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Original Article

Pediatric bipolar spectrum disorder and ADHD: comparison and comorbidity in the LAMS clinical sample

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Objective: To compare attention-deficit hyperactivity disorder (ADHD), bipolar spectrum disorders (BPSDs), and comorbidity in the Longitudinal Assessment of Manic Symptoms (LAMS) study.

Methods: Children ages 6–12 were recruited at first visit to clinics associated with four universities. A BPSD diagnosis required that the patient exhibit episodes. Four hypotheses were tested: (i) children with BPSD + ADHD would have a younger age of mood symptom onset than those with BPSD but no ADHD; (ii) children with BPSD + ADHD would have more severe ADHD and BPSD symptoms than those with only one disorder; (iii) global functioning would be more impaired in children with ADHD + BPSD than in children with either diagnosis alone; and (iv) the ADHD + BPSD group would have more additional diagnoses.

Results: Of 707 children, 421 had ADHD alone, 45 had BPSD alone, 117 had both ADHD and BPSD, and 124 had neither. Comorbidity (16.5%) was slightly less than expected by chance (17.5%). Age of mood symptom onset was not different between the BPSD + ADHD group and the BPSD-alone group. Symptom severity increased and global functioning decreased with comorbidity. Comorbidity with other disorders was highest for the ADHD + BPSD group, but higher for the ADHD-alone than the BPSD-alone group. Children with BPSD were four times as likely to be hospitalized (22%) as children with ADHD alone.

Conclusions: The high rate of BPSD in ADHD reported by some authors may be better explained as a high rate of both disorders in child outpatient settings rather than ADHD being a risk factor for BPSD. Co-occurrence of the two disorders is associated with poorer global functioning, greater symptom severity, and more additional comorbidity than for either single disorder.

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Both bipolar spectrum disorders (BPSDs) and attention-deficit hyperactivity disorder (ADHD) manifest symptoms of impulsivity, hyperactivity, and irritability, with impairments in social relations, increased substance use, and underachievement. The relationship between the two disorders has been widely studied and discussed in recent

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years, with some disagreements. Several (1, 2) but not all (3) research groups report that having an ADHD diagnosis is associated with earlier onset of BPSD. Similarly, some report chronic (2), while others report an episodic course (4) in children and adolescents with comorbid BPSD and ADHD. Various clinical studies have reported a range from 11% to 98% of ADHD in children and adolescents with BPSD (5–9). These discrepant findings likely result from differing definitions of BPSD and the methods used to assess study participants, with varying strategies used to 'count' overlapping symptoms, as well as actual differences between samples. Although recommendations have been made that ADHD diagnoses not be made when symptoms occur exclusively in mood episodes (10, 11), not all studies follow this guideline.

Because ADHD is more common than BPSD, a lower percentage of children and adolescents with ADHD also have or develop BPSD than the converse. Biederman et al. (5), allowing overlap among symptoms and not requiring episodicity, reported that 11% of children with ADHD also satisfied criteria for BPSD diagnosis, and at a four-year follow-up, 21% had a lifetime history of BPSD. However, the Multimodal Treatment Study of children with ADHD (MTA) in its eight-year follow-up reported that mania rates were low and had not changed significantly over time. At baseline (ages 7–9), 14 participants (2.4%) had mania or hypomania as for determined by the Diagnostic Interview Schedule for Children (DISC) and licensed-clinician interview, and 25 (4.3%) had depression (personal communication, C. Galanter, Columbia University). At eight-year follow-up, eight (1.8%) met criteria for mania, hypomania, or psychosis (12) and 5.8% met criteria for depression (personal communication, B.S.G. Molina, University of Pittsburgh). Two other studies also reported minimal overlap of mania with ADHD. Hazell and colleagues (13) reported that in a cohort of 9–12-year-olds followed to age 15–21, only one participant with ADHD + mania at baseline still met criteria for mania at follow-up. Bagwell et al. (14) found no difference in rates of anxiety and mood disorders between adolescents with a history of ADHD and those without.

Greater functional impairment and younger age of onset appear related to comorbid ADHD + mania. Two studies have reported lower global assessment scores: one in a group of youth with ADHD + mania compared to those with ADHD alone or a control comparison group (13), and one in youth with ADHD who went on to develop bipolar I disorder (BD-I) compared to youth with ADHD who did not develop BD-I (15).

Two studies reported younger age of onset with comorbidity: one in children with BPSD with comorbid ADHD compared to children with BPSD but no ADHD (2, 16), and one in children with baseline BD-I + ADHD compared to children with BD-I without ADHD (15). It has even been suggested that age of onset may identify a subtype of BPSD highly comorbid with ADHD (5), with poorer treatment response. In a further examination of the Geller sample, Tillman et al. (17) found that ADHD often preceded mania onset in youth with prepubertal and early adolescent BD-I.

Although many researchers assume that ADHD and BPSD are separate disorders even when comorbid, others argue that behavior disorders such as ADHD and oppositional defiant disorder (ODD) may actually represent early manifestations of BPSD rather than independent disorders (18). In a meta-analysis, Kowatch et al. (9) reported that ADHD is the most common comorbidity with BPSD (62%), but ODD is a close second (53%). However, many children with disruptive disorders do not go on to develop BPSD (5), which suggests that children with ADHD or ODD who later develop BPSD may have either unique forms of ADHD or ODD or other characteristics that lead them to later develop BPSD.

Some of the association between ADHD and BPSD reported above may be artifacts of differing BPSD definitions. For example, Geller's group (19) and Biederman's group (5) allowed overlap in symptoms, counting symptoms such as hyperactivity for both disorders. Biederman's group (5) does not require episodes for BPSD diagnosis, thus allowing a youngster with severe tantrums, ADHD, and some mood symptoms to be diagnosed as BPSD.

