Current concepts in the validity, diagnosis and treatment of paediatric bipolar disorder

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Abstract

Despite ongoing controversy, the view that paediatric bipolar disorder is rare or non-existent has been increasingly challenged not only by case reports but also by systematic research. This research strongly suggests that paediatric bipolar disorder may not be rare but that it may be difficult to diagnose. Since children with bipolar disorder are likely to become adults with bipolar disorder, the recognition and characterization of childhood-onset bipolar disorder may help identify a meaningful developmental subtype of bipolar disorder worthy of further investigation. As recommended by Robins and Guze [American Journal of Psychiatry (1970), 126, 983–987], a psychiatric disorder may be considered a valid diagnostic entity if it can be shown to have differentiating features, evidence of familiality, specific treatment responsivity and a unique course. The goal of this article is to review our work and the extant literature within this framework to describe the evidence supporting bipolar disorder in children as a valid clinical diagnosis.

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Introduction

Despite continued debate and controversy over the diagnosis of bipolar disorder in children (Biederman, 1998; Klein et al., 1998), exhaustive reviews support the existence of the disorder in youth (Faedda et al., 1995; Geller and Luby, 1997; Weller et al., 1995). Yet, lingering concerns remain as to its validity. As recommended by Robins and Guze (1970), a psychiatric disorder may be considered a valid diagnostic entity if it can be shown to have differentiating features, evidence of familiality, specific treatment responsivity and a unique course. Considering that the controversy surrounding this disorder and diagnostic nihilism inhibits the study and treatment of these children, application of these criteria to this condition is sorely needed. The purpose of this review is to summarize our programme of research and the research of others within this framework in order to document what is known regarding bipolar disorder in children.

Historical overview

Over the last two decades, the view that bipolar disorder in children is extremely rare or non-existent 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 bipolar disorder and responsive to lithium carbonate. Carlson (1984) suggested that prepubertal bipolar disorder 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 bipolar disorder, 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 ad 1982 and identified 157 cases which would probably 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 paediatric bipolar disorder may not be rare, but difficult to diagnose.
Differentiating features

**Atypical clinical presentation**

The atypicality (by adult standards) of the clinical picture of childhood bipolar disorder has long been recognized (Davis, 1979; Weinberg and Brumbach, 1976). Notably, the literature consistently shows that bipolar disorder 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 severe, persistent, and often violent (Wozniak et al., 1995a). The outbursts often include threatening or attacking behaviour 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. 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 paediatric bipolar disorder, its natural course is also atypical compared with the natural course of adult bipolar disorder. The course of paediatric bipolar disorder 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 yr of research on paediatric bipolar disorder, Geller and Luby (1997) concluded that childhood-onset bipolar disorder is a non-episodic, 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 bipolar disorder on structured diagnostic interview, presented with chronic, and mixed presentation. Carlson et al. (2000) reported that early-onset manics were more likely to have comorbid behaviour disorders in children and to have fewer episodes of remission of a 2-yr period than were adult onset cases of bipolar disorder. Thus, paediatric bipolar disorder 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, bi-phasic, and episodic course.

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

While the adult course of paediatric bipolar disorder 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 bipolar disorder. 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 neuropsychological 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 paediatric bipolar disorder. These findings suggest that paediatric cases with bipolar disorder 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 bipolar disorder is its symptomatic overlap with ADHD. Systematic studies of children and adolescents show that rates of ADHD range from 60 to 90% in paediatric patients with bipolar disorder (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 bipolar disorder is universally high, the age at onset modifies the risk for comorbid ADHD. For example, while Wozniak (1995a) found that 90% of children with bipolar disorder also
had ADHD, West et al. (1995), reported that only 57% of adolescents with bipolar disorder were comorbid with ADHD. Examining further developmental aspects of paediatric bipolar disorder, Faraone et al. (1997b) found that adolescents with childhood-onset bipolar disorder had the same rates of comorbid ADHD as manic children (90%) and that both these groups had higher rates of ADHD than adolescents with adolescent-onset bipolar disorder (60%). Furthermore, 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 age 19 yr. The mean onset of bipolar disorder in those with a history of childhood ADHD was 12.1 yr (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 onset of bipolar disorder in adults with bipolar disorder and a history of ADHD was 11.3 yr. These findings suggested that age of onset of bipolar disorder, rather than chronological age at presentation, may be the critical developmental variable that identifies a highly virulent form of the disorder that is heavily comorbid with ADHD.

One problem facing studies of ADHD and bipolar disorder 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 bipolar disorder, two different techniques of correcting for overlapping diagnostic criteria have been used to evaluate the association between ADHD and paediatric bipolar disorder (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 as that required for the original diagnosis (Milberger et al., 1995). Using these methods, Biederman et al. (1996) showed that 48% of children with bipolar disorder continued to meet criteria by the subtraction method and 69% by the proportion method. A total of 89% of children with bipolar disorder 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 paediatric bipolar disorder is not a methodological artifact due to diagnostic criteria shared by the two disorders.

