rater drift following training, interviewers rated taped

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administrations of the K-SADS-PL-W, CDRS-R, and the YMRS. The kappa for K-SADS-PL-W psychiatric diagnoses was 0.82. More specifically, the kappa for bipolar diagnoses was 0.93. In addition, the kappa for the CDRS-R and the YMRS were (k=0.47) and (k=0.41) respectively, which are within the acceptable levels of item level weighted kappa suggested in the literature.[35]

Statistical Analyses

Fisher exact tests were used to test for possible differences in distribution of: sex; race; ethnicity; Medicaid status; intact families; rates of special education placements, psychiatric hospitalization, DSM-IV psychiatric diagnoses, family history of elevated mood and current and past medications in the ESM+ versus ESM− groups and in the ESM+ group with versus without BPSD. Independent *t*-tests were used to examine differences in CGAS, YMRS, PGBI-10M, CDRS-R, CAASI-4R, and SCARED-P scores between ESM+ and ESM− groups and ESM+ youth with versus without BPSD.

The alpha level for statistical significance was set at $p \leq 0.05$. It was not adjusted for multiple comparisons performed due to the exploratory nature of this work.

Results

Participant Characteristics

Demographics for the 707 participants appear in Table 1. Compared to ESM− participants, ESM+ participants were significantly less likely to be living in intact families and had significantly lower CGAS scores, indicative of poorer overall functioning. As ESM+ and ESM− participants had been matched on demographic variables, these two groups did not differ significantly in regard to age, sex, race (White versus other races), ethnicity (Hispanic versus non-Hispanic), or those receiving public insurance (compared to all other insurance groups). Moreover, the ESM+ and ESM− groups did not differ in the proportion having received special education or in the number of prior psychiatric hospitalizations (See Table 1).

DSM-IV Psychiatric Disorders

Current diagnoses (as defined by DSM-IV criteria) and symptoms at baseline appear in Tables 2, 3, and 4. Fourteen participants (9 [1.4%] ESM+ and 5 [5.8%] ESM) did not meet criteria for a current DSM-IV diagnosis. The average number of current diagnoses at baseline was 2.5 (standard deviation [*SD*] = 1.3). Members of the ESM+ group had more diagnoses (mean=2.6, *SD*=1.3) than the ESM− comparison group (mean=2.0, *SD*=1.2; t=3.95, df=705, p<.001).

Mood Disorders and Mood Symptoms—As shown in Table 2, when compared to ESM− youth, the ESM+ group more frequently met DSM-IV criteria for a mood disorder and bipolar spectrum disorders and had significantly higher YMRS scores at baseline. As expected, the mean PGBI-10M score in the ESM+ group was significantly greater than the ESM− group. While ESM+ and ESM− groups did not differ significantly in the rate of depressive disorders, the ESM+ group received significantly higher CDRS-R scores over the previous two weeks (see Table 2).

ADHD and Disruptive Behavior Disorders—ESM groups did not differ significantly in rates of current attention-deficit/hyperactivity disorder (ADHD), but the ESM+ group scored significantly higher on all three CAASI-4R ADHD subscales (see Table 3). In addition, compared to the ESM− group, the ESM+ group reported more disruptive behavior

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disorders (53.1% versus 36.0%) and higher oppositional defiant disorder (ODD) and conduct disorder (CD) subscale scores on the CAASI-4R (see Table 3).

Other Psychiatric Disorders—Table 4 provides comparisons of psychotic, anxiety, adjustment and pervasive developmental disorders between groups. There was a trend for the ESM− group to have a greater rate of pervasive developmental disorders (11.6%) compared to the ESM+ group (5.6%). ESM+ and ESM− groups did not differ significantly in the occurrence of psychotic disorders, anxiety disorders, or adjustment disorders. However, SCARED-P total scores were higher in the ESM+ group than in the ESM− group, indicative of more anxiety symptoms over the previous 6 months. Of note, no participants met DSM-IV criteria for a substance use disorder.

