Pediatric Mania: A Developmental Subtype of Bipolar Disorder?

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Despite ongoing controversy, the view that pediatric mania is rare or nonexistent has been increasingly challenged not only by case reports, but also by systematic research. This research strongly suggests that pediatric mania may not be rare but that it may be difficult to diagnose. Since children with mania are likely to become adults with bipolar disorder, the recognition and characterization of childhood-onset mania may help identify a meaningful developmental subtype of bipolar disorder worthy of further investigation. The major difficulties that complicate the diagnosis of pediatric mania include: 1) its pattern of comorbidity may be unique by adult standards, especially its overlap with attention-deficit/hyperactivity disorder, aggression, and conduct disorder; 2) its overlap with substance use disorders; 3) its association with trauma and adversity; and 4) its response to treatment is atypical by adult standards. Biol Psychiatry 2000;48: 458–466 © *2000 Society of Biological Psychiatry*

Key Words: Bipolar disorder, child, age of onset

Introduction

Over the last two decades, the view that mania in children is extremely rare or nonexistent has been increasingly challenged by many case reports and series. DeLong and Nieman (1983) described a series of children presenting with severe symptoms highly suggestive of mania and responsive to lithium carbonate. Carlson (1984) suggested that prepubertal mania may be characterized by severe irritability, absence of episodes, and high levels of hyperactivity. Similarly, Akiskal et al (1985) reported on the case histories of a large group of adolescent relatives of "classic" adult bipolar patients. They found that despite frank symptoms of depression and mania, and frequent mental health contacts, none of these youth had been diagnosed with an affective disorder. Weller et al (1986) then reviewed over 200 articles published between the years of 1809 and 1982 and identified 157 cases that would likely be considered manic by modern standards; however, 48% of those subjects retrospectively diagnosed as manic according to DSM-III criteria were not considered so at the time of referral. Taken together, these reports suggested that pediatric mania may not be rare, but is difficult to diagnose.

Despite continued debate and controversy over the validity of the diagnosis of mania in children (Biederman 1998; Klein et al 1998), there is a growing consensus that many seriously disturbed children are afflicted with severe affective dysregulation and high levels of agitation, aggression, and dyscontrol that pose severe diagnostic and therapeutic challenges to the practicing community. These children have received increased clinical and scientific attention, as is evident in the scheduling of two National Institute of Mental Health workshops on bipolar disorder in children and adolescents (Carlson et al 1998; Nottelmann 1995) and in exhaustive reviews that have supported the validity of the disorder in youth (Faedda et al 1995; Geller and Luby 1997; Weller et al 1995).

In this review we integrate the existing literature on pediatric mania into a conceptual framework to understand its historical misdiagnosis. Specifically, we show that pediatric mania may represent a developmental subtype of bipolar disorder that differs in its presentation, correlates, and treatment from the adult form of the disorder, and that this atypicality poses diagnostic and nosologic dilemmas that complicate its identification.

The Atypicality of Pediatric Mania

The atypicality (by adult standards) of the clinical picture of childhood mania has long been recognized (Davis 1979; Weinberg and Brumback 1976). Notably, the literature consistently shows that mania in children is seldom characterized by euphoric mood (Carlson 1983, 1984). Rather, the most common mood disturbance in manic children is severe irritability, with "affective storms," or prolonged and aggressive temper outbursts (Davis 1979). The type of irritability observed in manic children is very

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severe, persistent, and often violent (Wozniak et al 1995a). The outbursts often include threatening or attacking behavior towards family members, other children, adults, and teachers. In between outbursts, these children are described as persistently irritable or angry in mood (Carlson 1983, 1984; Geller and Luby 1997). Thus, it is not surprising that these children frequently receive the diagnosis of conduct disorder (CD). Aggressive symptoms may be the primary reason for the high rate of psychiatric hospitalization noted in manic children (Wozniak et al 1995a).

In addition to the predominant abnormal mood in pediatric mania, its natural course is also atypical, as compared with the natural course of adult mania. The course of pediatric mania tends to be chronic and continuous rather than episodic and acute (Carlson 1983, 1984; Feinstein and Wolpert 1973; McGlashan 1988). For example, in a recent review of the past 10 years of research on pediatric mania Geller and Luby (1997) concluded that childhood-onset mania is a nonepisodic, chronic, rapid-cycling, mixed manic state. Such findings have also been reported by Wozniak et al (1995a), who found that the overwhelming majority of 43 children from an outpatient psychopharmacology clinic who met diagnostic criteria for mania on structured diagnostic interview had chronic and mixed presentation. Carlson et al (2000) reported that early-onset manics were more likely to have comorbid behavior disorders in childhood and to have fewer episodes of remission of a 2-year period than did those with adult-onset cases of mania. Thus, pediatric mania appears to present with an atypical picture characterized by predominantly irritable mood, mania mixed with symptoms of major depression, and chronic as opposed to euphoric, biphasic, and episodic course.

