Attention-Deficit Hyperactivity Disorder and Juvenile Mania: An Overlooked Comorbidity?

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ABSTRACT

Objective: To evaluate the psychiatric, cognitive, and functional correlates of attention-deficit hyperactivity disorder (ADHD) children with and without comorbid bipolar disorder (BPD). **Method:** *DSM-III-R* structured diagnostic interviews and blind raters were used to examine psychiatric diagnoses at baseline and 4-year follow-up in ADHD and control children. In addition, subjects were evaluated for cognitive, academic, social, school, and family functioning. **Results:** BPD was diagnosed in 11% of ADHD children at baseline and in an additional 12% at 4-year follow-up. These rates were significantly higher than those of controls at each assessment. ADHD children with comorbid BPD at either baseline or follow-up assessment had significantly higher rates of additional psychopathology, psychiatric hospitalization, and severely impaired psychosocial functioning than other ADHD children. The clinical picture of bipolarity was mostly irritable and mixed. ADHD children with comorbid BPD also had a very severe symptomatic picture of ADHD as well as prototypical correlates of the disorder. Comorbidity between ADHD and BPD was not due to symptom overlap. ADHD children who developed BPD at the 4-year follow-up had higher initial rates of comorbidity, more symptoms of ADHD, worse scores on the CBCL, and a greater family history of mood disorder compared with non-BPD, ADHD children. **Conclusions:** The results extend previous results documenting that children with ADHD are at increased risk of developing BPD with its associated severe morbidity, dysfunction, and incapacitation. *J. Am. Acad. Child Adolesc. Psychiatry,* 1996, 35(8):997–1008. **Key Words:** bipolar disorder, attention-deficit hyperactivity disorder, comorbidity.

Reports in pediatric and adult samples document the co-occurrence of attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BPD), yet little is known about the comorbid condition (Butler et al., 1995; Carlson, 1984; Potter, 1983; Poznanski et al., 1984). Butler et al. (1995) found high rates of BPD (22%) in a hospitalized sample of ADHD patients. West et al. (1995) reported that 57% of adolescents with BPD also had ADHD. In an adult sample, Winokur et al. (1993) showed that traits of childhood hyperactivity were more common among BPD patients and their BPD relatives compared with depressed patients. These findings were consistent with the many case reports of bipolar children that noted a frequent co-occurrence between manic and ADHD symptomatology (Potter, 1983; Poznanski et al., 1984). Considering the severity of BPD, its comorbidity with ADHD can lead to a most severe clinical picture that can greatly influence diagnosis, prognosis, and treatment of ADHD children (Angold and Costello, 1993; Maser and Cloninger, 1990), making it of high clinical and scientific relevance.

We do not know why there have been so few systematic studies of the overlap between ADHD and mania, but likely reasons are the prevailing skepticism about the very existence of childhood BPD (Goodwin

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and Jamison, 1990) and the clinical difficulties in distinguishing ADHD from mania in children due to symptomatic overlap (Carlson, 1984). An additional source of diagnostic uncertainty is that childhood mania may present differently from its adult counterpart (Biederman et al., 1995; Cantwell and Carlson, 1983; Carlson, 1983; Davis, 1979; Feinstein and Wolpert, 1973; McGlashan, 1988). Notably, unlike adult BPD patients, manic children are seldom characterized by euphoric mood (Carlson, 1983, 1984). Rather, the most common mood disturbance in manic children has been characterized as irritable, with "affective storms" or prolonged and aggressive temper outbursts (Davis, 1979). In addition, it has been suggested that the course of childhood-onset BPD tends to be chronic and continuous rather than episodic and acute, as is characteristic of the adult disorder (Carlson, 1983, 1984; Feinstein and Wolpert, 1973; McGlashan, 1988).

Wozniak et al. (1995a) examined 262 clinically referred preadolescent children and showed that (1) 16% met diagnostic criteria for mania; (2) the clinical picture in these children was predominantly irritable and mixed; (3) 98% of children meeting criteria for mania met criteria for ADHD; and (4) children with mania-like symptoms were at risk for major depression, psychosis, psychiatric hospitalization, and severely impaired psychosocial functioning. These BPD children were also found to have significant elevations in all of the clinical scales of the Child Behavior Checklist (CBCL) compared with other ADHD children, particularly in Delinquent Behavior, Aggressive Behavior, Anxious/Depressed, and Thought Problems scales (Biederman et al., 1995). Taken together, these studies provided converging evidence that children who meet criteria for BPD had a severe psychiatric condition that manifested a wide range of psychopathology and dysfunction.

The significance of distinguishing mania in children and adolescents with ADHD goes beyond resolving a vexing nosological question. Although limited, the available data suggest that children with ADHD plus BPD may account for a substantial number of child psychiatric hospitalizations and that they are plagued with chronic psychiatric and psychosocial disability (Wozniak et al., 1995a). Thus, the identification of a subtype of comorbid ADHD plus mania would provide improved guidelines for diagnosis and, eventually, for treatment. Since prophylactic pharmacotherapy can reduce the psychiatric and psychosocial morbidity associated with BPD, clarification of these issues could benefit the youngsters who suffer from this severe disorder.

In this study we evaluate the psychiatric, cognitive, and functional correlates of ADHD children with and without comorbid BPD, using data from a 4-year family and follow-up study of ADHD (Biederman et al., 1996, in press). Our goal was to use the follow-up data to determine whether ADHD with comorbid BPD could be differentiated from other cases of ADHD based on course and outcome. We also sought to determine whether bipolar onsets during the follow-up period could be predicted by the baseline condition of the child (e.g., we would expect baseline major depression to predict subsequent BPD). We also hypothesized that children with both mania and ADHD would have the clinical features of both disorders and that the clinical picture of childhood mania would be irritable and mixed.