Psychotropic Medication Exposure

Currently prescribed and past trials of psychotropic medications for participants appear in Table 5. At baseline, 63% (*n*=443) of the youth were prescribed at least one psychotropic medication. Neither current nor past prescription rates differed significantly for ESM+ and ESM− groups (Current-- ESM+ vs. ESM−: M [SD]=1.1 [1.1] vs. 1.0[1.0]; *t*=0.38, *df*=705, *p*=0.71; Past-- ESM+ vs. ESM− M[SD]=1.4[2.0] vs. 1.6[2.1]; *t*=0.62, *df*=705, *p*=0.53). Similarly, prescription rates for specific categories of medication (lithium, anticonvulsants, antidepressants, antipsychotics, stimulants, or alpha-two agonists) did not differ between groups (See Table 5).

ESM+ with Bipolar Disorder vs ESM+ without Bipolar Disorder

Table 6 includes the comparisons of demographics, family history, diagnoses, currently prescribed medication groups, and current mood symptoms for ESM+ participants with and without BPSD. As shown in Table 6, ESM+ participants with BPSD had more psychiatric hospitalizations and were older, lower functioning, and more likely to have biological mothers and fathers with elevated mood (ever experienced a period of feeling extremely happy or high) than ESM+ participants without BPSD. In addition, ESM+ youth with BPSD had a higher rate of currently prescribed antipsychotics, mood stabilizers, and anticonvulsants. Finally, as expected, ESM+ youth with BPSD had higher scores on all unfiltered mood symptom ratings (PGBI-10M, YMRS, and CDRS-R). However, ESM+ youth without a BPSD had more current disruptive behavior disorders (CD, ODD and/or disruptive behavior not otherwise specified).

Discussion

These findings underscore several crucial points. ESM appear to be a common concern in outpatient psychiatric settings, consistent with emerging literature about the relatively high rate of manic symptoms in other studies. Second, ESM are associated with substantially increased rates of bipolar disorder, which is why measures assessing ESM may prove useful as screening aids.[17, 36] Third, ESM are associated with other, non-bipolar diagnoses, and/or may be a marker of severe pathology rather than a specific marker of a bipolar diathesis.

In the 707 children and adolescents of the LAMS cohort, the diagnoses most frequently assigned at baseline were: ADHD (76.1%), other disruptive behavior disorders (51.1%), mood disorders (40.5%) and anxiety disorders (31.3%). Further, the entire cohort had high rates of comorbidity. Of note, the ESM+ group met criteria for more diagnoses and had poorer overall functioning than the ESM− group. Furthermore, preliminary results indicate that ESM+ youth with BPSD have lower overall functioning, more psychiatric hospitalizations, and more parents with elevated mood compared to ESM+ youth without BPSD.

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Similar to the children described by Carlson & Kelly,[6] many youth who were identified as experiencing ESM did not meet diagnostic criteria for BPSD. Whether or not these children with ESM will eventually develop a bipolar diagnosis, either confirming or refuting the findings of Lewinsohn et al.[10] and Hazell et al.[8] that no or few youth with manic symptoms will later develop BPSD, will be assessed through longitudinal assessments of this study cohort. This question is a key specific aim of the LAMS study.

As expected, there were some differences in rates of diagnoses between the ESM groups. For instance, ESM+ youth were diagnosed with more bipolar spectrum disorders than those in the ESM− group. However, only one-quarter of youth with ESM actually met diagnostic criteria for a bipolar spectrum disorder. (Interestingly, most of that quarter of ESM+ children with BPSD met diagnostic criteria for either BP-NOS (48%) or BP1 (43%), with very few meeting criteria for BP2 or cyclothymia.) ESM+ youth were, in fact, more likely to have a disruptive behavior disorder diagnosis than a bipolar diagnosis. More specifically, over half of the ESM+ group was diagnosed with a disruptive behavior disorder, primarily ODD, compared to only 36% of the ESM− group.