In sum, these conflicting reports suggested that the following hypotheses needed to be tested in a new sample, the 707 children in the Longitudinal Assessment of Manic Symptoms (LAMS) study.

1. Children with comorbid BPSD + ADHD will have younger age of onset of mood symptoms than children with BPSD but no ADHD.
2. Children with comorbid BPSD + ADHD will have more severe ADHD symptoms than those with only ADHD and more severe BPSD symptoms than those with only BPSD.
3. Global functioning will be more impaired in children with comorbid ADHD + BPSD than in those with either diagnosis alone.
4. Children with comorbid ADHD + BPSD will have greater rates of other comorbidities than children with ADHD alone or BPSD alone.

Materials and methods

Study sites and participants

The data analyzed here are from the initial assessments of the National Institute of Mental Health (NIMH)-supported LAMS study. All procedures were approved by the local university Institutional Review Boards. Written informed consent from the parents/guardians and assent from the children were obtained.

Participants were recruited from 9 child outpatient mental health clinics (2 in Cleveland, 1 in Pittsburgh, 5 in Columbus, and 1 in Cincinnati) associated with Case Western Reserve University, University of Pittsburgh, Ohio State University, and University of Cincinnati. Eligible children were new evaluations aged 6–12 at the respective clinics. Parents/guardians accompanying eligible children were asked to complete the Parent General Behavior Inventory–10 Item Mania Scale (PGBI-10M) (20, 21) to screen for elevated symptoms of mania (ESM). The PGBI-10M items, scored 0–3, describe hypomanic, manic, and biphasic symptoms and best discriminate bipolar disorder from other diagnoses (20). Total scores range from 0 to 30. All patients whose parent/guardian rated them at or above 12 (ESM+) were invited to participate. In addition, some patients with scores 11 or lower (ESM−) were selected by a matching procedure. Details of subject ascertainment and the rationale for the cut score of 12 on the PGBI-10M are described separately (22).

Baseline assessment

Diagnostic procedures. Patients selected as above were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (23) with additional mood onset and offset items derived from the Washington University St. Louis Kiddie Schedule for Affective Disorders (K-SADS-PL-W) (24, 25). For a diagnosis of BPSD, we required episodes and did not count symptoms for ADHD that occurred only during episodes nor did we count symptoms for BPSD that were chronic ADHD symptoms; we attempted differential diagnoses.

The LAMS study used the following criteria for BPSD not otherwise specified [which were the same as used in the Course and Outcome of Bipolar Youth study (COBY) (10, 26)]: (i) elated mood plus at least two associated symptoms of mania (e.g., grandiosity, decreased need for sleep, pressured speech, racing thoughts, and increased goal-directed activity), or irritable mood plus at least three associated symptoms of mania; (ii) change in the participant's level of functioning (increase or decrease); and (iii) symptoms present for a total of at least four hours within a 24-hour period on at least four days in his/her lifetime. A licensed child psychiatrist or psychologist reviewed and confirmed all diagnoses. Inter-rater reliability was assured by the interviewers rating taped administrations of the K-SADS-PL-W, Children's Depression Rating Scale-Revised (CDRS-R) (27, 28), and the Young Mania Rating Scale (YMRS) (29). The kappa for K-SADS-PL-W psychiatric diagnoses was 0.82 and more specifically, the kappa for bipolar diagnoses was 0.93. For age of onset of BPSD symptoms, the earliest of the following was used: BPSD diagnosis, any manic symptoms, or any depressive symptoms.

We followed DSM-IV criteria for which symptoms counted towards diagnoses of ADHD, mania, depression, and other diagnoses. When the same symptom could be potentially counted towards multiple disorders, raters found the best match based on clinical context, using the presence or absence of episode and/or the associated symptoms to decide between mood and other candidate diagnoses. For example, *difficulty concentrating* could be a symptom of ADHD, or of a depressed or manic episode. It also is a diagnostic feature of post traumatic stress disorder and generalized anxiety disorder. At the outset of the K-SADS interview, raters gathered a developmental history and began to establish whether there was a history of mood episodes versus a more chronic history of problems (or both superimposed). When faced with a report of *difficulty concentrating*, interviewers asked whether this was a chronic issue, or something that was present only sometimes (a more episodic presentation). If mood episodes emerged during the developmental history or via the probing around the symptoms in the mood modules (which come first in the K-SADS), then the interviewer would specifically ask if the poor concentration occurred only in the mood episode, or if it intensified during the mood episode. Symptoms occurring only episodically, in the company of other mood symptoms, were scored in the mood module (mania or depression). Symptoms with a more chronic presentation that clearly extended beyond the limits of a mood episode were coded towards other disorders. If the symptoms predated a mood episode but clearly worsened during the mood episode, then they could be counted towards both diagnoses, a *comorbid* presentation. The interpretive guides of *episodicity* and associated features made it possible to assign symptoms, including irritability, that

might otherwise be ambiguous to either mood or non-mood diagnoses or to both. A detailed description is provided in Findling et al. (30).

Additional measures. Global functioning was measured by the Children's Global Assessment Scale (CGAS) (31). *Unfiltered* manic symptoms (i.e., directly from informant with no attempt to classify symptoms into particular categories, in contrast to the *clinician-filtered* ratings used on the K-SADS described above) were assessed by parent report on the PGBI-10M and by interview of child and parent with the YMRS. Similarly, unfiltered depressive symptoms were assessed using the CDRS-R. Parent-reported symptoms of ADHD, ODD, and conduct disorder (CD) subscales were examined by the Child and Adolescent Symptom Inventory-4-Parent Version (CASI-4R), on which items are rated on a 0–3 scale (32). The Services Assessment of Children and Adolescents (SACA), parent report version, was used to gather information about hospitalization and other treatments (33).