METHOD

Subjects

The original sample included a total of 260 children (140 ADHD and 120 normal controls) chosen from psychiatric and nonpsychiatric, pediatric settings (Biederman et al., 1992). Within each setting, ADHD children and normal controls were included. We screened controls only for the presence of ADHD. The psychiatric sample consisted of consecutively ascertained outpatients from the pool of existing and new referrals to a specialized child psychiatric service and medical pediatric clinics at the same institution. Eligible ADHD subjects met clinical criteria for the *DSM-III-R* diagnosis of ADHD based on a standard child psychiatric evaluation conducted by a child psychiatrist.

As previously reported (Biederman et al., 1992), eligible subjects were Caucasian, non-Hispanic, male children and adolescents, 6 to 17 years of age, with an IQ greater than 80. We excluded adopted and stepchildren, children with major sensorimotor handicaps (paralysis, deafness, blindness), and children or parents with mental retardation or very severe and unstable psychopathology (psychosis, autism, suicidality) that was active at the time of assessment. Subjects with a history of such psychopathology were not excluded. Also, subjects from the lowest socioeconomic class were excluded to avoid the confounds of extreme social adversity.

Measures

Probands and their relatives were assessed at baseline and then again 1 and 4 years later. We examined their parents at baseline only. A proband was defined as having a family history of a disorder if a parent or sibling had the disorder at the baseline assessment. All diagnostic assessments used *DSM-III-R*–based structured interviews.

Psychiatric assessments of children relied on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E) (Orvaschel and Puig-Antich, 1987). We assessed both lifetime and current diagnoses, but only lifetime diagnoses are used in this report. We chose this interview because it is widely used, establishes *DSM-III-R* diagnoses, can be effectively administered by clinicians or trained interviewers, and has established psychometric properties. Diagnoses were based on independent interviews with the mothers and direct interviews of probands and siblings, except for children younger than 12 years of age, who were not directly interviewed. Diagnostic assessments of parents were based on direct interviews with each parent, using the Structured Clinical Interview for *DSM-III-R* (SCID) (Spitzer et al., 1990). To assess childhood diagnoses in the parents, we administered unmodified modules from the K-SADS-E. At baseline and year 1, the structured interviews assessed lifetime history of psychopathology; at year 4, these assessments reflected the interval since the prior assessment.

The interviewers had undergraduate degrees in psychology and were trained to high levels of interrater reliability. We computed κ coefficients of agreement by having three experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 173 interviews the median κ was .86, and for the disorders of most relevance to this article, the κ values were .99 for ADHD, .93 for conduct disorder, .83 for major depression, and .94 for BPD. Diagnoses having κ values below the median were alcohol abuse (.64), antisocial personality (.66), dysthymia (.79), and obsessive-compulsive disorder (.51). As Faraone et al. (1995) reported in detail, the 1-year test-retest κ values were .95 for ADHD, .66 for major depression, and .71 for BPD. These interrater and test-retest κ values were all within the range described as substantial to almost perfect by Landis and Koch (1977).

The interviewers participated in a full-time, rigorous training program lasting 3 to 4 months. Training included mastery of the instruments, learning about *DSM-III-R* criteria, watching training tapes, observing interviews performed by experienced raters, and rating several subjects under the supervision of the project coordinator. Throughout the study, the interviewers were supervised by board-certified child and adolescent psychiatrists. This supervision included weekly meetings and additional consultations as needed. Before doing study interviews, interviewers must have achieved high levels of interrater reliability with these psychiatrists. During the study, all interviews were audiotaped for random quality-control assessments by the supervising psychiatrists.

In addition to psychiatric data we assessed dimensional measures of psychopathology with the CBCL, Full Scale IQ based on the Vocabulary and Block Design subtests from the Wechsler intelligence tests (Sattler, 1988), social functioning with the Global Assessment of Functioning Scale of the *DSM-III-R*, socioeconomic status (Hollingshead, 1975), divorce or separation of parents in family of origin, special class placement as reported by the parent, and psychiatric hospitalization as reported by the parent. All follow-up assessments were blind to baseline data collected on the same subjects.

Diagnostic Procedures

The interviewers were instructed to take extensive notes about the symptoms for each disorder. For every diagnosis, information was gathered regarding the ages at onset and offset of symptoms, number of episodes, and treatment history. The interviewer's notes and structured interview results were reviewed by a committee of four board-certified child and adult psychiatrists chaired by the senior author (J.B.). The committee was blind to the subjects' ascertainment group, ascertainment site, and all data collected from other family members. Diagnoses were considered positive if *DSM-III-R* criteria were unequivocally met. The committee members were also made blind to prior diagnoses of the same subjects and their family members.

Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful. By "clinically meaningful" we mean that the data collected from the structured interview indicated that the diagnosis should be a clinical concern because of the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. Only the committee approved diagnoses were used for the data analyses reported in this article.

The diagnosis of BPD was especially dependent on the committee's assessment. In making these diagnostic decisions, the committee referred to the coded diagnostic items from the structured interview, extensive margin notes made by the interviewers, information about the persistence and consequences of the symptoms, associated clinical features, severity of mood instability, treatment history, and prior hospitalizations. Thus, the resulting diagnosis was a clinical "best estimate" diagnosis, not a simple enumeration of criteria coded by the interviewer.