The ESM+ and ESM− groups did not differ significantly in the number of youth currently diagnosed with a depressive disorder, ADHD, or anxiety disorder. Despite this lack of categorical differences between groups, parents of children in the ESM+ group endorsed significantly greater depressive, ADHD, and anxiety symptoms on the CAASI-4R and SCARED compared to the ESM− group. This suggests the ESM+ group is more symptomatic across a variety of domains even if these symptoms do not (yet) translate to significantly more diagnoses within those domains.

With such diagnostic diversity found in the ESM+ group, it may be argued that the PGBI-10M cut score was set too low. However, the PGBI-10M cut score of 12 for the ESM groups was purposely set to keep sensitivity to true bipolar cases high, and also capture a large number of other cases showing similar symptoms for different diagnostic reasons. The second, heterogeneous group will be the more interesting one to follow longitudinally.

Not surprisingly, with over three-fourths of LAMS participants meeting diagnostic criteria for ADHD, stimulants were the most frequently prescribed class of current and past medication. However, with 76% of the overall sample having an ADHD diagnosis, only 39% of the LAMS cohort was currently prescribed a stimulant. Antipsychotic medications were prescribed at a relatively high rate, with nearly a quarter (22%) of all 707 LAMS participants prescribed an antipsychotic at the time of assessment. Although ESM+ and ESM− groups differed in the rates of bipolar spectrum disorders and disruptive behavior disorders, neither current nor past exposure to any medication class examined in this study differed significantly between the groups. However, when examining the ESM+ group, those children with BPSD were prescribed significantly more antipsychotics (41% vs. 17%), anticonvulsants, and mood stabilizers compared to ESM+ participants without BPSD. Finally, although approximately 30% of the participants were diagnosed with an anxiety disorder and 18% of the youth met criteria for a depressive disorder, rates of current selective serotonin reuptake inhibitor (SSRI) prescriptions were relatively low (8.9%). This modest rate may reflect the effect of the Black Box warning for SSRIs.[37] A more detailed examination of community-based prescribing practices is warranted in future examinations of the LAMS study sample.

When examining the ESM+ group, the fact that the children without a bipolar disorder had a greater rate of disruptive behavior disorders (DBD) supports the possibility that there are two main paths that lead to ESM+ : (a) having a bipolar disorder, (b) having DBD and some mood symptoms without meeting diagnostic symptoms criteria for a bipolar disorder.

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Limitations

Limitations of this study include the fact that the sample of children was obtained only from outpatient mental health centers associated with university partners. Therefore, the sample does not include children whose parents sought care in other settings or who were currently hospitalized. The sample was focused in Ohio and Western Pennsylvania and might not reflect outpatient mental health services utilization patterns in other regions. Further, given that these were all children and families seeking care, they are not representative of the general population of children.

Clinical Implications

Although ESM may be commonly found in children and adolescents, this does not necessarily indicate that BPSD is common in youth. In fact, the children and adolescents in the ESM+ group were more likely to have an ADHD and/or disruptive behavior disorder rather than a BPSD. Screening for ESM did increase the base rate of BPSD to a quarter of the sample, however, higher than would be anticipated in a general outpatient clinic.[38]

In conclusion, although LAMS participants were selected based on the presence of ESM, their subsequent structured interviews revealed a diverse range of psychiatric disorders. Furthermore, while ESM were associated with higher rates of BPSD, most of these youth did not meet diagnostic criteria for BPSD. Rather, ESM+ youth more commonly had a disruptive behavior disorder. Perhaps most surprising is the fact that the ESM+ youth did not differ from ESM− in number of psychotropic medications, a finding that warrants further investigation. The data will provide the opportunity to examine medication use in youth with considerable psychiatric morbidity. Results suggest the longitudinal assessment of ESM is needed to examine which factors are associated with diagnostic evolution to a bipolar spectrum disorder in patients with ESM+, and whether such evolution even occurs. Longitudinal data are also needed to identify risk and protective factors associated with long-term outcomes in this vulnerable population.