Current and past global social adjustment and overall interpersonal function were assessed by Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE) interview (34). Lower scores on these domains are indicative of higher functioning, with a score of '1' being very good and a score of '5' being very poor. The Clinical Global Impressions Scale-Severity (CGI-S) (35) assessed general psychiatric symptom severity with ratings ranging from 1 (normal, not ill) to 7 (very severely ill).

Statistical analysis

Descriptive statistics, including means and percentages, were computed for the demographic, functional, and diagnostic variables. Participants were divided into four diagnostic groups to be compared: ADHD without BPSD (ADHD alone), BPSD without ADHD (BPSD alone), comorbid ADHD + BPSD, and other or no diagnosis. Note that the word *alone* after ADHD or BPSD merely means without the other diagnosis, not necessarily without all comorbidity (e.g., there could be comorbid anxiety or conduct disorder). Fisher's exact test evaluated associations among categorical variables and diagnostic groups. Independent *t*-tests examined differences between diagnostic groups on continuous variables.

To evaluate Hypothesis 1, a Cox regression analysis was computed with age of onset of BPSD symptoms as the endpoint and presence of comorbid ADHD as the covariate. A second Cox regression analysis was computed in which age at first visit was the endpoint; this was done to determine whether the time of presentation to a mental health provider differed between groups.

Hypotheses 2–4 were evaluated using separate analyses of variance (ANOVAs) with the four diagnostic groups as the independent variable and the outcome of interest as the dependent variable (Hypothesis 2: parent and teacher CASI-R ADHD and mania symptom scales, PGBI, and YMRS; Hypothesis 3: CGAS ratings; Hypothesis 4: number of comorbid diagnoses). Secondary outcome measures were examined in a similar fashion and results are presented in the text and tables. Subsequently, sex, insurance status (Medicaid versus not Medicaid) and age at baseline assessment, which differed significantly among the diagnostic groupings, were added as covariates to each ANOVA to adjust for possible confounding variables. The presence/absence of comorbid disruptive behavior disorders [ODD, CD, or disruptive behavior disorder (DBD) not otherwise specified], reported by some authors to have predictive value, also served as covariates.

For the specific hypotheses we used an alpha of 0.05, but to protect against type I error from multiple tests, we corrected the exploratory comparisons by Holm's stepdown Bonferroni correction (36, 37), which provides a good balance between the risk of false negatives and the risk of false positives. This procedure tests the most significant result by full Bonferroni, and if it passes, then only the remaining results are considered for correction of the next most significant, and the process is repeated sequentially until a p-value that is not significant after correction is encountered; all p-values below that are considered as nonsignificant. This process is first applied to the omnibus tests within each table, then to each column of paired comparisons following the significant omnibus tests. (Paired comparisons for nonsignificant omnibus tests are automatically nonsignificant.) Those not significant after correction are indicated by pound signs in the tables.

Results

Of the 2,622 consecutive first clinic visits available, 707 children met criteria and consented for baseline evaluation (CONSORT chart; Fig. 1). Of the 707 children at initial evaluation, 421 had ADHD without BPSD (ADHD alone), 45 had BPSD without ADHD (BPSD alone), 117 had comorbid ADHD and BPSD, and 124 had neither ADHD nor BPSD. Of the 162 with BPSD, 71 had BD-I (22 in BPSD alone), 3 had bipolar II disorder (all in BPSD alone), 11 had cyclothymic disorder (2 in BPSD alone), and 77 had bipolar disorder not

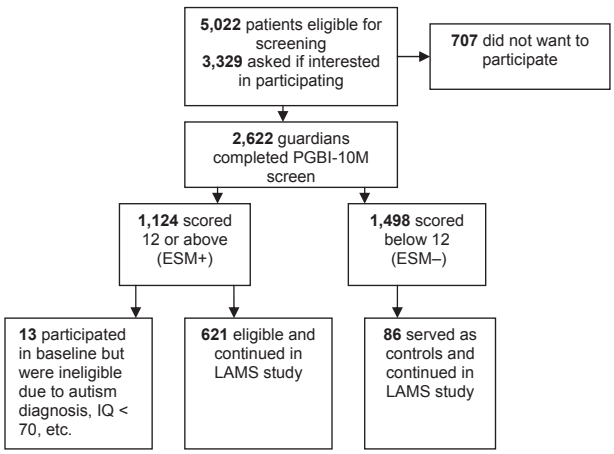

Fig. 1. Breakdown of patients eligible for screening and the resulting patients who participated in the Longitudinal Assessment of Manic Symptoms (LAMS) study. PGBI-10M = Parent General Behavior Inventory–10 Item Mania Scale; ESM = elevated symptoms of mania.

otherwise specified (18 in BPSD alone). With 76.2% of the sample having ADHD and 22.9% having BPSD, the expected comorbidity by chance would be 17.5%; actual comorbidity was 16.5%. Table 1 shows the descriptive comparisons of those diagnostic groupings, with statistical tests of the differences.

Hypothesis 1: Children with BPSD + ADHD show younger age of onset of BPSD symptoms than those with BPSD alone

The tendency in the predicted direction did not reach significance, either clinically or statistically (Table 1). Children with BPSD + ADHD had onset of mood symptoms at 6.7 years and those with BPSD alone had onset at 6.9 years ($p = 0.8$). However, the age of first visit to the LAMS-site clinic was almost one year younger for the comorbid group than for the group with BPSD alone [9.6 versus 10.5 years ($p < 0.01$)]. Similar, but not statistically significant, results were noted for the age of first coming to clinical evaluation anywhere: 5.5 years versus 6.8 years ($p = 0.10$).