At baseline, 13 probands met criteria for BPD on the K-SADS-E, but only 9 (75%) of these had BPD diagnosed by the committee. Of 9 subjects meeting subthreshold BPD criteria (i.e., they met all criteria but one) at baseline, 5 (55%) had BPD diagnosed by the committee on the basis of the additional information described above. At the 4-year follow-up, 28 probands met criteria for BPD on the K-SADS-E, but only 14 (50%) of these had BPD diagnosed by the committee. Of 6 subjects meeting subthreshold BPD criteria at follow-up, 1 (17%) had BPD diagnosed by the committee on the basis of additional information. At both baseline and follow-up, the subjects not meeting criteria for either full or subthreshold BPD were all considered non-BPD by the committee.

To provide an additional level of clinical validity for the bipolar diagnoses, two board-certified child and adolescent psychiatrists reviewed the audiotaped interviews of each bipolar proband and examined medical records when these were available. The diagnosis of BPD was retained only if the psychiatrist agreed that the subject clearly and unequivocally met criteria for mania based on this additional information.

To be given the lifetime diagnosis of mania, the child had to meet full *DSM-III-R* criteria for a manic episode with associated impairment. Thus, a child must have met criterion A for a period of extreme and persistently elevated, expansive, or irritable mood, *plus* criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance, plus criterion C, associated impairment. Rapid cycling was defined as having four or more episodes per year according to the operational definition outlined by Goodwin and Jamison (Goodwin and Jamison, 1990).

For children older than 12 years, the diagnosticians combined data from direct and indirect interviews by considering a diagnostic criterion positive if endorsed in either interview. At baseline and year 1, assessments were lifetime; at year 4, assessments reflected the interval since the prior assessment. As suggested by others (Gershon et al., 1982; Weissman et al., 1984), we diagnosed major depression only if the depressive episode was associated with marked impairment. Since the anxiety disorders comprise many syndromes

with a wide range of severity, we used two or more anxiety disorders to indicate the presence of a clinically meaningful anxiety syndrome and refer to this as "multiple anxiety disorders" as we have elsewhere.

Data Analysis

Group comparisons used the Pearson χ^2 test for categorical data and analysis of variance for continuous data. When variances differed between groups, nonparametric methods were used. To reduce the probability of type I errors, we used .01 as our threshold of statistical significance. The .05 level of significance is reported to indicate trends that may be of interest for hypothesis generation in future work.

RESULTS

Demographics and Clinical Features

At the 4-year follow-up, 91% of the 140 ADHD children and 91% of the 120 normal controls seen at baseline were successfully recruited (Biederman et al., in press). The rates of successful follow-up at 4 years did not differ between groups. There were no significant differences between subjects successfully followed up and those lost to follow-up on each of the measures used in this study (all p values $> .01$; detailed information available on request).

At baseline, 15 ADHD children (11%) satisfied diagnostic criteria for BPD (baseline BPD). Fifteen new cases of mania out of 128 subjects available at follow-up (12%) developed at 4-year follow-up (F-U BPD) among ADHD children and 99 ADHD children did not have mania at either baseline or follow-up (non-BPD ADHD). Thus, a total of 30 of the 140 ADHD children (21%) had a lifetime history of BPD. Compared with controls, ADHD children had higher rates of mania at both baseline (11% versus 0%, $p < .001$) and follow-up (12% versus 1.8%, $p < .001$). One of the 15 ADHD children with comorbid mania at baseline was lost to follow-up and 2 of the 109 normal controls developed mania at follow-up. Thus, comparisons were made between 107 normal controls and three groups of ADHD children: 14 with baseline BPD, 15 with F-U BPD, and 99 non-BPD ADHD children without mania at either baseline or follow-up.

The most common presentation of BPD at either baseline or follow-up was mixed, with major depression and mania co-occurring simultaneously (n = 8, 57% and n = 7, 47% for baseline and follow-up bipolar groups, respectively). The least common was biphasic, with separate episodes of mania and major depression (n = 8, 57% and n = 7, 47% for baseline and follow-up bipolar groups, respectively). While baseline BPD children tended to have a simultaneous emergence of manic and depressive symptomatology, the majority of F-U BPD children manifested major depression first (11% versus 70%, $p \leq .01$, depression onset first for baseline versus follow-up bipolar groups, respectively).

There were significant differences among the three ADHD groups and controls in socioeconomic status, intactness of the family, and family history of psychiatric disorders (Table 1). Both BPD groups had elevated rates of familial ADHD that did not differ from the rate of familial ADHD observed in non-BPD ADHD children. In contrast, familial BPD and familial major depression were markedly elevated in the BPD groups but not in the non-BPD ADHD group. The rates of familial anxiety were elevated in all three ADHD groups but were highest among the two BPD groups.

Psychiatric and Functional Outcomes

There were striking similarities between the two BPD groups in their elevated rates of severe major depression, multiple anxiety disorders, conduct disorder, and oppositional defiant disorder, and in the mean number of comorbid disorders per child at both baseline and follow-up assessments compared with non-BPD ADHD probands. This was so despite the fact that F-U BPD probands did not have BPD at baseline. In addition, F-U BPD children, but not baseline BPD children, had an increased risk for substance use disorder and psychosis at follow-up compared with non-BPD ADHD children (Table 2). As depicted in Table 2, there were striking similarities between the baseline and follow-up bipolar groups for concurrent psychiatric correlates, as well.

Figure 1 displays CBCL findings at the baseline and 4-year follow-up assessments. Although they did not always reach statistical significance, the following findings are noteworthy: (1) CBCL clinical scales were much worse in baseline and F-U BPD children compared with non-BPD ADHD children; (2) mean CBCL scale scores were relatively stable over time in both BPD groups; (3) F-U BPD children had similarly abnormal CBCL scales before and after the onset of mania; and (4) ADHD children with and without comorbid BPD had similar elevations in the Attention Problems scale, which indexed ADHD symptoms, but BPD children had marked differences in anxiety/depression, delinquency, and aggression before and after the development of mania.