The potential for different rates of comorbidity with bipolar disorder in the combined-subtype, inattentive-subtype and hyperactive-impulsive-subtype of ADHD requires further research. Faraone et al. (1998a) studied 301 ADHD children and adolescents consecutively referred to a paediatric 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 conduct disorder (CD)**

Like ADHD, CD is also strongly associated with paediatric bipolar disorder. This has been seen separately in studies of children with CD, ADHD and bipolar disorder. Wozniak et al. (1995a) reported that preadolescent children satisfying structured interview criteria for bipolar disorder 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 bipolar disorder. Similar findings were reported by Kutcher et al. (1989) who found that 42% of hospitalized youths with bipolar disorder had comorbid CD. The Zurich longitudinal study, found that hypomanic cases had more disciplinary difficulties at school and 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 bipolar disorder (Geller et al., 1994; Strober and Carlson, 1982).

Biederman et al. (1997, 1999) investigated the overlap between bipolar disorder 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 in the features of bipolar disorder regardless of comorbid CD. Additionally, the age at onset of bipolar disorder was similar in subjects with or without comorbid CD. In both groups, mania presented with a predominantly irritable mood, 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 bipolar disorder with CD group compared to the bipolar disorder-only group. Similarly, there were few differences in the frequency of CD symptoms between CD youth with and without comorbid bipolar disorder.
Although children with CD and bipolar disorder had a higher rate of ‘vandalizing’ compared to CD-only subjects, this difference was not statistically significant.

Both the comorbid and non-comorbid subjects with mania had high rates of major depression, anxiety disorders, oppositional disorder, and psychosis than CD and ADHD children (Biederman et al., 1997, 1999). In addition bipolar disorder comorbid with CD was associated with poorer functioning and an increased risk for psychiatric hospitalization (Biederman et al., 1997). Subjects with both CD and bipolar disorder 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., 1998b).

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

Paediatric bipolar disorder and trauma
Although it has been long suspected that bipolar disorder in children may be the result of trauma and associations between trauma and bipolar disorder have been reported in adults, there has been relatively limited systematic research of this issue. Kessler et al. (1995) found elevated lifetime rates of bipolar disorder among adult and adolescent subjects with post-traumatic 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 bipolar disorder was primary or secondary to the trauma. This report further suggested that behavioural problems including ‘stealing, lying, truancy, vandalism, running away, fighting, misbehaviour at school, early sexual experience, substance abuse, school expulsion or suspension, academic underachievement, and delinquency’ prior to age 15 yr predicted later PTSD (Helzer et al., 1987). Not surprisingly, the authors concluded that ‘this association may mean that persons with such behaviour in childhood had a greater likelihood of experiencing trauma later on’.

Since juvenile bipolar disorder is commonly associated with extreme violence and severe behavioural dysregulation (Wozniak et al., 1995a), as well as hyper-sexuality, bipolar disorder 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 paediatric bipolar disorder as an important antecedent for, rather than consequence of, traumatic life events. This temporal relationship between bipolar disorder 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. Longitudinal research, however, suggests the opposite; bipolar disorder may be an antecedent risk factor for later trauma and not represent a reaction to the trauma (Wozniak et al., 1999).

Familial aggregation
Although there are no twin or adoption studies of paediatric bipolar disorder, family studies strongly suggest that the paediatric onset form of the disorder has a strong familial component (Faraone et al., 1997a; Strober, 1992; Strober et al., 1988; Todd et al., 1996; Wozniak et al., 1995b). Strober (1992), Strober et al. (1988) and Todd et al. (1993) proposed that paediatric bipolar disorder might be a distinct subtype of bipolar disorder with a high familial loading. In examining the comorbidity between bipolar disorder in children and ADHD or CD, we have reported on the familiality of bipolar disorder in families ascertained via child probands (Faraone et al., 1997a, 2001; Wozniak et al., 1995b).

We first examined the familiality of bipolar disorder in children in a pilot sample of 16 families ascertained via a child proband with the disorder (Wozniak et al., 1995b). We compared the relatives of manic children to the relatives of ADHD children without bipolar disorder and to normal controls. Among the 46 first-degree relatives of 16 children with bipolar disorder, 13% (n = 6) met criteria for bipolar disorder with associated impairment. This differed significantly from both the ADHD (2%; n = 7) and normal control (3%; n = 7) groups. The relatives of ADHD and control probands did not differ in their risk for bipolar disorder. Almost identical findings were obtained in two independently defined family studies of ADHD probands with and without comorbid bipolar disorder (Faraone et al., 1998b, 2001). In a sample of boys with ADHD and their relatives, we found an increased family risk of bipolar disorder in children with bipolar disorder (16%) compared to relatives of non-maniac children (3%). Likewise, among families ascertained via girls with ADHD the rate of bipolar disorder in relatives of ADHD girls with comorbid bipolar
disorder was significantly greater (13%) than either ADHD girls without bipolar disorder (5%) or in the relatives of normal control girls (3%) (Faraone et al., 2001).