Hypothesis 2: Children with BPSD + ADHD have more severe ADHD symptoms than those with ADHD alone and more severe bipolar symptoms than those with BPSD alone

As shown in Table 1, parent CASI ratings of inattentive and hyperactive-impulsive symptoms were higher for comorbid ADHD + BPSD than for ADHD alone (2.39 versus 2.08, $p = 0.001$; 2.17 versus 1.92, $p = 0.001$, respectively) or BPSD alone. The same does not hold true for bipolar symptoms, however. On both the YMRS and PGBI-10M, parents of children with BPSD + ADHD reported greater severity of manic symptoms than parents of children with ADHD alone but not parents of children with BPSD alone. Thus, parent ratings showed the expected greater severity of ADHD symptoms in the comorbid group but greater severity of mood symptoms only over ADHD alone, not over BPSD alone.

Teachers provided a different perspective. For both ADHD and BPSD symptoms, they rated children with BPSD + ADHD as more severe than children with BPSD alone, but not more severe than children with ADHD alone. On the CASI-R mania subscale teachers scored comorbid children higher than those with BPSD alone but not significantly different from those with ADHD alone, whereas parents scored comorbid children higher than those with ADHD alone but not significantly different from those with BPSD alone. Thus this hypothesis was partially upheld: by parent ratings for ADHD symptoms, and by teacher ratings for BPSD symptoms. It should be noted that children with complete teacher data ($n = 466$) did not differ significantly from children without teacher CASIs ($n = 241$) in sex distribution ($p = 0.55$), medical coverage by Medicaid ($p = 0.47$), the presence of a comorbid diagnosis ($p = 0.30$), the number of diagnoses ($t = 1.31$, df $= 705$, $p = 0.19$), age of onset of manic or depressive symptoms ($t = 0.22$, df $= 157$, $p = 0.83$), age of onset of ADHD symptoms ($t = 1.20$, df $= 460$, $p = 0.23$), or YMRS scores ($t = 0.82$, df $= 705$, $p = 0.41$).

Individual symptom comparison

Table 2 illustrates differential rates of individual ADHD and manic symptom endorsement on the

Table 1. Characterization of children with attention-deficit hyperactivity disorder (ADHD) alone, bipolar spectrum disorder (BPSD) alone, the combination of both disorders, and neither

Demographic and clinical characteristics	ADHD alone[a]	BPSD alone[a]	BPSD + ADHD	Other diagnoses or no current diagnosis	Statistic, p-value	ADHD alone[a] versus BPSD + ADHD p-value	BPSD alone[a] versus BPSD + ADHD p-value
	(n = 421)	**(n = 45)**	**(n = 117)**	**(n = 124)**			
Age at study entry, years, mean (SD)	9.21 (1.89)	10.48 (2.12)	9.56 (2.00)	9.51 (1.80)	$F = 6.53$, df = 3, $p < 0.001$	0.08	0.01
Age of first clinical treatment, years, mean (SD)	6.26 (2.49)	6.80 (3.28)	5.54 (2.37)	6.81 (2.64)	$F = 5.57$, df = 3, $p < 0.001$	0.03[b]	0.10
Age of onset of ADHD, years, mean (SD)	4.77 (1.73)		4.22 (1.61)		$t = 2.92$, df = 460, $p = 0.004$[b]	0.004[b]	–
Age of onset of manic or depressive symptoms, years, mean (SD)		6.88 (2.67)	6.68 (2.57)		$t = 0.25$, df = 44, $p = 0.806$	–	0.81
Male, n (%)	318 (75.5)	24 (53.3)	68 (58.1)	68 (54.8)	$\chi^2 = 30.31$, df = 3, $p < 0.001$	< 0.001	0.60
White, n (%)	257 (61.0)	35 (77.8)	78 (66.7)	85 (68.5)	$\chi^2 = 6.77$, df = 3, $p = 0.08$	0.28	0.19
Latino, n (%)	20 (4.8)	2 (4.4)	6 (5.1)	3 (2.4)	$\chi^2 = 1.43$, df = 3, $p = 0.70$	0.81	1.00
Medicaid only, n (%)	242 (57.5)	16 (35.6)	61 (52.1)	51 (41.1)	$\chi^2 = 15.79$, df = 3, $p < 0.001$	0.34	0.08
Diagnostic groups, n (%)							
Psychosis	7 (1.7)	0	3 (2.6)	6 (4.8)	$\chi^2 = 5.50$, df = 3, $p = 0.14$	0.46	0.56
Disruptive behavior disorders	247 (58.7)	7 (15.6)	61 (52.1)	46 (37.1)	$\chi^2 = 42.19$, df = 3, $p < 0.001$	0.21	< 0.001
Pervasive developmental disorders	22 (5.2)	3 (6.7)	2 (1.7)	18 (14.5)	$\chi^2 = 19.00$, df = 3, $p < 0.001$	0.13	0.13
Anxiety disorders	126 (29.9)	16 (35.6)	33 (28.2)	46 (37.1)	$\chi^2 = 3.21$, df = 3, $p = 0.36$	0.82	0.45
More than two current other diagnoses at baseline?	194 (46.1)	10 (22.2)	84 (71.8)	26 (21.0)	$\chi^2 = 75.59$, df = 3, $p < 0.001$	< 0.001	< 0.001
Number of current other diagnoses at baseline	2.57 (1.19)	1.87 (0.97)	3.27 (1.16)	1.72 (1.26)	$F = 39.57$, df = 3, $p < 0.001$	< 0.001	< 0.001
Ever hospitalized	22 (5.2)	10 (22.2)	26 (22.2)	7 (5.6)	$\chi^2 = 42.75$, df = 3, $p < 0.001$	< 0.001	1.00
Scales, mean (SD)							
CDRS-R	33.29 (10.13)	37.43 (11.21)	39.21 (11.09)	34.69 (11.12)	$F = 10.65$, df = 3, $p < 0.001$	< 0.001	0.34
Baseline PGBI-10M total score	12.14 (6.99)	15.96 (5.90)	17.09 (6.08)	10.13 (7.17)	$F = 26.05$, df = 3, $p < 0.001$	< 0.001	0.34
Young Mania Rating Scale	14.71 (7.44)	25.96 (10.17)	25.51 (8.43)	12.38 (7.45)	$F = 92.52$, df = 3, $p < 0.001$	< 0.001	0.75
CGI-S current score	3.31 (1.12)	3.69 (1.00)	4.03 (1.09)	3.18 (1.36)	$F = 14.57$, df = 3, $p < 0.001$	< 0.001	0.10
CGI-S past 6 months	3.45 (1.11)	4.20 (0.89)	4.28 (0.94)	3.36 (1.31)	$F = 23.53$, df = 3, $p < 0.001$	< 0.001	0.67
CGI-S worst lifetime	3.64 (1.17)	4.44 (1.04)	4.51 (0.94)	3.60 (1.33)	$F = 23.14$, df = 3, $p < 0.001$	< 0.001	0.74
Child's Global Social Adjustment–past	3.05 (0.68)	3.18 (0.89)	3.24 (0.72)	2.94 (0.84)	$F = 3.83$, df = 3, $p = 0.01$[b]	0.02[b]	0.62
Child's Global Social Adjustment–current	2.94 (0.68)	2.98 (0.92)	3.15 (0.70)	2.86 (0.82)	$F = 3.42$, df = 3, $p = 0.02$[b]	0.01[b]	0.18
Child's Overall Interpersonal Functioning–past	2.77 (0.74)	2.96 (0.93)	2.93 (0.81)	2.65 (0.88)	$F = 3.29$, df = 3, $p = 0.02$[b]	0.06	0.86
Child's Overall Interpersonal Functioning–current	2.68 (0.73)	2.78 (0.97)	2.88 (0.81)	2.55 (0.85)	$F = 3.73$, df = 3, $p = 0.01$[b]	0.02[b]	0.46
Current CGAS	55.15 (9.51)	54.45 (9.55)	50.03 (9.13)	56.87 (12.80)	$F = 10.41$, df = 3, $p < 0.001$	< 0.001	0.01