TABLE 1
Sociodemographic and Clinical Characteristics of Sample

	ADHD Probands				
	Baseline BPD (n = 14)	Follow-up BPD (n = 15)	Non-BPD (n = 99)	Normal Controls (n = 107)	Statistical Significance (df = 3)
Sociodemographics					
Age (years)					
Baseline	10.7 ± 2.9	10.7 ± 3.2	10.5 ± 3.0	11.5 ± 3.6	.183
Follow-up	14.6 ± 2.9	14.6 ± 3.4	14.3 ± 3.1	15.2 ± 3.7	.354
Socioeconomic status at baseline	2.2 ± 1.1[a,b]	2.2 ± 1.1[b]	1.7 ± 0.9[b']	1.5 ± 0.7	.001
Parents divorced or separated at baseline (%)	57[a,b]	33	22	18	.008
Psychiatric family history (%)					
Bipolar disorder	29[a,b]	20	7	7	.018
Major depression	57[a',b]	53[a',b]	27	19	.001
Anxiety disorder	71[b]	60[b']	48[b]	32	.004
ADHD	29[b]	47[b]	40[b]	0	.001

Note: ADHD = attention-deficit hyperactivity disorder; BPD = bipolar disorder.
[a] $p \leq .01$, [a'] $p \leq .05$ versus ADHD probands without BPD; [b] $p \leq .01$, [b'] $p \leq .05$ versus control probands by Pearson χ^2 analysis (df = 1). Nonparametric tests were used for ordinal data and when variances were not equal.

Analyses of individual symptoms showed that ADHD children satisfying criteria for BPD at baseline and follow-up assessments had prominent prototypical symptoms of mania, with severe agitation and irritability rather than euphoria dominating the clinical picture (Fig. 2). In addition, they also had the prototypical symptoms of ADHD. At baseline, the number of ADHD symptoms did not differ significantly among the baseline BPD (10.6 ± 4.7), F-U BPD (12.3 ± 1.6), and non-BPD (10.7 ± 3.2) ADHD children. At follow-up, the number of ADHD symptoms also did not differ significantly among groups (baseline BPD: 8.4 ± 4.8; F-U BPD: 10.5 ± 3.8; non-BPD: 7.9 ± 3.8). Examination of the clinical features of manic children with ADHD revealed that BPD tended to have its onset in childhood (mean age 5 for baseline BPD and 11 for F-U BPD), to have multiple episodes (mean of 19 for baseline BPD and 7 for F-U BPD), and to have many symptoms (mean of 6 for both groups).

Significant differences among the groups were also found in all cognitive and functional variables assessed (Table 3). These were more impaired in the three ADHD groups irrespective of comorbid BPD status. Both groups of BPD children had markedly more impaired scores on the global assessment of functioning than did other ADHD children, and both had a significantly higher rate of placement in special classes at both baseline and follow-up assessments. Significant differences among the groups were also observed in history of psychiatric hospitalization, accounted for by higher rates in the two BPD groups than in non-BPD ADHD children (Table 3).

Symptom Overlap Analyses

Of seven *DSM-III-R* criteria for a manic episode, three are shared with the *DSM-III-R* criteria for ADHD: distractibility, motoric hyperactivity, and talkativeness. To avoid counting symptoms twice toward the diagnosis of both ADHD and mania, we reassessed each individual by using two different techniques that corrected for the overlapping diagnostic criteria. We did not adjust for items that were criteria for one disorder that might be considered an "associated feature" of the other (e.g., decreased need for sleep). The symptom "fidgety" was used as the index of motor hyperactivity for the ADHD diagnosis.

The first approach, which we refer to as the *subtraction method*, involved subtracting the overlapping symptoms and applying the same criteria required in *DSM-III-R*. However, the subtraction method is overly stringent because the exclusion of overlapping symptoms reduces the number of possible symptoms that can be endorsed. To adjust for this stringency, the diagnosis of ADHD was reevaluated using a second

TABLE 2
Pattern of Psychiatric Comorbidity at Baseline and 4-Year Follow-up

	ADHD Probands				
	Baseline BPD (n = 14)	Follow-up BPD (n = 15)	Non-BPD (n = 99)	Normal Controls (n = 107)	Statistical Significance (df = 3)
Major depression (severe) (%)					
Baseline	64[a, b]	33[b]	23[b]	2	.001
Follow-up	93[a, b]	73[a, b]	34[b]	6	.001
Multiple (≥ 2) anxiety disorders (%)					
Baseline	50[a', b]	33[b]	23[b]	5	.001
Follow-up	64[a, b]	47[a, b]	29[b]	9	.001
Conduct disorder (%)					
Baseline	57[a, b]	53[a, b]	12[b]	2	.001
Follow-up	71[a, b]	67[a, b]	16[b]	5	.001
Oppositional defiant disorder (%)					
Baseline	93[a, b]	80[b]	59[b]	8	.001
Follow-up	93[a, b]	100[a, b]	66[b]	15	.001
Psychoactive substance use disorder (%)					
Baseline	7	0	2	6	.421
Follow-up	14	40[a, b]	11	15	.035
Psychosis (%)					
Baseline	0	0	0	1	.753
Follow-up	7	13[b]	3	1	.047
No. of comorbid disorders*					
Baseline	3.8 ± 0.9[a, b]	3.2 ± 1.3[a, b]	2.3 ± 1.2[b]	0.3 ± 0.7	.001
Follow-up	3.9 ± 0.7[a, b]	3.7 ± 1.1[a, b]	2.4 ± 1.2[b]	0.7 ± 1.0	.001

Note: ADHD = attention-deficit hyperactivity disorder; BPD = bipolar disorder.
[a] $p \leq .01$, [a'] $p \leq .05$ versus ADHD probands without BPD; [b] $p \leq .01$ versus control probands by Pearson χ^2 analysis (df = 1). Nonparametric tests were used for ordinal data and when variances were not equal.
* ADHD and BPD were included in the total number of psychiatric disorders.

technique which we call the *proportion method.* This approach required that the observed proportion of symptoms in the reduced set of symptoms be at least as large as the proportion of symptoms required by the original criteria (Milberger et al., 1995). For example, *DSM-III-R* requires 8 (57%) of 14 symptoms for the diagnosis of ADHD. Using the proportion method, we discard three symptoms from the criterion set and are left with 11 diagnostic criteria. Fifty-seven percent of 11 is 6.3. Thus, the proportion method requires that 6 of 11 symptoms are present to diagnose ADHD.

