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Clinical Child Psychology and Psychiatry 2000: 5; 595
DOI: 10.1177/1359104500005004012

The online version of this article can be found at:
http://ccp.sagepub.com/cgi/content/abstract/5/4/595
Early-Onset Bipolar Disorder and ADHD:
Diagnostic Confusion Due to Co-morbidity?

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ABSTRACT
Bipolar disorder in children is more common than has been acknowledged previously. However, the clinical presentation, particularly when of early onset, is more often atypical, co-morbid with other conditions and lacking in discrete episodes compared with adult-onset illness. This article reviews the literature on pre-pubertal bipolar disorder, particularly when co-morbid with ADHD, using a MEDLINE search and other sources. Four clinical cases are presented highlighting some of the diagnostic dilemmas associated with co-morbidity.

KEYWORDS
ADHD, co-morbidity, early onset bipolar disorder

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Background

Bipolar disorder in children, especially pre-pubertal, has attracted only recent attention in the research literature although there are case reports in the literature dating back to 1845 describing mania in pre-pubertal children (Esquirol, 1845). In adults, bipolar disorder is characterized by repeated cycles of disturbance in patient's mood and level of activity. The 'manic' or 'hypomanic' phase is associated with elated and grandiose mood and increased activity and energy levels, while the 'depressed' phase is associated with lowering of mood and activity level. Episodes are usually discrete with full recovery in between. While this description is typical of adult presentation, it does not accurately describe the presentation in childhood and early adolescence.

There are only two syndrome-specific symptoms, that of 'euphoria' and 'grandiosity' and both of these are recognized to be relatively rare in children (Carlson, 1999). Both may well be symptoms along a dimension and the difficulty arises in trying to decide on the cut-off between normal and abnormal features and what is developmentally appropriate, especially in the younger child. Given the diagnostic salience placed on the episodic nature of a bipolar disorder, it becomes important to define what is regarded as an episode. The clear pattern of onset and offset lasting one week is easy to identify but should we also consider as an episode a pattern lasting a couple of hours or a couple of days? Even with adult criteria it is recognized that between 20 and 40% of patients are not in fact episodic and do not revert to improved functioning in between episodes.

In the DSM-IV criteria pertaining to children, there is recognition that children may present more often with irritability rather than elated mood and that grandiosity is also infrequent (American Psychiatric Association, 1994). A duration of one week is required for a manic episode and four days for a hypomanic episode. Similarly, the duration for major depressive disorder is two weeks and one week for a mixed depressive and manic diagnosis. Children presenting in the pre-pubertal age group may more often have a first episode of the major depressive type; their episodic type may be cycling rapidly (occurring more frequently) with little improved functioning in between. There is often associated aggression, hyperactivity, a greater familial loading and a higher proportion of males. These children are often refractory to lithium treatment (Table 1).

Reviewing the literature, Carlson (1983) identifies a difference of presentation based on age. Before the age of nine children present with a predominant mood of irritability and emotional lability, while presentations after age nine are associated with euphoria, elation, paranoia and grandiose ideation. It is difficult to identify a discrete episode and children often present with a worsening of sleeping difficulties, impulsivity, overactivity, inattention and a reduced frustration tolerance or explosive angry outbursts. Geller and Luby (1997) have also reported this in a review of the last 10 years.

The problem of co-morbidity

The other diagnostic difficulty in pre-pubertal children is the fact that early-onset bipolar disorder shares symptoms with a number of other conditions and may be co-morbid with other disorders including attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), anxiety, depressive disorders and learning disabilities. ADHD is a heterogeneous behavioural disorder characterized by overactivity, impulsivity and inattention. In addition, hyperkinetic children may also present with social disinhibition, irritability and emotional lability, symptoms which are characteristic of bipolar disorder leading to diagnostic confusion and the possibility of an artefactually increased co-morbidity.