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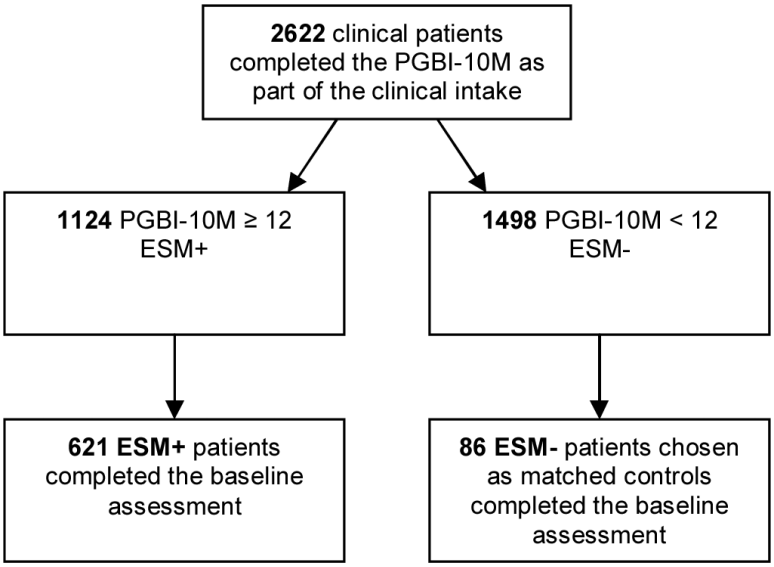

Figure 1.
Subject ascertainment

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Table 1

Demographic and Clinical Characteristics of ESM+ and ESM− Participants

Characteristics	ESM+ Participants (*n* = 621)	ESM− Participants (*n* = 86)	All Participants (*N*=707)	Statistic, p value
Age, mean (*SD*)	9.4 (2.0)	9.7 (1.7)	9.4 (1.9)	t=1.37, df=705, p=0.17
Male *n* (%)	413 (66.5)	65 (75.6)	478 (67.6)	Fisher's Exact Test p=0.11
White *n* (%)	395 (63.6)	60 (69.8)	455 (64.4)	Fisher's Exact Test p=0.28
Hispanic *n* (%)	26 (4.2)	5 (5.8)	31 (4.4)	Fisher's Exact Test p=0.41
Health Insurance Coverage *n* (%)				Fisher's Exact Test p=0.07
Medicaid	333 (53.6)	37 (43.0)	370 (52.3)	
Private Insurance	242 (39.0)	41 (47.7)	283 (40.0)	
Private Insurance & Medicaid	39 (6.3)	5 (5.8)	44 (6.2)	
Self Pay	7 (1.1)	3 (3.5)	10 (1.4)	
Living with both biological parents (% yes)	187 (30.1)	36 (41.9)	223 (31.5)	Fisher's Exact Test p< 0.05
Ever in special education (% yes)	183 (29.5)	24 (27.9)	207 (29.3)	Fisher's Exact Test p=0.80
Psychiatric hospitalizations, mean (*SD*)	0.2 (1.3)	0.1 (0.5)	0.2 (1.2)	t=0.83, df=705, p=0.41
Overall functioning, CGAS mean (*SD*)	54.0 (10.0)	59.0 (11.1)	54.6 (10.3)	t=4.29, df=701, p<.001
Family History of Elevated Mood				
Biological Mother *n* (%)	99 (15.9)	13 (15.1)	112 (15.8)	Fisher's Exact Test, p=1.00
Biological Father *n* (%)	55 (8.9)	6 (7.0)	61 (8.6)	Fisher's Exact Test, p=0.68