Although the atypical features noted in children with maniclike symptoms raises the possibility of misdiagnosis, adolescents with bipolar disorder may provide a valuable touchstone for evaluating the validity of the diagnosis made in children, since mania in adolescence has been more readily accepted (Ballenger et al 1982; McGlashan 1988). Faraone et al (1997) compared the features of the mania in children with the diagnosis, in adolescents with child-onset mania, and in adolescents with adolescent-onset mania. With the exception of more euphoria among adolescents with adolescent-onset mania, the frequencies of other symptoms of mania were strikingly similar between children and adolescent youth with mania. As was the case for children, the clinical presentation of mania among adolescents with childhood onset was rarely biphasic: it was usually chronic and mixed with a simultaneous onset of depression and mania (Faraone et al 1997). These results suggested that despite atypicality the profile of manic features associated with childhood mania may in fact represent a clinically meaningful manic syndrome.

Whereas the adult course of pediatric mania awaits data from longitudinal studies, the adult literature provides some interesting clues on the subject. A review by McElroy et al (1992) described "mixed mania," which affects 20–30% of adults with mania. Subjects with mixed mania tend to have a chronic course, absence of discrete episodes, onset of the disorder in childhood and adolescence, a high rate of suicide, poor response to treatment, and an early history of neuropsychologic deficits highly suggestive of attention-deficit/hyperactivity disorder (ADHD). Thus, McElroy et al (1992) identified a manic syndrome in adults that shows the atypical features of pediatric mania. These findings suggest that those with pediatric cases of mania may develop into adults with mixed mania and thereby provide further evidence that the atypical manic features of children constitute a valid disorder.

Comorbidity with ADHD

A leading source of diagnostic confusion in childhood mania is its symptomatic overlap with ADHD. Systematic studies of children and adolescents show that rates of ADHD range from 60% to 90% in pediatric patients with mania (Borchardt and Bernstein 1995; Geller et al 1995; West et al 1995; Wozniak et al 1995a). Although the rates of ADHD in samples of youth with mania are universally high, the age at onset modifies the risk for comorbid ADHD. For example, although Wozniak et al (1995a) found that 90% of children with mania also had ADHD, West et al (1995) reported that only 57% of adolescents with mania were comorbid with ADHD. Examining further developmental aspects of pediatric mania, Faraone et al (1997) found that adolescents with childhood-onset mania had the same rates of comorbid ADHD as manic children (90%) and that both of these groups had higher rates of ADHD than adolescents with adolescent-onset mania (60%). Most recently, Sachs et al (2000) reported that, among adults with bipolar disorder, a history of comorbid ADHD was only evident in those subjects with onset of bipolar disorder before 19 years of age. The mean onset of bipolar disorder in those with a history of childhood ADHD was 12.1 years of age (Sachs et al 2000). Similarly, Chang et al (2000) studied the offspring of patients with bipolar disorder and found that 80% of manic children had comorbid ADHD and that the mean onset of mania in adults with bipolar disorder and a history of ADHD was 11.3 years. These findings suggested that age of onset of mania, rather than chronologic age at presentation, may be the critical developmental variable

that identifies a highly virulent form of the disorder that is heavily comorbid with ADHD.

Although ADHD has a much earlier onset than pediatric mania, the symptomatic and syndromatic overlap between pediatric mania and ADHD raises a fundamental question: do children presenting with symptoms suggestive of mania and of ADHD have ADHD, mania, or both? One method used to address these uncertainties has been to examine the transmission of comorbid disorders in families (Faraone et al 1999; Faraone and Tsuang 1995). If ADHD and mania are associated due to shared familial etiologic factors, then family studies should find mania in families of ADHD patients and ADHD in families of manic patients.

Studies that examined rates of ADHD (or ADD, hyperactivity) among the offspring of adults with bipolar disorder all found higher rates of ADHD among these children, as compared with control subjects (Faraone et al 1998). Although the difference in rates attained statistical significance in only one study, Faraone and colleagues' meta-analysis (Faraone et al 1998) documented a statistical and bidirectional significant association between bipolar disorder in parents and ADHD in their offspring as well as between ADHD in a child proband and mania in relatives.

Wozniak et al (1995b) used familial risk analysis to examine the association between ADHD and mania within families of manic children. They found that relatives of children with mania were at high risk for ADHD that was indistinguishable from the risk in relatives of children with ADHD and no mania; however, mania and the comorbid condition of mania plus ADHD selectively aggregated among relatives of manic youth, as compared with those with ADHD and comparison children (Wozniak et al 1995b). Almost identical findings were obtained in two independently defined family studies of ADHD probands with and without comorbid mania (Faraone et al 1998, in press). This pattern of transmission in families suggested that mania in children might be a familially distinct subtype of either bipolar disorder or ADHD. The existence of a familial, developmental subtype is consistent with the work of Strober et al (Strober 1992; Strober et al 1988) and Todd et al (1993), who proposed that pediatric mania might be a distinct subtype of bipolar disorder with a high familial loading.

One problem facing studies of ADHD and mania is that these disorders share diagnostic criteria. 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, two different techniques of correcting for overlapping diagnostic criteria have been used to evaluate the association between ADHD and pediatric mania (Biederman et al 1996).

In the subtraction method, overlapping symptoms are simply not counted when making the diagnosis. In the proportion method, overlapping symptoms are not counted, but the diagnostic threshold is lowered to require that the same proportion of symptoms from the reduced set is required for the original diagnosis (Milberger et al 1995). Using these methods, Biederman et al (1996) showed that 48% of children with mania continued to meet criteria by the subtraction method, and 69% by the proportion method. Eighty-nine percent of children with mania maintained a full diagnosis of ADHD using the subtraction method, and 93% maintained the ADHD diagnosis by the proportion method. Taken together, these results suggest that the comorbidity between ADHD and pediatric mania is not a methodological artifact due to diagnostic criteria shared by the two disorders.