Table 1. (Continued)

Demographic and clinical characteristics	ADHD alone[a]	BPSD alone[a]	BPSD + ADHD	Other diagnoses or no current diagnosis	Statistic, p-value	ADHD alone[a] versus BPSD + ADHD p-value	BPSD alone[a] versus BPSD + ADHD p-value
CASI-4R ratings by parent, mean (SD)	**(n = 412)**	**(n = 45)**	**(n = 117)**	**(n = 119)**			
ADHD Inattentive subscale	2.08 (0.63)	1.59 (0.80)	2.39 (0.53)	1.46 (0.85)	$F = 45.56$, df = 3, $p < 0.001$	< 0.001	< 0.001
ADHD Hyperactive subscale	1.92 (0.68)	1.40 (0.71)	2.17 (0.67)	1.13 (0.73)	$F = 57.55$, df = 3, $p < 0.001$	0.001	< 0.001
ADHD Combined 18-item subscale	2.00 (0.56)	1.49 (0.68)	2.28 (0.51)	1.30 (0.72)	$F = 68.23$, df = 3, $p < 0.001$	< 0.001	< 0.001
ODD subscale	1.83 (0.76)	1.98 (0.71)	2.23 (0.63)	1.91 (0.82)	$F = 8.70$, df = 3, $p < 0.001$	< 0.001	0.06
Conduct disorder subscale	0.33 (0.30)	0.38 (0.32)	0.56 (0.41)	0.28 (0.33)	$F = 17.77$, df = 3, $p < 0.001$	< 0.001	0.002
Mania subscale	0.91 (0.64)	1.27 (0.61)	1.41 (0.64)	0.66 (0.53)	$F = 34.01$, df = 3, $p < 0.001$	< 0.001	0.20
CASI-R by teacher, mean (SD)	**(n = 291)**	**(n = 27)**	**(n = 73)**	**(n = 75)**			
ADHD Inattentive subscale	1.68 (0.80)	0.92 (0.64)	1.71 (0.88)	1.13 (0.81)	$F = 15.51$, df = 3, $p < 0.001$	0.78	< 0.001
ADHD Hyperactive-impulsive subscale	1.23 (0.89)	0.54 (0.66)	1.15 (0.88)	0.57 (0.64)	$F = 15.94$, df = 3, $p < 0.001$	0.44	0.002
ADHD Combined 18-item subscale	1.46 (0.74)	0.73 (0.57)	1.43 (0.80)	0.85 (0.64)	$F = 20.15$, df = 3, $p < 0.001$	0.77	< 0.001
ODD subscale	1.03 (0.88)	0.77 (0.70)	1.07 (0.97)	0.65 (0.73)	$F = 4.73$, df = 3, $p = 0.003$	0.71	0.13
Conduct disorder subscale	0.31 (0.43)	0.21 (0.37)	0.39 (0.50)	0.17 (0.25)	$F = 4.09$, df = 3, $p = 0.007$[b]	0.16	0.06
Mania subscale	0.95 (0.68)	0.60 (0.60)	0.99 (0.72)	0.56 (0.58)	$F = 8.92$, df = 3, $p < 0.001$	0.63	0.01

ADHD = attention-deficit hyperactivity disorder; BPSD = bipolar spectrum disorder; PGBI-10M = Parent General Behavior Inventory-10 Item Mania Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGI-S = Clinical Global Impression Scale of Severity; CGAS = Children's Global Assessment Scale; CASI-4R = Child and Adolescent Symptom Inventory-4-Parent Version; ODD = oppositional defiant disorder; SD = standard deviation.

[a]ADHD alone means without BPSD, not necessarily with no other comorbidity (e.g., anxiety or ODD); BPSD alone means without ADHD, not necessarily with no other comorbidity.

[b]Indicates not significant after Holm's stepdown Bonferroni correction for multiple exploratory tests.