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Table 2

Current Mood Diagnoses of Participants with ESM and Comparison Participants

Diagnosis, *n* (%)	ESM+ Participants (*n* = 621)	ESM−Participants (*n* = 86)	Statistic, p value**
Mood Disorders	267 (43.0)	19 (22.1)	Fisher's Exact Test p< 0.001
Bipolar Spectrum Disorder	155 (25.0)	7 (8.1)	Fisher's Exact Test p<0.001
BP1	66 (10.6)	5 (5.8)	
BP2	3 (0.5)	0	
Cyclothymia	11 (1.8)	0	
BP NOS	75 (12.1)	2 (2.3)	
Manic Symptoms			
PGBI-10M, mean(SD)	13.9 (6.8)	5.3 (5.2)	t=11.27, df=690, p <0.001
YMRS, mean (SD)	17.7 (9.1)	10.4 (7.0)	t=7.17, df=705, p<0.001
Depressive Disorder Spectrum *	112 (18.0)	12 (14.0)	Fisher's Exact Test p=0.45
Current MDD	42 (6.8)	7 (8.1)	
Past MDD	13 (2.1)	3 (3.5)	
Current Dysthymia	14 (2.3)	2 (2.3)	
Past Dysthymia	1 (0.2)	0	
Current Depressive Disorder NOS	57 (9.2)	3 (3.5)	
Past Depressive Disorder NOS	6 (1.0)	3 (3.5)	
Depressive Symptoms			
CDRS-R, mean (*SD*)	35.3 (10.7)	30.8 (10.1)	t=3.70, df=705, p<0.001
Mood Disorder NOS	11 (1.8)	0	

* One participant met criteria for more than one depressive spectrum disorder diagnosis ESM=elevated symptoms of mania; BP=bipolar disorder; PGBI-10M=Parent General Behavior Inventory-10 Item Mania Scale; YMRS=Young Mania Rating Scale; MDD = major depressive disorder; CDRS-R=Children's Depression Rating Scale-Revised.

** Comparisons between ESM groups were only examined in rates of mood disorders, bipolar spectrum disorders, and depressive disorders diagnoses as well as mean total PGBI-10M, YMRS and CDRS-R scores.

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Table 3

Current ADHD and DBD Diagnoses of Participants with ESM and Comparison Participants

Diagnosis, *n* (%)	ESM+ Participants (*n* = 621)	ESM−Participants (*n* = 86)	Statistic, p value*
Current ADHD Diagnosis	**474 (76.3)**	**64 (74.4)**	Fisher's Exact Test p=0.69
Combined Type	278 (44.8)	29 (33.7)	
Inattentive Type	90 (14.5)	18 (20.9)	
Hyperactive/Impulsive Type	45 (7.2)	4 (4.7)	
NOS	61 (9.8)	13 (15.1)	
Past ADHD Diagnosis	11 (2.0)	2 (2.4)	
ADHD Symptoms, CAASI-4R ADHD Subscales, mean (SD)			
Inattentive	18.2 (6.5)	16.1 (7.3)	t=2.81,df=690, p<.01
Hyperactive-Impulsive	16.7 (6.7)	11.8 (6.9)	t=6.24 df=690, p<.001
Combined	34.9 (11.7)	27.9 (12.8)	t=5.11, df=691, p<.001
Disruptive Behavior Disorders	**330 (53.1)**	**31 (36.0)**	Fisher's Exact Test p<0.01
ODD	228 (36.7)	18 (20.9)	
Past ODD	12 (1.9)	1 (1.2)	
CD	52 (8.4)	2 (2.3)	
Disruptive Behavior Disorder NOS	50 (8.1)	11 (12.8)	
ODD Symptoms, CAASI-4R ODD Subscale, *M (SD)*	**16.0 (5.8)**	**11.1 (6.2)**	t=7.28, df=690, p=<.001
CD Symptoms, CAASI-4R CD Subscale, *M (SD)*	**5.8 (5.2)**	**2.8 (3.1)**	t=5.32, df=691, p=<.001

DBD=disruptive behavior disorders; ESM=elevated symptoms of mania; ADHD = attention-deficit/hyperactivity disorder; NOS=not otherwise specified; ODD = oppositional-defiant disorder; CD = conduct disorder; CAASI-4 = Child & Adolescent Symptom Inventory for DSM-IV.