The potential for different rates of comorbidity with mania in the combined subtype, inattentive subtype, and hyperactive impulsive subtype of ADHD requires further research. Faraone et al (1998) studied 301 ADHD children and adolescents consecutively referred to a pediatric psychopharmacology clinic. Among these, 185 (61%) were the combined type, 89 (30%) the inattentive type, and 27 (9%) the hyperactive/impulsive type. Bipolar disorder was highest among combined-type youth (26.5%) but was also elevated among hyperactive impulsive (14.3%) and inattentive (8.7%) youth.

Comorbidity with CD

Like ADHD, CD is also strongly associated with pediatric mania. This has been seen separately in studies of children with CD, ADHD, and mania. Wozniak et al (1995a) reported that preadolescent children satisfying structured interview criteria for mania often had comorbid CD. Kovacs and Pollock (1995) reported a 69% rate of CD in a referred sample of manic youth and found that the presence of comorbid CD heralded a more complicated course of mania. Similar findings were reported by Kutcher et al (1989), who found that 42% of hospitalized youths with mania had comorbid CD. The Zurich longitudinal study found that hypomanic cases had more disciplinary difficulties at school and committed more thefts during their juvenile years than other children (Wicki and Angst 1991). These reports are consistent with the well-documented comorbidity between CD and major depression (Angold and Costello 1993), considering that juvenile depression often presages mania (Geller et al 1994; Strober and Carlson 1982).

Biederman et al (1997a, 1999) investigated the overlap between mania and CD in a consecutive sample of referred youth and in a sample of ADHD subjects to clarify its prevalence and correlates. They found a striking similarity

Table 1. Symptoms of Mania and CD

	Mania, no CD (N = 110)	Mania + CD (N = 76)	CD, no mania (N = 116)
	N (%)	N (%)	N (%)
Symptoms of Mania			
Euphoria, no irritability	10 (9)	1 (1)	
Irritability, no euphoria	70 (63)	51 (67)	
Euphoria and irritability	17 (16)	18 (24)	
Full of energy/many thoughts	86 (78)	61 (81)	
Grandiosity	56 (50)	50 (66)	
Decreased sleep	58 (53)	41 (53)	
Pressured speech	78 (71)	49 (64)	
Racing thoughts	81 (74)	50 (66)	
Distractibility	102 (93)	71 (93)	
Increased social activity	44 (40)	35 (46)	
Increased school activity	29 (26)	20 (26)	
Increased interest in sex	28 (26)	18 (23)	
Physically restless	94 (86)	74 (97)	
Poor judgement	94 (85)	74 (97)	
Symptoms of CD			
Truant		13 (17)	20 (17)
Runs away		10 (13)	12 (10)
Starts fights		51 (67)	63 (55)
Uses weapons		36 (48)	41 (35)
Animal cruelty		25 (33)	28 (24)
People cruelty		25 (33)	33 (28)
Vandalizes		50 (65)	55 (47)
Sets fires		18 (24)	23 (20)
Lies		60 (79)	78 (67)
Breaking-in		10 (13)	19 (16)
Steals without confrontation		28 (36)	50 (43)
Steals with confrontation		2 (3)	1 (1)
Stays out at night		26 (34)	32 (28)

CD, conduct disorder.

in the features of mania regardless of comorbid CD. Additionally, the age at onset of mania was similar in subjects with or without comorbid CD. In both groups, mania presented with a predominantly irritable mood and a chronic course, and was mixed with symptoms of major depression. Only two manic symptoms differed between these groups: "physical restlessness" and "poor judgement" were more common in the mania with CD group, as compared with the mania-only group (Table 1). Similarly, there were few differences in the frequency of CD symptoms between CD youth with comorbid mania and those without. Although children with CD and mania had a higher rate of "vandalizing" than CD-only subjects, this difference was not statistically significant.

Both the comorbid and noncomorbid subjects with mania had higher rates of major depression, anxiety disorders, oppositional disorder, and psychosis than CD and ADHD children (Biederman et al 1997a, 1999). In addition, mania comorbid with CD was associated with poorer functioning and an increased risk for psychiatric hospitalization (Biederman et al 1997a). Subjects with both CD and mania also had a higher familial and personal risk for mood disorders than other CD subjects who had a higher personal risk for antisocial personality disorder (Faraone et al 1998).

Wozniak et al (unpublished data) compared relatives of four groups of clinically referred probands defined as having 1) both CD and mania (N = 26 probands, 92 relatives), 2) mania without CD (N = 19 probands, 53 relatives), 3) CD without mania (N = 16 probands, 58 relatives), and 4) control subjects without mania or CD (N = 102 probands, 338 relatives). The risk for mania in relatives of nonmanic, non-CD probands was 4%, and their risk for antisocial disorders was 7%. In reference to the control relatives, relatives of both manic groups had increased risks for mania (14% in each group), and relatives of both groups of CD probands had increased risks for antisocial disorder (34% and 19%); however, the risk of antisocial disorders was not elevated in relatives of manic-only probands (8%), and the risk for mania was not increased in the relative of CD-only probands (9%).