Fifty percent (n = 7) of the 14 baseline BPD children continued to meet criteria for mania by the subtraction method and 79% (n = 11) by the proportion method of overlapping symptom correction. Forty-seven percent (n = 7) of the F-U BPD children maintained the diagnosis of BPD by the subtraction method and 60% (n = 9) by the proportion method. Eighty-six percent (n = 12) of the baseline BPD children maintained a full diagnosis of ADHD by the subtraction method and 93% (n = 13) maintained the diagnosis by the proportion method after correcting for the three overlapping diagnostic criteria. Ninety-three percent (n = 14) of the F-U BPD children maintained the ADHD diagnosis by both the subtraction and proportion methods.

DISCUSSION

Our systematic evaluation of structured interview–derived data from a sample of ADHD children showed that (1) a clinical picture compatible with the diagnosis of BPD was identified in 11% of ADHD children at baseline and in an additional 12% at 4-year follow-up by midadolescence, rates that were significantly higher than those of controls at each assessment; (2)

the clinical picture of mania in these ADHD children was predominantly irritable, and mixed with rapid cycles *and increased activity*; (3) compared with other ADHD children, those with comorbid BPD at either baseline or follow-up had significantly higher rates of major depression, conduct disorder, oppositional defiant disorder, anxiety disorders, psychiatric hospitalization, and severely impaired psychosocial functioning, findings previously associated with juvenile mania (Wozniak et al., 1995a); (4) ADHD children with comorbid BPD had a very severe symptomatic picture of ADHD and prototypical correlates of ADHD; (5) comorbidity between ADHD and BPD was not due to diagnostic criteria shared by the two disorders. These findings suggest that BPD may represent a serious comorbidity of ADHD that deserves careful clinical and scientific attention.

The 23% rate of BPD in our sample of pediatrically and psychiatrically referred ADHD children and adolescents is consistent with the 16% rate of mania we found in a separate sample of preadolescent psychiatrically referred children (Wozniak et al., 1995a), the 22% rate of mania reported by Weller et al. (1986) among severely disturbed children, and a 22% rate among hospitalized ADHD children recently reported by Butler et al. (1995). Taken together, these findings not only challenge the commonly held notion that mania is rare or nonexistent in children but also document that BPD is overrepresented in ADHD children and adolescents.

Our finding that mania may be an important comorbidity of ADHD supports previous studies of juvenile mania (Potter, 1983; Poznanski et al., 1984), studies of childhood histories of bipolar adults (Sachs et al.,