From these three studies, we estimate that the rate of bipolar disorder in relatives of manic children was 2.6–5.3 times higher than in non-manic children. Thus, the evidence from these samples clearly indicates that the disorder may be highly familial.

**Longitudinal course**

Recently, Geller et al. (2002) reported on the 2-yr outcome of a longitudinal sample of children with paediatric bipolar disorder. This study found that by the last follow-up period 65% of subjects recovered from bipolar disorder but that 55% relapsed after recovery. However, since this study focused exclusively on full syndromatic persistence of manic symptomatology, it did not address the possibility of continued affective instability in the form of sub-syndromal symptoms of the disorder and its associated impairments.

We recently estimated the course of bipolar disorder in children with ADHD over a period covering 10 yr (J. Biederman et al., unpublished observations) with different forms of persistence. As recently proposed by Keck et al. (1998) the distinction between different types of remission may clarify components of complex recovery processes. These investigators suggested three levels of remission for psychiatric disorders: syndromatic, symptomatic and functional. Symptomatic remission refers to the loss of full diagnostic status; symptomatic remission refers to the loss of partial diagnostic status; functional remission refers to the loss of partial diagnostic status plus functional recovery (full recovery). For bipolar disorder, another critical dimension in assessing patterns of remission is the persistence of depressive symptomatology since some subjects may remit from mania but may continue to manifest depression. Thus, Euthymia was defined by failing to meet criteria for manic episode or for major depressive episode at follow-up.

We found that the course of bipolar disorder was chronic, protracted, and dysfunctional. Although 50% of bipolar youth remitted from the full syndrome of bipolar disorder at follow up (i.e. they no longer met full diagnostic criteria), 80% failed to attain functional remission or euthymia over a course of 10 yr. Our results were in line with those of Geller et al. (2002) who reported that 65% of a sample of 89 subjects with prepubertal onset bipolar disorder had recovered by the 2-yr follow-up assessment, but that 55% reported a relapse during the same interval. Thus, at the 2-yr follow up, only 29% (the 45% of the recovered 65% that did not relapse) of the original sample would be considered in remission, overall. In our study, the definition of remission that most closely replicates what Geller et al. (2002) studied was syndromatic remission that we estimated to be 27% at 2 yr.

While the literature examining the long-term follow-up of children with bipolar disorder is scant it documents that the disorder is not transient. Even the most optimistic definition of remission (syndromatic remission), was attained by only 30% of subjects over a 2-yr period. That less than 20% of subjects attained functional remission or euthymia over the entire time-period evaluated provides further evidence that paediatric bipolar disorder is a chronic mood disorder with a poor prognosis.

**Treatment response**

In a series of controlled clinical trials Campbell and colleagues (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 anti-manic treatments could have been due to the anti-manic effects in treating aggressive manic children satisfying criteria for CD.

Biederman et al. (1998) systematically reviewed the clinical records of all paediatrically referred patients who, at initial intake satisfied diagnostic criteria for bipolar disorder 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 manic-like symptoms that their psychiatrists had recorded in the medical record. In contrast, antidepressants, typical antipsychotics, and stimulants were not associated with improvement of manic-like symptoms. For both lithium carbonate and carbamazepine higher and more therapeutic doses predicted greater decreases in the manic-like symptoms recorded by the treating clinician in the medical record.

Although treatment with mood stabilizers was associated with a statistically significant decrease in manic-like 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.
in this area is sorely needed and will be forthcoming associated with atypical neuroleptics. More research estimate the side-effects or adverse events that may be necessary to determine the true treatment effect and to controlled randomized clinical trials. Large studies are finding in the literature at this stage is the lack of stabilizers.

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 wk of monotherapy on doses ranging from 2.5 to 20 mg/d.

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 bipolar disorder or the atypical cases of paediatric bipolar disorder that are more commonly comorbid with CD. Thus the randomized clinic trial of Findling et al. (2000) may provide replication of the chart reviews and open trials of Frazier et al. (1999a,b) 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.

While there is converging evidence from open trials and clinical chart reviews, perhaps the most striking finding in the literature at this stage is the lack of controlled randomized clinical trials. Large studies are necessary to determine the true treatment effect and to estimate the side-effects or adverse events that may be associated with atypical neuroleptics. More research in this area is sorely needed and will be forthcoming once issues surrounding the validity of bipolar disorder in children are adequately addressed.

Summary

The emerging literature indicates that bipolar disorder 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 bipolar disorder 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, and increased risk to relatives. Initial clinical evidence suggests that atypical neuroleptics may play a unique therapeutic role in the management of such youth. The high level 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 paediatric bipolar disorder is a valid developmental subtype of bipolar disorder. With this foundation and continued pilot research of promising psychopharmacological interventions, the field will be able to ethically conduct large-scale, randomized clinical trials and, only then, will proven treatment options emerge.

References