Taken together, these studies suggest that subjects who receive diagnoses of both CD and mania may in fact have both disorders. Although the resolution of this important issue awaits further research, the mere diagnosis of mania in some CD children offers important therapeutic possibilities, since delinquency and mania require very different treatment strategies.

Comorbidity with Anxiety Disorders

Although anxiety is frequently overlooked in studies of mania, pediatric studies of youth with panic disorder and youth with mania document an important and bidirectional overlap between anxiety and mania. In an examination of the clinical correlates of panic disorder, Biederman et al (1997b) found that subjects with panic disorder and agoraphobia had very high rates of mania (52% and 31%) that were greater than observed among psychiatric control subjects (15%). Wozniak et al (1995a) reported significantly more panic and other anxiety disorders in children with mania. Similar findings have been reported by Bowen et al (1994), who found that, of 108 patients in a panic disorder treatment program, 23% had bipolar or cyclothymic mood disorder. Young et al (1993) reported that patients with mania and high anxiety scores were more likely to display suicidal behavior, abuse alcohol, and have cyclothymia, anxiety disorders, and a trend toward lithium nonresponsiveness. Chen and Dilsaver (1995) examined the relationship between panic and bipolar disorders using the Epidemiologic Catchment Area data base. They reported that the lifetime prevalence of panic disorder was

21% among subjects with bipolar disorder, as compared with only 0.8% among subjects who had neither bipolar nor unipolar depression. These findings strongly indicate that mania—at any age—is frequently comorbid with severe anxiety that requires additional clinical and scientific attention.

Correspondence between Categoric and Dimensional Measures

Many comorbidity findings in studies of juvenile mania have relied on structured diagnostic methodology delivered by trained raters. Although this method is considered "state of the art" for clinical research, it could be vulnerable to an assessor bias. Thus, it is useful to consider studies using methods that are independent of assessor training or expertise. One such measure is the Child Behavior Checklist (CBCL), one of the best-studied psychometric measures of psychopathology in children (Achenbach 1991; Achenbach and Edelbrock 1983). The CBCL records, in standardized format, the behavioral problems and competencies of children aged 4 to 18, as reported by their parents or parent surrogates. It is scored on the recently revised social competence and behavior problem scales of the Child Behavior Profile. The scales were originally constructed from analyses of parent ratings of 2300 clinically referred children and normed on 1300 nonreferred children.

Four studies have used the CBCL to characterize children and adolescents with categorical clinical diagnoses of pediatric mania (Biederman et al 1995; Carlson and Kelly 1998; Geller et al 1998; Hazell et al 1999). The results from these reports have been strikingly consistent; all found that children satisfying diagnostic criteria for mania have a highly abnormal profile, which is consistent with structured diagnostic interview findings (Biederman et al 1995; Carlson and Kelly 1998; Geller et al 1998; Hazell et al 1999). Each study found significantly elevated *t* scores on the Aggressive Behavior subscale. Biederman et al, Geller et al, and Hazell et al found increased *t* scores on the Delinquent Behavior scale, and Biederman et al, Carlson and Kelly, and Hazell et al found increased *t* scores for the Thought Problems scale.

Although Carlson and Kelly (1998) did not find significant differences in the CBCL delinquent behavior scale in comparisons between hospitalized manic and ADHD children, the mean *t* score of this scale was clearly in the clinical range in both groups. Considering the empirical nature of the CBCL, the distinctly abnormal CBCL profiles in manic youth, as compared with those with ADHD, strongly suggest that psychopathologic correlates of pediatric mania are not a function of assessor bias. The correspondence between clinical diagnoses and content-congruent scales of the CBCL also suggest that it should be evaluated as a potential screening instrument for pediatric mania in referred children.

Comorbidity with Substance Use Disorders

An emerging literature suggests an extensive and bidirectional overlap between pediatric mania and substance use disorders (SUDs) in youth (Biederman et al 1997c; West et al 1996; Wilens et al 1997a). This literature also suggests that juvenile-onset mania may be a risk factor for SUD. For example, a prospective study of children and adolescents with and without ADHD found that early-onset mania was a risk factor for SUD independently of ADHD (Biederman et al 1997c). Similarly, controlled studies in adults show that mania is often an antecedent and is strongly associated with SUD (Wilens et al 1997b). Mania has also been shown to be overrepresented among youth with SUD. For example, Wilens et al (1997a) reported that psychiatrically referred adolescent outpatients with SUD were more likely than those without SUD to have comorbid mania, and West et al (1996) reported that 40% of inpatient adolescents with mania suffered from SUD.

Wilens et al (1999) found that mania significantly increased the risk for SUD independently of CD. Furthermore, they reported that the risk for SUD was carried by those subjects with an adolescent-onset form of mania. Whereas this may be consistent with the notion that, like adults, adolescents self-medicate manic symptoms with substances of abuse (Khantzian 1997), it is also consistent with the hypothesis that child- and adolescent-onset mania are etiologically distinct forms of the disorder with different risk profiles and natural courses.