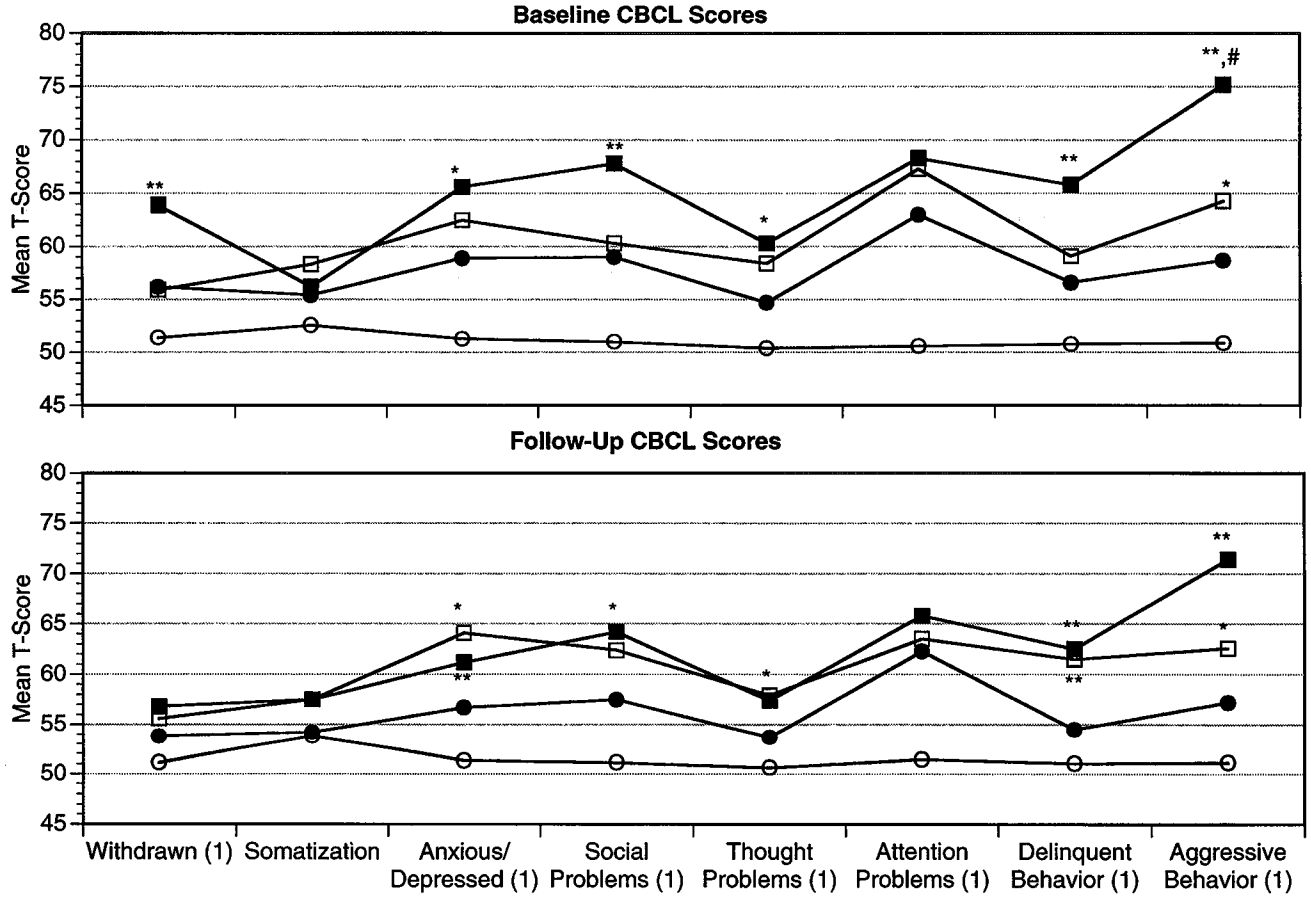

Fig. 1 Child Behavior Checklist (CBCL) scores for the baseline BPD group (*black boxes*), follow-up BPD group (*white boxes*), non-BPD ADHD group (*black circles*), and normal controls (*white circles*). $^{**}p < .01$, $^{*}p < .05$ versus non-BPD group; $\#p < .05$ versus follow-up BPD group; (1) $p < .01$ versus controls for all ADHD groups. BPD = bipolar disorder; ADHD = attention-deficit hyperactivity disorder.

1993; Winokur et al., 1993), and high-risk studies of children of bipolar parents (Grigoroiu-Serbanescu et al., 1989; Kestenbaum, 1979). For example, West et al. (1995) found that 57% of adolescent bipolar patients met criteria for ADHD. Winokur et al. (1993) showed that bipolar adults and their adult bipolar relatives were more likely to have had a childhood history of hyperactivity compared with findings in unipolar subjects. Sachs et al. (1993) found comorbid ADHD exclusively among early-onset (before age 18) bipolar adults.

The significantly elevated rates of major depression, psychosis, and psychiatric hospitalization as well as the higher familiality of mania and major depression in ADHD+BPD children compared with other ADHD children support the validity of the mania diagnoses. Similarly, the patterns of familiality of ADHD, cognitive deficits, and school failure identified in ADHD children with comorbid BPD are consistent with findings in ADHD children without mania in this study as well as with findings reported in other samples of ADHD children reviewed elsewhere (Faraone and Biederman, 1994a,b; Faraone et al., 1993; Semrud-Clikeman et al., 1992). That ADHD children with comorbid BPD show the psychopathological, cognitive, and familial features of both disorders suggests that both disorders had been validly diagnosed.

Our CBCL findings are consistent with our previous work documenting CBCL scale elevations for Delinquent Behavior, Aggressive Behavior, Somatic Complaints, Anxious/Depressed, and Thought Problems in a sample of consecutively ascertained bipolar children