*Comparisons between ESM groups were only examined in rates of an ADHD diagnosis, DBD diagnoses, and mean CAASI-4 scores.

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Table 4

Other Most Commonly Found Current Psychiatric Diagnoses of Participants with ESM and Comparison Participants

Diagnosis, *n* (%)	ESM+ Participants (*n* = 621)	ESM− Participants (*n* = 86)	Statistic, p value*
Psychotic Disorders	**15 (2.4)**	**1 (1.2)**	Fisher's Exact Test *p*=0.071
Schizophrenia	2 (0.3)	1 (1.2)	
Psychotic Disorder NOS	13 (2.1)	0	
Current Anxiety Disorders	**198 (31.9)**	**23 (26.7)**	Fisher's Exact Test *p*=0.39
Past Anxiety Disorders	36 (5.8)	9 (10.5)	Fisher's Exact Test *p*=0.10
Current Post Traumatic Stress Disorder	15 (2.4)	0	
Past Post Traumatic Stress Disorder	9 (1.4)	2 (2.3)	
Acute Stress Disorder	1 (0.2)	0	
Obsessive Compulsive Disorder	11 (1.8)	1 (1.2)	
Current Panic Disorder	6 (1.0)	0	
Past Panic Disorder	3 (0.5)	0	
Current Separation Anxiety Disorder	59 (9.5)	6 (7.0)	
Past Separation Anxiety Disorder	19 (3.1)	4 (4.7)	
Current Specific Phobia	56 (9.0)	10 (11.6)	
Past Specific Phobia	5 (0.8)	4 (4.7)	
Current Social Phobia	15 (2.4)	5 (5.8)	
Past Social Phobia	4 (0.6)	0	
Current Generalized Anxiety Disorder	60 (9.7)	6 (7.0)	
Past Generalized Anxiety Disorder	2 (0.3)	0	
Current Anxiety Disorder NOS	46 (7.4)	1 (1.2)	
Past Anxiety Disorder NOS	10 (1.6)	1 (1.2)	
Anxiety Symptoms, SCARED-P, mean (*SD*)	**18.9 (13.7)**	**12.9 (13.4)**	*t*=3.78, *df*=690, *p*<.001
Current Adjustment Disorders	**11 (1.8)**	**2 (2.3)**	Fisher's Exact Test *p*=0.67
Past Adjustment Disorders	**15 (2.4)**	**1 (1.2)**	
Pervasive Developmental Disorders	**35 (5.6)**	**10 (11.6)**	Fisher's Exact Test *p*=0.05
Pervasive Developmental Disorder NOS	15 (2.4)	6 (7.0)	
Asperger's Disorder	12 (1.9)	2 (2.3)	
Autistic Disorder	8 (1.3)	2 (2.3)	
Elimination Disorders	127 (20.4)	13 (15.2)	
Encopresis	12 (1.9)	1 (1.2)	
Enuresis and Encopresis	11 (1.8)	1 (1.2)	
Past Enuresis	50 (8.1)	8 (9.3)	
Past Encopresis	18 (2.9)	1 (1.2)	
Disorders Due to Medical Conditions	6 (1.0)	0	
Tourette's Disorder	10 (1.6)	1 (1.2)	
Current Chronic Motor or Vocal Tic Disorder	7 (1.1)	0	
Past Chronic Motor or Vocal Tic Disorder	2 (0.3)	0	
Tic Disorder NOS	3 (0.5)	0	

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Diagnosis, *n* (%)	ESM+ Participants (*n* = 621)	ESM− Participants (*n* = 86)	Statistic, p value*
Transient Tic Disorder	3 (0.5)	0	
Past Transient Tic Disorder	11 (1.8)	0	
Eating Disorder NOS	3 (0.5)	0	

ESM=elevated symptoms of mania; SCARED-P= Screen for Child Anxiety Related Emotional Disorders-Parent.