Biederman et al (unpublished data) recently used the family study design to address the putative familial risk of SUD associated with bipolar and conduct disorder (in the same sample as Wozniak et al [unpublished data] described earlier). After CD was accounted for in probands, mania in probands remained a risk factor for SUDs in relatives, including both drug and alcohol addiction. Rather than concluding that the effects of CD or mania accounted for the relationship of the other with SUD, they reported results consistent with the idea that the effects of CD and mania on the risk for SUD were additive. Given this emerging literature on mood, conduct, and SUD, more work is needed to characterize the developmental relationship between substance use and mood dysregulation in adolescents. This is especially important given that substance abuse is frequently treatment refractory. It may be that the early identification and treatment of youth with mania could prevent the onset or complications of SUDs.

Pediatric Mania and Trauma

Although it has long been suspected that mania in children may be the result of trauma, and associations between trauma and mania have been reported in adults, there has been relatively limited systematic research of this issue. Kessler et al (1995) found elevated lifetime rates of mania among adult and adolescent subjects with posttraumatic stress disorder (PTSD). Helzer et al (1987) reported a strong association between manic–depressive illness and PTSD in adult subjects but did not determine if mania was primary or secondary to the trauma. This report further suggested that behavior problems including "stealing, lying, truancy, vandalism, running away, fighting, misbehavior at school, early sexual experience, substance abuse, school expulsion or suspension, academic underachievement, and delinquency" before age 15 predicted later PTSD (Helzer et al 1987). Not surprisingly, the authors concluded that "this association may mean that persons with such behavior in childhood had a greater likelihood of experiencing trauma later on."

Since juvenile mania is commonly associated with extreme violence and severe behavioral dysregulation (Wozniak et al 1995a) as well as hypersexuality, mania in children could either be a reaction to or a risk factor for trauma exposure. Using data from a longitudinal sample of boys with and without ADHD, Wozniak et al (1999) identified pediatric mania as an important antecedent for, rather than consequence of, traumatic life events. This temporal relationship between mania and traumatic events could have important clinical and therapeutic implications. When traumatized children present with severe irritability and mood lability, there may be a tendency by clinicians to attribute these symptoms to having experienced a trauma. To the contrary, longitudinal research suggests the opposite: mania may be an antecedent risk factor for later trauma and not represent a reaction to the trauma (Wozniak et al 1999).

Treatment Response

In a series of controlled clinical trials Campbell et al (Campbell et al 1984, 1995; Cueva et al 1996) documented the efficacy of mood stabilizers (lithium carbonate and carbamazepine) in the treatment of aggressive CD children; however, these psychiatrically hospitalized CD youth were treated for severe, uncontrollable, and disorganized aggression and not necessarily for delinquency. Thus, it is possible that the therapeutic benefits observed in these children with antimanic treatments could have been due to their antimanic effects in treating aggressive manic children satisfying criteria for CD.

Biederman et al (1998) systematically reviewed the clinical records of all pediatrically referred patients who at initial intake satisfied diagnostic criteria for mania based on a structured diagnostic interview with the mother. Mood stabilizers were frequently used in these children, and their use was associated with significant improvement of maniclike symptoms that their psychiatrists had recorded in the medical record. In contrast, antidepressants, typical antipsychotics, and stimulants were not associated with improvement of maniclike symptoms. For both lithium carbonate and for carbamazepine higher and more therapeutic doses predicted greater decreases in the maniclike symptoms recorded by the treating clinician in the medical record.

Although treatment with mood stabilizers was associated with a statistically significant decrease in maniclike symptoms, this improvement was slow to develop and was associated with frequent relapses. Although somewhat discouraging, these findings are consistent with outcome data from naturalistic follow-up studies of bipolar children and adults (Strober et al 1990, 1994). For example, the survival analysis from Biederman et al (1998) indicated that 65% of the children would improve if treated with lithium carbonate for 2 years. This finding is remarkably consistent with results from DeLong and Aldershof (1987), who reported a 66% response rate for manic children treated with lithium carbonate over a 10- to 70-month treatment period, and with findings reported by Strober et al (1994) showing that multiple relapses were most often seen in subjects with mixed mania.

More optimistic findings have resulted from investigations of atypical neuroleptics in the treatment of juveniles with bipolar disorder. In a retrospective chart review study of 28 youths with bipolar disorder, 82% of subjects showed improvement in both manic and aggressive symptoms with risperidone treatment (Frazier et al 1999b). In contrast to the duration of treatment required for improvement with mood stabilizers, the average time to optimal response was 1.9 ± 1.0 months of therapy. Moreover, no serious adverse effects were observed. Similarly encouraging results were reported by Frazier et al (1999a) in an open trial of olanzapine monotherapy. They found that treatment with olanzapine was associated with significant improvements in both the Children's Depression Inventory and the Young Mania Rating scale in 23 manic children after 8 weeks of monotherapy on doses ranging from 2.5 to 20 mg/day.

Similarly, Findling et al (2000) recently reported that risperidone was effective in treating aggression in children with CD. Although affective disorders were reported to have been excluded, it is unclear if this refers to the very rare "classic" episodes of mania or the atypical cases of pediatric mania that are more commonly comorbid with CD. Thus Findling and colleagues' (Findling et al 2000)

randomized clinic trial may provide replication of Frazier and colleagues' (1999a, 1999b) chart reviews and open trials rather than demonstrating an effect on CD per se. These initial encouraging results support the need for additional short- and long-term controlled trials of atypical neuroleptics in the treatment of juvenile bipolar disorder, either as monotherapy or in combination with mood stabilizers.