Table 2. Frequency of parent-endorsed Child and Adolescent Symptom Inventory-4-Parent Version (CASI-4R) child individual attention-deficit hyperactivity disorder (ADHD) and manic symptoms in the four diagnostic groupings

	ADHD alone[a] (%)	BPSD alone[a] (%)	BPSD + ADHD (%)	Other diagnoses or no current diagnosis (%)	Omnibus statistic, p-value	ADHD alone[a] versus BPSD + ADHD p-value[b]	BPSD alone[a] versus BPSD + ADHD p-value[b]
ADHD items							
Does not pay attention to details	73	49	88	39	$\chi^2 = 79.55$, df = 3, $p < 0.001$	0.002	< 0.001
Difficulty paying attention to tasks	82	47	92	40	$\chi^2 = 125.72$, df = 3, $p < 0.001$	0.02[c]	< 0.001
Does not listen when spoken to directly	70	49	87	44	$\chi^2 = 55.63$, df = 3, $p < 0.001$	< 0.001	< 0.001
Difficulty following through on instructions	71	56	88	48	$\chi^2 = 47.42$, df = 3, $p < 0.001$	< 0.001	< 0.001
Difficulty organizing work and activities	70	53	88	40	$\chi^2 = 64.23$, df = 3, $p < 0.001$	< 0.001	< 0.001
Avoids doing tasks that require a lot of meant effort	72	49	84	49	$\chi^2 = 41.87$, df = 3, $p < 0.001$	0.02[c]	< 0.001
Loses things necessary for activities	55	40	76	41	$\chi^2 = 32.16$, df = 3, $p < 0.001$	0.001	< 0.001
Is easily distracted by other things	86	51	94	57	$\chi^2 = 91.49$, df = 3, $p < 0.001$	0.06	< 0.001
Is forgetful in daily activities	63	47	79	38	$\chi^2 = 42.57$, df = 3, $p < 0.001$	0.004[c]	< 0.001
Fidgets with hands, squirms in seat	76	51	85	38	$\chi^2 = 85.57$, df = 3, $p < 0.001$	0.12	< 0.001
Has difficulty remaining seated	70	44	77	22	$\chi^2 = 110.21$, df = 3, $p < 0.001$	0.24	< 0.001
Runs about and climbs on things	54	40	64	26	$\chi^2 = 41.75$, df = 3, $p < 0.001$	0.11	0.01
Seems restless or jittery	65	36	80	32	$\chi^2 = 72.45$, df = 3, $p < 0.001$	0.003	< 0.001
Has difficulty playing or doing things quietly	55	27	64	27	$\chi^2 = 46.67$, df = 3, $p < 0.001$	0.14	< 0.001
Is on the go or acts as if driven by a motor	67	44	80	26	$\chi^2 = 89.26$, df = 3, $p < 0.001$	0.02[c]	< 0.001
Talks excessively	66	56	77	36	$\chi^2 = 46.35$, df = 3, $p < 0.001$	0.05[c]	0.01
Blurts out answers before question completed	56	38	68	23	$\chi^2 = 57.87$, df = 3, $p < 0.001$	0.05[c]	0.001
Has difficulty waiting turn in group activities	59	38	72	24	$\chi^2 = 65.68$, df = 3, $p < 0.001$	0.03[c]	< 0.001
Interrupts or butts in to other peoples' activities	71	53	81	44	$\chi^2 = 42.90$, df = 3, $p < 0.001$	0.06	0.001
Mania items							
More cheerful than usual	12	24	21	5	$\chi^2 = 19.23$, df = 3, $p < 0.001$	0.02	0.68
More irritable or explosive than usual	31	62	57	32	$\chi^2 = 38.47$, df = 3, $p < 0.001$	< 0.001	0.60
Becomes more active or busy than usual	22	42	42	14	$\chi^2 = 32.34$, df = 3, $p < 0.001$	< 0.001	1.00
Needs far less sleep than usual	11	24	33	5	$\chi^2 = 49.16$, df = 3, $p < 0.001$	< 0.001	0.34
Is much more talkative than usual	31	49	54	17	$\chi^2 = 49.42$, df = 3, $p < 0.001$	< 0.001	0.60
Is far more distractible than usual	34	40	62	15	$\chi^2 = 57.32$, df = 3, $p < 0.001$	< 0.001	0.01[c]
Does far more reckless or silly things	27	42	53	15	$\chi^2 = 43.96$, df = 3, $p < 0.001$	< 0.001	0.29
Switches rapidly from one topic to another	33	42	58	16	$\chi^2 = 44.44$, df = 3, $p < 0.001$	< 0.001	0.08
Believes they have special abilities that are unrealistic	10	11	17	3	$\chi^2 = 12.06$, df = 3, $p < 0.01$	0.05	0.47

[a]ADHD alone means without bipolar spectrum disorder (BPSD), not necessarily with no other comorbidity (e.g., anxiety or oppositional defiant disorder); BPSD alone means without ADHD, not necessarily with no other comorbidity.
[b]Fisher's exact test.
[c]Indicates not significant after Holm's stepdown Bonferroni correction for multiple tests within domain.

parent-rated CASI (defined as a rating of 2 or 3 on the 0–3 scale). For the ADHD items, there was a near-perfect decreasing pattern, with comorbid children the highest, followed by ADHD alone, then BPSD alone, with the neither-diagnosis group the lowest.

Hypothesis 3. Global functioning is more impaired in BPSD + ADHD patients than in those with either diagnosis alone

As shown in Table 1, findings were in the predicted direction: CGAS scores were significantly worse for the comorbid group (50.0) than for either the ADHD-alone (55.2) ($p < 0.001$) or the BPSD-alone (54.5) ($p < 0.01$) group. Both were medium effect sizes (Cohen's $d \sim 0.5$). Thus, this hypothesis was supported, although secondary measures of global severity in Table 1 (CGI-S, Child's Global Social Adjustment, Child's Current Overall Interpersonal Functioning) are significant only for comorbid BPSD + ADHD versus ADHD alone; with the comparable tendency for comorbid versus BPSD alone not reaching statistical significance.