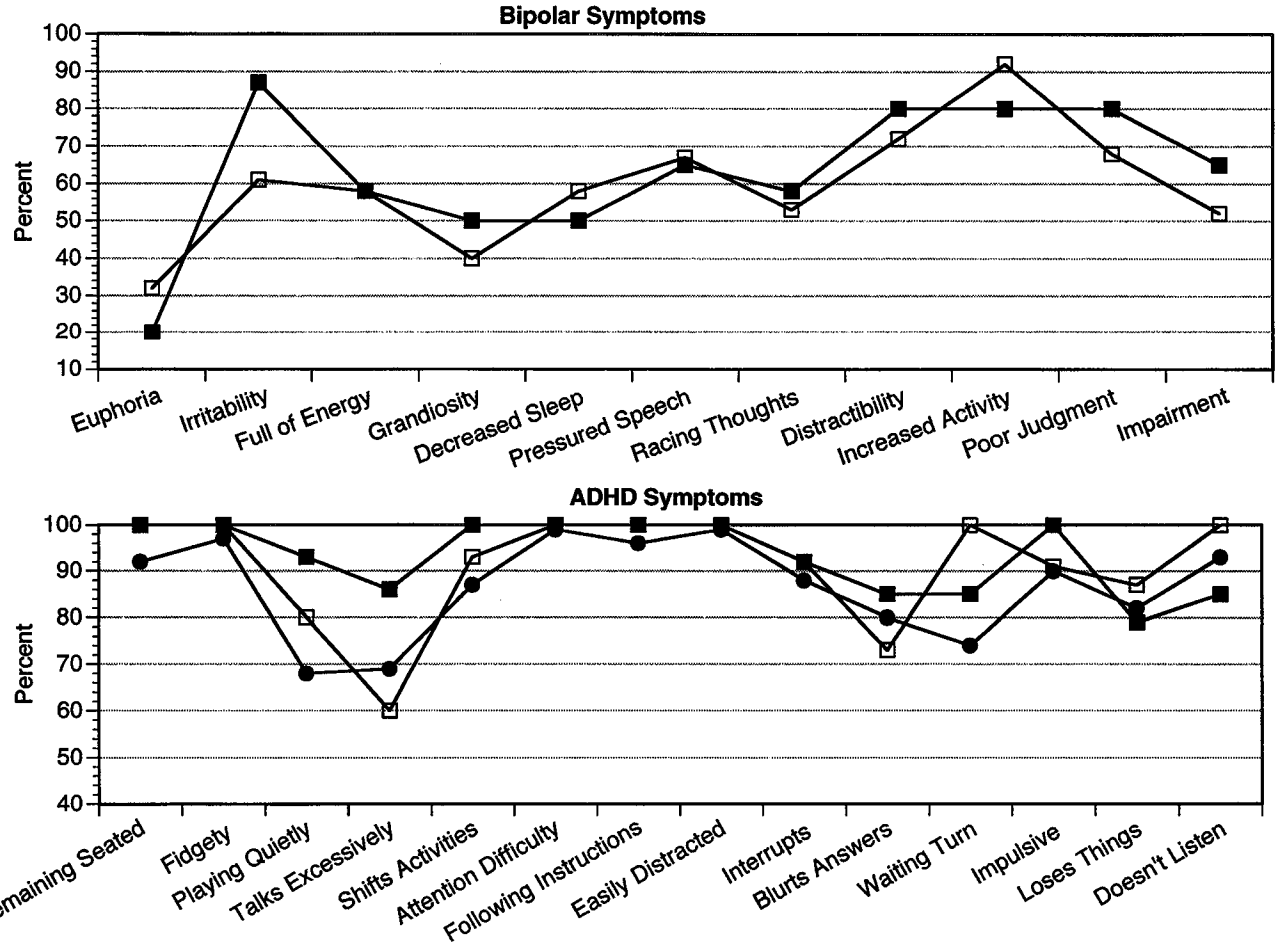

Fig. 2 Frequency of individual symptoms in ADHD probands: baseline BPD group (*black boxes*), follow-up BPD group (*white boxes*), non-BPD ADHD group (*black circles*). BPD = bipolar disorder; ADHD = attention-deficit hyperactivity disorder.

TABLE 3
Functional Measures

	ADHD Probands				
	Baseline BPD (n = 14)	Follow-up BPD (n = 15)	Non-BPD (n = 99)	Normal Controls (n = 107)	Statistical Significance (df = 3)
Estimated Full Scale IQ					
Baseline	107.8 ± 11.3[b]	100.5 ± 14.9[a, b]	111.1 ± 13.2[b]	118.3 ± 10.0	.001
Follow-up	104.6 ± 12.6[b']	104.1 ± 11.7[b]	107.8 ± 14.2[b]	116.5 ± 10.4	.001
Global Assessment of Functioning					
Baseline	38.3 ± 5.4[a, b, c]	46.3 ± 6.1[b]	49.9 ± 6.8[b]	70.0 ± 10.0	.001
Follow-up	48.2 ± 7.6[a, b]	45.1 ± 8.0[a, b]	55.1 ± 6.9[b]	67.2 ± 7.4	.001
Special class (%)					
Baseline	57[a, b]	67[a', b]	23[b]	1	.001
Follow-up	71[a', b]	73[a, b]	38[b]	2	.001
Psychiatric hospitalization* (%)					
Baseline	0	0	2	0	.428
Follow-up	21[a, b]	20[a, b]	3	0	.001

Note: ADHD = attention-deficit hyperactivity disorder; BPD = bipolar disorder.
[a] $p \leq .01$, [a'] $p \leq .05$ versus ADHD probands without BPD; [b] $p \leq .01$, [b'] $p \leq .05$ versus control probands; [c] $p \leq .01$ versus ADHD probands with onset of BPD at follow-up by Pearson χ^2 analysis (df = 1). Nonparametric tests were used for ordinal data and when variances were not equal.
* Psychiatric hospitalization was determined by parental report.

(Biederman et al., 1995). In the present sample, ADHD children with BPD tended to have higher CBCL scores than other ADHD children, especially for Delinquent Behavior, Aggressive Behavior, and Social Problems. Although there is no pathognomonic CBCL profile for BPD, it is reassuring that the dimensional approach of the CBCL is consistent with the categorical structured interview data in showing that ADHD with BPD is associated with more severe levels of psychopathology than are other cases of ADHD.

We found that the predominant mood in the children meeting criteria for mania was that of severe irritability rather than euphoria. This is consistent with other work documenting that manic episodes in young children are seldom characterized by euphoric mood (Carlson, 1983, 1984; Faedda et al., 1995). Of course, irritability is a common symptom in childhood psychopathology, and tantrums are common among children with ADHD. However, the type of irritability observed in ADHD children with mania was very severe and often associated with violence. This type of severe irritability and "affective storms," associated with prolonged and nonpredatory aggressive outbursts (Davis, 1979), is precisely the one identified in the literature dealing with childhood-onset mania.

Our results also indicate that childhood-onset mania is commonly mixed, with symptoms of depression and mania occurring simultaneously, with rapid cycling. These findings are consistent with a literature suggesting that the earlier the onset of BPD, the greater the frequency of mixed states (Goodwin and Jamison, 1990; McElroy et al., 1992; Ryan and Puig-Antich, 1986). Given the possible continuity of BPD from childhood to adulthood, it is conceivable that childhood-onset mania increases the risk for a mixed disorder and perhaps rapid cycling throughout the life into adulthood.

Our data on symptom expression for ADHD and mania show that the comorbidity between ADHD and mania could not be accounted for by the diagnostic criteria shared by the two disorders (distractibility, motoric hyperactivity, and talkativeness). The ability to retain diagnostic status for both mania and ADHD after removing overlapping diagnostic criteria supports the assertion that each diagnosis was made robustly, with more than the minimum criteria met.