Summary

The explosive developments in the neurosciences, neurobiology, genetics, and neuroimaging will undoubtedly help advance the understanding of this complex and crippling disorder (Hyman 2000), particularly its relationship to ADHD, CD, and other psychotic and nonpsychotic neuropsychiatric disorders. It is hoped that such advances can shed light on the etiology and underlying pathophysiology, including the identification of dysfunctional brain circuits that may underlie pediatric mania. For example, an emerging literature on the subjects has identified genetic markers associated with bipolar features in children with velocardiofacial syndrome (Papolos et al 1996). More imaging research is needed to document the neuroanatomic underpinnings associated with pediatric mania. These scientific approaches can also be used in the identification of endophenotypes in unaffected relatives of youth with bipolar disorder.

The symptomatic overlap and co-occurrence of mania with ADHD has produced debate as to whether these children have ADHD, mania, or both. Despite this debate, many clinicians recognize that a substantial minority of children suffer from an extraordinarily severe form of psychopathology associated with extreme irritability, violence, and incapacitation that is highly suggestive of mania. Clarifying the diagnoses of these very ill children would have substantial clinical implications.

The emerging literature indicates that mania can be identified in a substantial number of referred children using systematic assessment methodology. Thus, this disorder may not be as rare as previously considered. Children with mania frequently demonstrate an atypical picture by adult standards, with a chronic course, severely irritable mood, and a mixed picture with depressive and manic symptoms co-occurring. Most children with childhood-onset mania may also have ADHD, which requires additional treatment. Initial clinical evidence suggests that atypical neuroleptics may play a unique therapeutic role in the management of such youth. The high levels of comorbidity with other disorders is common, further requiring the cautious use of a combined pharmacotherapy approach. More research is needed to build a scientific foundation for the notion that pediatric mania is a unique developmental subtype of bipolar disorder.

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References

Achenbach TM (1991): *Manual for the Child Behavior Checklist/4-18 and 1991 Profile.* Burlington: University of Vermont, Department of Psychiatry.

Achenbach TM, Edelbrock C (1983): *The Child Behavior Checklist.* Burlington: University Associates in Psychiatry.

Akiskal HS, Downs J, Jordan P (1985): Affective disorders in referred children and younger siblings of manic-depressives: Mode of onset and prospective course. *Arch Gen Psychiatry* 42:996–1003.

Angold A, Costello EJ (1993): Depressive comorbidity in children and adolescents: Empirical, theoretical and methodological issues. *Am J Psychiatry* 150:1779–1791.

Ballenger JC, Reus VI, Post RM (1982): The "atypical" picture of adolescent mania. *Am J Psychiatry* 139:602–606.

Biederman J (1998): Resolved: Mania is mistaken for ADHD in prepubertal children. Affirmative. *J Am Acad Child Adolesc Psychiatry* 37:1091–1093.

Biederman J, Faraone S, Hatch M, Mennin D, Taylor A, George P (1997a): Conduct disorder with and without mania in a referred sample of ADHD children. *J Affect Disord* 44:177–188.

Biederman J, Faraone SV, Chu MP, Wozniak J (1999): Further evidence of a bidirectional overlap between juvenile mania and conduct disorder in children. *J Am Acad Child Adolesc Psychiatry* 38:468–476.

Biederman J, Faraone SV, Marrs A, Moore P, Garcia J, Ablon JS, et al (1997b): Panic disorder and agoraphobia in consecutively referred children and adolescents. *J Am Acad Child Adolesc Psychiatry* 36:214–223.

Biederman J, Faraone SV, Mick E, Wozniak J, Chen L, Ouellette C, et al (1996): Attention deficit hyperactivity disorder and juvenile mania: An overlooked comorbidity? *J Am Acad Child Adolesc Psychiatry* 35:997–1008.

Biederman J, Mick E, Bostic J, Prince J, Daly J, Wilens T, et al (1998): The naturalistic course of pharmacologic treatment of children with manic-like symptoms: A systematic chart review. *J Clin Psychiatry* 59:628–637.

Biederman J, Wilens TE, Mick E, Faraone SV, Weber W, Curtis S, et al (1997c): Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry* 36:21–29.

Biederman J, Wozniak J, Kiely K, Ablon S, Faraone S, Mick E, et al (1995): CBCL clinical scales discriminate prepubertal children with structured-interview derived diagnosis of mania

from those with ADHD. *J Am Acad Child Adolesc Psychiatry* 34:464–471.

Borchardt CM, Bernstein GA (1995): Comorbid disorders in hospitalized bipolar adolescents compared with unipolar depressed adolescents. *Child Psychiatry Hum Dev* 26:11–18.

Bowen R, South M, Hawkes J (1994): Mood swings in patients with panic disorder. *Can J Psychiatry* 39:91–94.

Campbell M, Adams P, Small A, Kafantaris V, Silva R, Shell J, et al (1995): Lithium in hospitalized aggressive children with conduct disorder: A double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 34:445–453.