Hypothesis 4: Children with ADHD + BPSD will have higher rates of other diagnoses than children with ADHD alone or BPSD alone

As shown in Table 1, the number of additional diagnoses for the ADHD + BPSD group was 3.27, greater than for BPSD alone (1.87, $p < 0.001$) or ADHD alone (2.57, $p < 0.001$). Thus this hypothesis was upheld.

Covariate analyses

To examine the robustness of the results, ANOVAs were repeated using four variables as covariates: the presence/absence of comorbid disruptive behavior disorders, age, sex, and Medicaid status (as a proxy for socioeconomic status) at baseline. Adjusting for these covariates did not change the significance of the main effects for diagnostic groups described earlier, except for teacher-reported ODD and CD symptoms (which obviously would be strongly related to the presence or absence of a comorbid DBD diagnosis). Details of which covariates showed significant associations with each dependent variable are available upon request.

Discussion

This clinical sample of 707 outpatients was enriched with children whose parents scored them ≥ 12 on the PGBI-10M (selecting for those with elevated symptoms of mania) at their first clinic visit. The majority (n = 589, 76.2%) had ADHD and a substantial proportion (n = 162, 22.9%) had BPSD (diagnosed with a requirement for episodes), with comorbid overlap of 16.5% (n = 117), slightly less than would be expected from multiplying the prevalence of the two disorders in this sample (17.5%, n ~ 124). The failure to find greater comorbidity is relevant to a current controversy about the relationship of the two disorders. Some (15, 38), but not all (12, 39) literature claims greater than chance development of BPSD in the presence of ADHD. The difference of our findings from those of some other authors may be partially accounted for by definitions of BPSD and our careful diagnostic sorting of symptoms as described in the *Materials and Methods* section. One might expect that the high proportion of shared symptoms would result in greater than chance overlap (40). Indeed, if one automatically counts such symptoms as hyperactivity and impaired attention towards both disorders without noting association with mood episodes, and especially if one does not require episodicity for BPSD, it may artificially inflate the comorbidity rate. The differences in the way those symptoms are inquired, as illustrated in Table 2, can make a critical difference in assignment to diagnosis. On the other hand, the reconciliation of these divergent findings may rest in the difference between a clinical sample and population rates (41). It seems that the increased risk of bipolar disorder reported in ADHD clinical samples, 10-fold or greater than the population base rate, may actually be the risk of being in a child mental health clinic population rather than being specific to ADHD.

Of the four hypotheses, two were supported (Hypothesis 3: function more impaired in the comorbid group by CGAS ratings; Hypothesis 4: number of other comorbid diagnoses greater in the comorbid ADHD + BPSD group). One (Hypothesis 2: more severe symptoms in the comorbid group) was partially supported, and one (Hypothesis 1: earlier age of onset in the comorbid group) clearly failed.

However, concerning Hypothesis 4, the increment of additional diagnoses appeared greater for adding ADHD to BPSD than the reverse. Children with ADHD alone, compared to those with BPSD alone, had more than twice the rate of two or more other diagnoses (46% versus 22%, both significantly less than the comorbid group, 71%). It appears that at this age, ADHD carries more comorbidity than BPSD. On the other hand, the need for hospitalization is carried by BPSD (22% versus 5%), and addition of ADHD does not increase the rate of hospitalization.

The failure to find earlier onset of BPSD in the comorbid group is at odds with other reports (2, 4, 16, 17). We are at a loss to explain this difference. It may have resulted from the method of ascertainment; the others started with children with diagnosed BPSD, whereas we started with an undiagnosed sample with elevated symptoms of mania (and a few without such elevation). Another difference might be the age of the sample. For example, Masi et al. (2) reported age 8 onset of BPSD for the comorbid group and age 11 onset for the BPSD-alone group. Because our sample was age 6–12, we may have sampled too young to capture most of those for whom comorbidity would make a difference in onset age. This possibility is partially supported by the fact that those with BPSD without ADHD averaged a year older ($p = 0.01$) than the other diagnostic groupings at their first visit to the LAMS site clinic (an inclusion criterion was that this was the first visit to the respective clinic). Further, the BPSD + ADHD group first came to clinical attention at any clinic 1.3 years younger than the BPSD-alone group. Thus it appears that concurrent ADHD may bring the comorbid group to clinical attention a year or so sooner even if the age of onset is not different. This would be consistent with impairment being more severe in the comorbid group, which may precipitate clinical attention at a younger age. However, the age difference for first clinical presentation anywhere failed to reach significance by a conservative statistical test that allowed for unequal group variances ($p = 0.1$), so it must be interpreted with caution.

The difference between parent and teacher ratings deserves some comment. Parents in general reported worse ADHD symptoms in the comorbid group than in any other group and worse BPSD symptoms in the comorbid group than in ADHD alone. Teachers reported worse ADHD symptoms in the comorbid group than in the BPSD-alone group but not worse than in the ADHD-alone group. They reported the same pattern for BPSD symptoms: worse in the comorbid group than the BPSD-alone group but not worse than for ADHD alone. The parental findings seem intuitive in that (i) manic symptoms were linked to BPSD either alone or with ADHD, and (ii) severity of ADHD symptoms, which might also reflect BPSD symptoms, was exacerbated by comorbidity with BPSD. Unfortunately, we have no way of knowing whether parents (and teachers) reported the mood symptoms when the child was manic, hypomanic, depressed, or euthymic. Teachers rated ADHD symptoms more severe in comorbidity than in BPSD alone; this is compatible with the parent report and common sense. However, teachers did not rate ADHD symptoms more severe in the comorbid group than in the ADHD-alone group as parents did. Even more notable, teachers reported manic symptoms as more severe in the comorbid children than in the BPSD-alone group but not more severe than in the ADHD-alone group.