*Comparisons between ESM groups were only examined in rates of psychotic disorders, anxiety disorders, adjustment disorders, and developmental disorders diagnoses and mean SCARED-P total scores.

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Table 5

Psychotropic Medication Exposure in the LAMS participants*

	ESM+ (*n*=621)		ESM− (*n*=86)		
Medication, *n* (%)	**Present**	**Past**	**Present**	**Past**	**Fisher's Exact Test p values Present, Past Comparisons****
Stimulants	**237 (38.2)**	**257 (41.4)**	**39 (45.3)**	**36 (41.9)**	p=0.24, p=1.00
Methylphenidate-based	148 (23.8)	184 (29.6)	24 (27.9)	32 (37.2)	
Methylphenidate	110 (17.7)	171 (27.5)	21 (24.4)	31 (36.0)	
D-Methylphenidate	40 (6.4)	35 (5.6)	3 (3.5)	11 (12.8)	
Amphetamine-based	91 (14.7)	169 (27.2)	16 (18.6)	21 (24.4)	
D-Amphetamine	2 (0.3)	6 (1.0)	0	1 (1.2)	
Mixed Amphetamine Salts	82 (13.2)	167 (26.9)	13 (15.1)	20 (23.3)	
lisdexamfetamine dimesylate	7 (1.1)	2 (0.3)	3 (3.5)	0	
Atomoxetine	**45 (7.2)**	**102 (16.4)**	**6 (7.0)**	**14 (16.3)**	
Pemoline	**0**	**0**	**0**	**1 (1.2)**	
Alpha-2 Agonists	**62 (10.0)**	**37 (6.0)**	**9 (10.5)**	**6 (7.0)**	p=0.85, p=0.64
Guanfacine	16 (2.6)	6 (1.0)	4 (4.7)	1 (1.2)	
Clonidine	48 (7.7)	32 (5.2)	5 (5.8)	5 (5.8)	
Antidepressants	**75 (12.1)**	**62 (10.0)**	**10 (11.6)**	**10 (11.6)**	p=1.00, p=0.57
SSRIs	55 (8.9)	52 (8.4)	8 (9.3)	9 (10.5)	
Tricyclics	2 (0.3)	3 (0.5)	1 (1.2)	0	
Other antidepressants***	20 (3.2)	13 (2.1)	1 (1.2)	4 (4.7)	
Antipsychotics	**143 (23.0)**	**80 (12.9)**	**14 (16.3)**	**10 (11.6)**	p=0.17, p=0.86
Typical	0	3 (0.5)	0	0	
Aripiprazole	31 (5.0)	29 (4.7)	3 (3.5)	3 (3.5)	
Clozapine	1 (0.2)	0	0	0	
Ziprasidone	11 (1.8)	6 (1.0)	0	0	
Risperidone	69 (11.1)	48 (7.7)	5 (5.8)	7 (8.1)	
Quetiapine	35 (5.6)	31 (5.0)	6 (7.0)	3 (3.5)	

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Medication, *n* (%)	ESM+ (*n*=621) Present	ESM+ (*n*=621) Past	ESM− (*n*=86) Present	ESM− (*n*=86) Past	Fisher's Exact Test p values Present, Past Comparisons**
Olanzapine	3 (0.5)	11 (1.8)	0	1 (1.2)	
Paliperidone	1 (0.2)	0	0	0	
Mood Stabilizers	**45 (7.2)**	**53 (8.5)**	**6 (7.0)**	**4 (4.7)**	
Lithium	10 (1.6)	13 (2.1)	1 (1.2)	1 (1.2)	p=1.00, p=1.00
Anticonvulsants	38 (6.1)	50 (8.1)	5 (5.8)	4 (4.7)	p=1.00, p=0.39
Benzodiazapines	**1 (0.2)**	**7 (1.1)**	**0**	**1 (1.2)**	
Non-Benzodiazapines**	**9 (1.4)**	**2 (0.3)**	**0**	**0**	

* Participants may have been receiving multiple medications within the same group.