Campbell M, Small AM, Green WH, Jennings SJ, Perry R, Bennett WG, Anderson L (1984): Behavioral efficacy of haloperidol and lithium carbonate: A comparison in hospitalized aggressive children with conduct disorder. *Arch Gen Psychiatry* 41:650–656.

Carlson G, Kelly K (1998): Manic symptoms in psychiatrically hospitalized children—what do they mean? *J Affect Disord* 51:123–135.

Carlson GA (1983): Bipolar affective disorders in childhood and adolescence. In: Cantwell DP, Carlson GA, editors. *Affective Disorders in Childhood and Adolescence.* New York: Spectrum, 61–83.

Carlson GA (1984): Classification issues of bipolar disorders in childhood. *Psychiatr Dev* 2:273–285.

Carlson GA, Bromet EJ, Sievers S (2000): Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *Am J Psychiatry* 157:213–219.

Carlson GA, Jensen PS, Nottelmann ED (1998): Current issues in childhood bipolarity. *J Affect Disord* 51(2).

Chang KD, Steiner H, Ketter TA (2000): Psychiatric phenomenology of child and adolescetn bipolar offspring. *J Am Acad Child Adolesc Psychiatry* 39:453–460.

Chen Y, Dilsaver S (1995): Comorbidity of panic disorder in bipolar illness: Evidence from the epidemiologic catchment area survey. *Am J Psychiatry* 152:280–283.

Cueva J, Overall J, Small A, Armenteros J, Perry R, Campbell M (1996): Carbamazepine in aggressive children with conduct disorder: A double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 35:480–490.

Davis RE (1979): Manic-depressive variant syndrome of childhood: A preliminary report. *Am J Psychiatry* 136:702–706.

DeLong GR, Aldershof AL (1987): Long-term experience with lithium treatment in childhood: Correlation with clinical diagnosis. *J Am Acad Child Adolesc Psychiatry* 26:389–394.

DeLong GR, Nieman GW (1983): Lithium-induced behavior changes in children with symptoms suggesting manic-depressive illness. *Psychopharmacol Bull* 19:258–265.

Faedda G, Baldessarini R, Suppes T, Tondo L, Becker I, Lipschitz D (1995): Pediatric-onset bipolar disorder: A neglected clinical and public health problem. *Harvard Rev Psychiatry* 3:171–195.

Faraone SV, Biederman J, Mennin D, Russell RL (1998): Bipolar and antisocial disorders among relatives of ADHD children: Parsing familial subtypes of illness. *Neuropsychiatr Genet* 81:108–116.

Faraone SV, Biederman J, Monuteaux MC (in press): Attention deficit hyperactivity disorder with bipolar disorder in girls: Further evidence for a familial subtype? *J Affect Disord.*

Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D (1997): Is comorbidity with ADHD a marker for juvenile onset mania? *J Am Acad Child Adolesc Psychiatry* 36:1046–1055.

Faraone SV, Tsuang D, Tsuang MT (1999): *Genetics and Mental Disorders: A Guide for Students, Clinicians, and Researchers.* New York: Guilford.

Faraone SV, Tsuang MT (1995): Methods in psychiatric genetics. In: Tohen M, Tsuang MT, Zahner GEP, editors. *Textbook in Psychiatric Epidemiology.* New York: Wiley, 81–134.

Feinstein SC, Wolpert EA (1973): Juvenile manic-depressive illness: Clinical and therapeutic considerations. *J Am Acad Child Adolesc Psychiatry* 12:123–136.

Findling RL, McNamara NK, Branicky LA, Schluchter MD, Lemon E, Blumer JL (2000): A double-blind pilot study of risperidone in the treatment of conduct disorder. *J Am Acad Child Adolesc Psychiatry* 39:509–516.

Frazier J, Biederman J, Wilens T, Spencer T (1999a, October): Advanced issues in psychopharmacology: Psychotic disorders and bipolar disorders in children and adolescents. Presented at the 46th annual meeting of the American Academy of Child and Adolescent Psychiatry, Chicago.

Frazier JA, Meyer MC, Biederman J, Wozniak J, Wilens TE, Spencer TJ, et al (1999b): Risperidone treatment for juvenile bipolar disorder: A retrospective chart review. *J Am Acad Child Adolesc Psychiatry* 38:960–965.

Geller B, Fox L, Clark K (1994): Rate and predictors of prepubertal bipolarity during follow-up of 6-to 12-year-old depressed children. *J Am Acad Child Adolesc Psychiatry* 33:461–468.

Geller B, Luby J (1997): Child and adolescent bipolar disorder: A review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 36:1168–1176.

Geller B, Sun K, Zimmerman B, Luby J, Frazier J, Williams M (1995): Complex and rapid-cycling in bipolar children and adolescents: A preliminary study. *J Affect Disord* 34:259–268.

Geller B, Warner K, Williams M, Zimerman B (1998): Prepubertal and young adolescent bipolarity versus ADHD: Assessment and validity using the WASH-U-KSADS, CBCL and TRF. *J Affect Disord* 51:93–100.

Hazell P, Lewin T, Carr V (1999): Confirmation that Child Behavior Checklist clinical scales discriminate juvenile mania from attention deficit hyperactivity disorder. *J Paediatr Child Health* 35:199–203.

Helzer J, Robins L, McEvoy L (1987): Post-traumatic stress disorder in the general population. *N Engl J Med* 317:1630–1634.