This difference between parent and teacher ratings is an unexpected finding. To make sure the difference between parent and teacher ratings of manic symptoms was not a function of biased missing data (the n for teacher data was 466 compared to 692 for parent data), we repeated the parent-rated manic symptom analysis using parent ratings only from the subgroup that also had teacher ratings. The results showed essentially the same pattern as the whole sample. If this difference is replicated, it may reflect the following explanations, in order of probability. (i) Teachers tend to be better educated about, and more sensitized to, ADHD symptoms than bipolar symptoms, and might conflate ADHD symptoms with bipolar symptoms (42). In fact, Youngstrom et al. (42) and Kahana et al. (43) reported that teacher ratings for children with ADHD and BPSD look similar. Learning about ADHD is now a standard part of teacher training and it would be rare for BPSD to receive the same attention, so this possibility seems strong. (ii) There are undoubtedly different priorities for behavior in school than at home; this also seems an established fact. (iii) There are often actual differences in home and school behavior (24, 44–46). (iv) Somewhat less likely, informant perception may be colored by prior experience (i.e., the parent having a longer history with the child, including better opportunity to note mood episodes). (v) Although the type of school setting could make a difference, with special education teachers having a higher behavioral threshold for significant ratings, this is unlikely to explain the parent–teacher difference.

Generally, for ADHD symptoms teacher observations are considered more valid and sensitive to treatment effects because they have more experience with *norms* (other children), actually have age peers available for real-time comparison, see the child in task-demand situations that tend to bring out ADHD symptoms, and are usually more emotionally neutral and objective. These advantages may not apply to observation of mood states, in which parents, who see the child more hours per week and have a longer historical exposure to the child's usual state, may have an observational advantage (42). This issue warrants further study.

The fine-grained examination of individual ADHD and manic symptoms in Table 2 revealed

some interesting comparisons that appear to depend on how a question is framed; these have clinical diagnostic implications. When distractibility is asked about as a trait (*Is easily distracted*), ADHD either alone (86%) or with BPSD (94%) showed almost twice the prevalence found in BPSD alone (51%). But when asked about as a state (*Is far more distractible than usual*), the prevalence drops to 33.5% in ADHD alone, less than in BPSD alone (40%) and about half the rate in the comorbid group (62%). It is curious that even though the trait of distractibility is already high in ADHD, an increase in distractibility is noted substantially more often with the two disorders combined than with BPSD alone. A similar phenomenon can be noted for *talks excessively* versus *much more talkative than usual* and for *fidgets/squirms, difficulty remaining seated, runs/climbs*, and *on the go/driven by a motor* versus *more active/busier than normal*. These contrasts suggest that the extensive symptom overlap between ADHD and BPSD need not constitute a serious impediment to diagnostic distinction if questions are framed carefully (41). The pattern is consistent with the idea that ADHD has a more chronic presentation, whereas mood disorders tend to have a more episodic, fluctuating presentation (7, 10, 11, 47–50). Of course ADHD symptoms, no matter how severe, cannot alone justify a BPSD diagnosis without specific mood symptoms and episodicity. Nevertheless, it seems clear that all ADHD symptoms trend worse in the comorbid condition and some but not all manic symptoms also do. This, of course, is not specific to BPSD: ADHD symptoms get worse with depression, anxiety, or substance abuse, and during family conflicts or environmental stressors.

This difference in question formulation is critical clinically for distinguishing BPSD from ADHD. As explained in the *Materials and Methods* section, it is important to determine whether a symptom is worse during a mood episode, or possibly even restricted to the mood episode, before counting it towards a mood diagnosis. As defined in DSM-IV, ADHD is a *chronic* pattern of behavior, whereas BPSD is characterized by *episodes* of mood change (mood elevation or depression, uncharacteristic silliness, racing thoughts, etc.) with *increases* in troublesome activity, inattention, and other symptoms that in more chronic form characterize ADHD.

Limitations

The data presented here were collected once, at the baseline assessment, so any conclusions about longitudinal course, progression, or causality must be considered speculative. The same sample is being followed longitudinally with periodic assessments that will allow a careful examination of progression and course. The sample was enriched for symptoms of mania and thus is not representative of the whole child mental health clinic population. Rather, it is mainly representative of the subgroup of the child mental health clinic population that presents at first appointment with elevated symptoms of mania. For this reason, the proportions with BPSD and with ADHD (for which most, perhaps all, symptoms are similar to bipolar symptoms) are probably higher than in the general child mental health clinical population. Nevertheless, the actual diagnoses were carefully made by experienced research diagnosticians using information from reliability-trained interviewers, so that the comparisons between diagnoses should be valid. The small number (45) with BPSD without ADHD impaired power for some comparisons, possibly allowing some type 2 errors. The number of comparisons made also invited type 1 error, but we partially corrected for this by using Holm's stepdown Bonferroni correction for the exploratory comparisons (those not testing an *a priori* hypothesis), with corrected nonsignificance indicated by a superscript 'b' in Table 1 and a superscript 'c' in Table 2. Finally, this sample started at age 6–12, missing the early stages of ADHD and not yet tapping adolescence. Therefore, in addition to the prospective assessments being carried out on this sample, it would be desirable to recruit a sample aged 3–6 at baseline with ADHD and follow them prospectively.

In sum, these analyses of 707 carefully diagnosed children failed to find an excess of overlap between ADHD and BPSD or the expected earlier age of BPSD onset with comorbid ADHD, but did find greater symptom severity, greater functional impairment, and more additional comorbidity in the comorbid ADHD + BPSD group.

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