Our data suggest that the subsequent development of mania in ADHD children may be predictable from certain clinical features. Notably, ADHD children who developed BPD at the 4-year follow-up had higher

initial rates of comorbidity, more symptoms of ADHD, worse scores on the CBCL, and a greater family history of bipolar and non-bipolar mood disorder compared with non-BPD ADHD children. If confirmed, these findings could provide a means for predicting the onset of bipolarity in ADHD children.

Since ADHD and mania individually are associated with elevated morbidity and disability, their co-occurrence may herald a severe clinical picture of high morbidity and perhaps mortality. For example, in one study, adolescents who completed suicide had significantly higher rates of BPD, especially mixed subtype, and a higher rate of comorbid ADHD, than those who attempted suicide (Brent et al., 1988). Because ADHD compounds the impulsivity of a severe, mixed manic state, the combination of ADHD and mania may be potentially lethal.

ADHD children with comorbid BPD had a high degree of comorbidity with anxiety, conduct, and oppositional disorders. These findings are consistent with previous reports in the literature. Carlson and Kashani (1988) found that nonreferred adolescents with manic symptoms had increased rates of anxiety and disruptive disorders. Bashir et al. (1987) noted that anxiety disorders were present in 53% of 30 adolescents with mania or hypomania. Similarly, Zahn-Waxler et al. (1988) and Sachs et al. (1993) both reported an increased risk for anxiety in high-risk children of bipolar parents. The Epidemiologic Catchment Area data show that, even in nonreferred samples, a significant overlap exists between bipolar and panic disorders (Chen and Dilsaver, 1995).

Similarly, Lewinsohn and coworkers' (1995) epidemiological study of a representative community sample of 1,700 adolescents also found high rates of comorbidity of BPD with anxiety and disruptive behavior disorders. In that study, even a subthreshold BPD diagnosis was associated with a chronic course, significant functional impairment, high rates of suicide attempts, and high rates of mental health care utilization. Taken together these findings highlight the large clinical and public health significance of even the milder cases of juvenile BPD.

Since juvenile mania has high levels of irritability that can be associated with violence and antisocial behavior (McElroy et al., 1992; Ryan and Puig-Antich, 1986), this overlap between BPD and conduct disorder is not entirely surprising. Notably, Lewinsohn and coworkers' (1995) epidemiological study found high rates of comorbidity between bipolar and disruptive behavior disorders. If this overlap continues to be confirmed, these findings may provide some new leads as to the possibility of subtypes of mood-based antisocial disorders not previously recognized. It is possible that previously reported findings documenting the beneficial effects of lithium (Lena, 1980) and carbamazepine (Campbell et al., 1992) in children with conduct disorder may be accounted for by those with BPD (Campbell et al., 1995).

Although our data provide evidence for the validity of childhood mania in children with ADHD, they should be interpreted with caution. Although our BPD children satisfied full diagnostic criteria for mania, it is very difficult to make bipolar diagnoses in children, especially in the context of comorbid ADHD. Notably, the phenomenology of both disorders includes impulsivity, overactivity, poor judgment, and irritability. Nevertheless, we have shown here, and in a different sample (Milberger et al., 1995; Wozniak et al., 1995a), that these shared criteria cannot account for the observed comorbidity. Also, the presence of mixed symptoms with major depression makes this clinical picture of BPD in children "atypical" by adult standards and contributes to the difficulty in distinguishing these children from those with ADHD.

Thus, our work raises several nosological questions. Are children who meet criteria for mania severe cases of ADHD with affective dysregulation? If so, do they fall on a continuum of severity with other ADHD cases or do they constitute an etiologically or pathophysiologically distinct subtype? Alternatively, are these children truly cases of BPD? If so, is their disorder nosologically distinct from classic BPD or do their atypical symptoms and course indicate a varying developmental expression of BPD? Despite the debate about what to call ADHD+BPD children, most clinicians would agree that these children exist and that they exhibit a syndrome of severe, disabling psychopathology and mood dysregulation frequently leading to hospitalization and marked impairment. Treatment, family, and follow-up studies are needed to clarify the nosological status of children who meet criteria for mania.

Family-genetic data have been reported. Using familial risk analysis, we have shown in two separate studies that relatives of ADHD children with and without BPD are at greater risk for ADHD compared with

relatives of normal controls, but the risk for BPD was limited to relatives of ADHD with comorbid BPD (Faraone et al., unpublished; Wozniak et al., 1995b). These findings plus those showing that ADHD and BPD cosegregated in families suggest that ADHD children with BPD are familially distinct from other ADHD children and may have what others (Strober, 1992; Todd et al., 1993) have termed childhood-onset BPD.

Our findings should be evaluated in light of specific methodological limitations. Although reliability for the mood disorder modules of the K-SADS-E has been documented (Chambers et al., 1985), less is known about the validity of the modules. However, structured diagnostic interview techniques can minimize informant and clinician bias (Robins, 1985). Given a reluctance to diagnose BPD in young subjects, structured interviews provide a means of identifying cases that might otherwise have been misattributed. Moreover, structured interview data were always reviewed by experienced, board-certified child and adolescent psychiatrists before final diagnostic assignment, thereby enhancing the credibility of the findings. A potential source of bias stems from the lack of direct interviews with children younger than 12 years. This may have led to an underrepresentation of psychopathology, especially for "internalizing" disorders such as anxiety and depression.

Despite these limitations, our findings indicate that with systematic assessment methodology, a clinical picture compatible with the diagnosis of childhood mania can be identified in ADHD children. This clinical picture compatible with the diagnosis of mania is characterized by severe irritability, a mixed presentation with symptoms of depression and mania, and multiple episodes. These children exhibit a syndrome of severe, disabling psychopathology and mood dysregulation frequently leading to hospitalization and marked impairment.

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