Hyman SE (2000): The millennium of mind, brain, and behavior. *Arch Gen Psychiatry* 57:88–89.

Kessler R, Sonnega A, Bromet E, Hughes M, Nelson C (1995): Posttraumatic stress disorder in the national comorbidity survey. *Arch Gen Psychiatry* 52:1048–1060.

Khantzian E (1997): The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harvard Rev Psychiatry* 4:231–244.

Klein RG, Pine DS, Klein DF (1998): Resolved: Mania is mistaken for ADHD in prepubertal children. Negative. *J Am Acad Child Adolesc Psychiatry* 37:1093–1095.

Kovacs M, Pollock M (1995): Bipolar disorder and comorbid conduct disorder in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry* 34:715–723.

Kutcher SP, Marton P, Korenblum M (1989): Relationship between psychiatric illness and conduct disorder in adolescents. *Can J Psychiatry* 34:526–529.

McElroy SL, Keck J, Pope J, Hudson JI, Faedda G, Swann AC (1992): Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am J Psychiatry* 149:1633–1644.

McGlashan T (1988): Adolescent versus adult onset of mania. *Am J Psychiatry* 145:221–223.

Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT (1995): Attention Deficit Hyperactivity Disorder and comorbid disorders: Issues of overlapping symptoms. *Am J Psychiatry* 152:1793–1800.

Nottelmann ED (1995): Bipolar affective disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 34(6).

Papolos D, Gaedda G, Veit S, Goldbberg R, Morrow B, Kucherlapati R, Shprintzen R (1996): Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: Does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry* 153: 1541–1547.

Sachs GS, Baldassano CF, Truman CJ, Guille C (2000): Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. *Am J Psychiatry* 157:466–468.

Strober M (1992): Relevance of early age-of-onset in genetic studies of bipolar affective disorder. *J Am Acad Child Adolesc Psychiatry* 31:606–610.

Strober M, Carlson G (1982): Bipolar illness in adolescents with major depression: Clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. *Arch Gen Psychiatry* 39:549–555.

Strober M, Morrell W, Burroughs J, Lampert C, Danforth H, Freeman R (1988): A family study of bipolar I disorder in adolescence: Early onset of symptoms linked to increased familial loading and lithium resistance. *J Affect Disord* 15:255–268.

Strober M, Morrell W, Lampert C, Burroughs J (1990): Relapse following discontinuation of lithium maintenance therapy in adolescents with bipolar I illness: A naturalistic study. *Am J Psychiatry* 147:457–461.

Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M (1994): Recovery and relapse in adolecents with bipolar affective illness: A five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry* 34:724–731.

Todd R, Neuman R, Geller B, Fox L, Hickok J (1993): Genetic studies of affective disorders: Should we be starting with childhood onset probands? *J Am Acad Child Adolesc Psychiatry* 32:1164–1171.

Weinberg WA, Brumback RA (1976): Mania in childhood. *Am J Dis Child* 130:380–385.

Weller E, Weller R, Fristad M (1995): Bipolar disorder in children: Misdiagnosis, underdiagnosis, and future directions. *J Am Acad Child Adolesc Psychiatry* 34:709–714.

Weller RA, Weller EB, Tucker SG, Fristad MA (1986): Mania in prepubertal children: Has it been underdiagnosed? *J Affect Disord* 11:151–154.

West S, McElroy S, Strakowski S, Keck P, McConville B (1995): Attention deficit hyperactivity disorder in adolescent mania. *Am J Psychiatry* 152:271–274.

West SA, Strakowski SM, Sax KW, McElroy SL, Keck PE, McConville BJ (1996): Phenomenology and comorbidity of adolescents hospitalized for the treatment of acute mania. *Biol Psychiatry* 39:458–460.

Wicki W, Angst J (1991): The Zurich study. X. Hypomania in a 28- to 30-year-old cohort. *Eur Arch Psychiatry Clin Neurosci* 240:339–348.

Wilens T, Biederman J, Abrantes AM, Spencer TJ (1997a): Clinical characteristics of psychiatrically referred adolescent outpatients with substance use disorder. *J Am Acad Child Adolesc Psychiatry* 36:941–947.

Wilens T, Biederman J, Millstein R, Wozniak J, Hahsey A, Spencer T (1999): Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 36:680–685.

Wilens TE, Biederman J, Mick E, Faraone SV, Spencer T (1997b): Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance use disorders. *J Nerv Ment Dis* 185:475–482.

Wozniak J, Biederman J, Kiely K, Ablon S, Faraone S, Mundy E, Mennin D (1995a): Mania-like symptoms suggestive of childhood onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 34:867–876.

Wozniak J, Biederman J, Mundy E, Mennin D, Faraone SV (1995b): A pilot family study of childhood-onset mania. *J Am Acad Child Adolesc Psychiatry* 34:1577–1583.

Wozniak J, Crawford M, Biederman J, Faraone S, Spencer T, Taylor A, Blier H (1999): Antecedents and complications of trauma in boys with ADHD: Findings from a longitudinal study. *J Am Acad Child Adolesc Psychiatry* 38:48–55.

Young L, Cooke R, Robb J, Levitt A, Joffe R (1993): Anxious and non-anxious bipolar disorder. *J Affect Disord* 29:49–52.