** Comparisons between ESM groups were only examined in rates of prescribed stimulants, alpha-2 agonists, antidepressants, antipsychotics, lithium and anticonvulsants.

*** mirtazapine, bupropion, trazodone, venlafaxine.

**** buspirone, diphenhydramine, hydroxyzine

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Table 6

Demographic and Current Clinical Characteristics of ESM+ Participants with a Current BPSD compared to ESM+ Participants without BPSD

Characteristics	ESM+ Participants with a bipolar disorder (n=155)	ESM+ Participants without a bipolar disorder (n=466)	Statistic, p value
Age, mean ± *SD*	9.7 (2.1)	9.2 (1.9)	t=2.70, df=619, p=.007
Male *n*, (%)	89 (57.4)	324 (69.5)	Fisher's Exact Test, p=.008
White *n*, (%)	110 (71.0)	285 (61.2)	Fisher's Exact Test, p=.034
Hispanic *n*, (%)	5 (3.2)	21 (4.5)	Fisher's Exact Test, p=.645
Health Insurance Coverage *n* (%)			Fisher's Exact Test, p=.138
Medicaid	75 (48.4)	258 (55.4)	
Private Insurance	65 (41.9)	177 (38.0)	
Private Insurance & Medicaid	11 (7.1)	28 (6.0)	
Self Pay	4 (2.6)	3 (0.6)	
Living with both biological parents, % yes	53 (34.2)	134 (28.8)	Fisher's Exact Test, p=.266
Ever in special education, % yes	53 (34.2)	130 (27.9)	Fisher's Exact Test, p=.154
Psychiatric hospitalizations, mean ± *SD*	0.6 (1.8)	0.1 (1.0)	t=3.95, df=619, p<.001
Overall functioning, CGAS mean ± *SD*	50.8 (9.3)	55.0 (10.1)	t=4.48, df=615, p<.001
Family History of Elevated Mood			
Biological Mother *n*, (%)	39 (25.2)	60 (12.9)	Fisher's Exact Test, p=.001
Biological Father *n*, (%)	22 (14.2)	33 (7.1)	Fisher's Exact Test, p=.013
Diagnoses			
Any Attention Deficit Hyperactivity			
Disorder	114 (73.5)	360 (77.3)	Fisher's Exact Test, p=.383
Any Disruptive Behavior Disorder	68 (43.9)	262 (56.2)	Fisher's Exact Test, p=.009
Any Anxiety Disorder	48 (31.0)	150 (32.2)	Fisher's Exact Test, p=.842
Any Elimination Disorder	39 (25.2)	88 (18.9)	Fisher's Exact Test, p=.107
Any Pervasive Developmental Disorder	5 (3.2)	30 (6.4)	Fisher's Exact Test, p=.161
Currently Prescribed Medications			
Antipsychotics	64 (41.3)	79 (17.0)	Fisher's Exact Test, p<.001
Stimulants	58 (37.4)	179 (38.4)	Fisher's Exact Test, p=.849
Mood Stabilizers	26 (16.8)	19 (4.1)	Fisher's Exact Test, p<.001
Antidepressants	24 (15.5)	51 (10.9)	Fisher's Exact Test, p=.154
Anticonvulsant	21 (13.5)	17 (3.6)	Fisher's Exact Test, p<.001
Mood Symptoms			
Baseline PGBI-10M total score	17.0 (5.9)	12.9 (6.7)	t=6.74, df=606, p<.001
Baseline YMRS total score	26.0 (8.8)	14.9 (7.4)	t=15.29, df=619, p<.001
Baseline CDRS-R total score	39.0 (11.1)	34.1 (10.3)	t=4.98, df=619, p<.001

ESM=elevated symptoms of mania; BPSD=bipolar spectrum disorders; PGBI-10M=Parent General Behavior Inventory-10 Item Mania Scale; YMRS=Young Mania Rating Scale; CDRS-R=Children's Depression Rating Scale-Revised