Rates of reported co-morbidity of ADHD range from 57 to 98% in bipolar patients.
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Table 1. DSM-IV diagnostic criteria

**Manic episode**
- Duration one week
- Mood elated/irritable
- Three of: [grandiosity, reduced sleep, talkativeness, flight of ideas, distractibility, foolish behaviours]
- Not a mixed manic/depressed state
- Associated with impairment
- Not organic

**Hypomanic**
- Duration four days
- Three of [the above symptoms], four if mood irritable
- Uncharacteristic and observable by others
- Some impairment

**Major depressive disorder**
- Duration two weeks
- Discrete episode associated with impairment
- Depressed mood or loss of interest/pleasure
- Five of [depressed mood, loss of interest, weight loss, disturbed sleep, psychomotor retardation or agitation, fatigue, worthlessness, poor concentration, futility feelings]
- Not organic

**Mixed state**
- One week of manic and depressive symptoms with impairment

**Dysthymia**
- Duration > one year with no period of greater than two months symptom free

** Cyclothymia**
- Duration > one year, with hypomanic and depressive episodes, with no period of greater than two months symptom free

**Rapid cycling**
- At least four episodes of mood disturbance in the previous 12 months, partial or full remission in between two months or a switch to an episode of opposite polarity

(Borchardt & Bernstein, 1995; Geller et al., 1995; Wozniak et al., 1995), while rates of 11–22% have been cited for bipolar disorder in children with ADHD (children and adolescents) (Biederman et al., 1996; Butler, A rendondo, & McCloskey, 1995). However, when certain overlapping symptoms were removed (hyperactivity, over-talkativeness and distractibility) from the Biederman sample, only 47% of the children previously identified as having both disorders met the diagnostic criteria for bipolar disorder, thus highlighting the risk of inadvertently increasing rates of co-morbidity.

**What is the nature of the relationship between ADHD and bipolar disorder?**

The Harvard group (Faraone, Biederman, Mennin, Wozniak, & Spencer, 1997) looked at the transmission of co-morbid disorders in families and presented data suggesting that co-morbid ADHD and bipolar disorder is ‘familiarily distinct from other forms of ADHD’. In a sample of 140 children with ADHD, they found that there was an increased risk of bipolar disorder (five times) and severe depression in their relatives, compared with controls. Both ADHD and bipolar disorder occurred in the same relatives more often than expected by chance alone. ADHD co-morbid with bipolar disorder cannot be viewed as simply a severe form of ADHD as the combination conferred no additional risk of ADHD to their relatives. The limitations of this study, however, include the small sample that had co-morbid disorder (N = 15) and diagnosis based on parental interview alone, and the authors suggest that larger samples with co-morbid disorders are required to study the family genetics further. Other researchers have also found an increased risk...
of ADHD in children of bipolar parents compared with controls (Grigoroiu-Serbanescu et al., 1989; Zahn-Waxler et al., 1988). Geller and others have suggested that both ADHD and conduct disorder may be viewed as a forme fruste of prepubertal-onset bipolar disorder (Geller & Luby, 1997; Kovacs & Pollock, 1995).

Klein et al. expressed reservations regarding the Harvard group findings and these are presented eloquently in a debate forum (Biederman, Klein, Pine, & Klein, 1998), and conclude that bipolar disorder does not masquerade as ADHD. They express reservations about the methodology of the study, clinical sample and course. In particular, they argue that the atypical clinical course as described by Biederman et al. does not meet with the DSM-IV classification due to the non-episodic nature of the children’s illness. However, this atypical presentation in children has been well documented by others (Carlson, 1983; Geller & Luby, 1997). The finding that the very high rate of bipolar disorder in children with ADHD (16%) reported by the Biederman group decreased to 2% when certain overlapping symptoms were removed, i.e. overactivity, talkativeness and distractibility, is put forward by Klein et al. as evidence that ADHD was mistaken for mania on many occasions (Biederman et al., 1998). However, even a baseline rate of 2% in children with ADHD is significant and given the large number of children now being assessed for ADHD it is important to remain alert to this possibility.

Why is recognizing co-morbidity important?
While it is important to avoid symptoms that are overlapping between diagnoses, we do not yet know enough about early pre-pubertal bipolar disorder to discount them as prominent symptoms. It would seem prudent to consider both possible diagnoses because of the important predictive value of making a diagnosis and in considering maintenance treatment that will differ between disorders. Treatment of one disorder may adversely affect the course of the other; for example, treatment with stimulants may worsen the course of the bipolar illness (Koehler-Troy, Strober, & Malenbaum, 1986). The presence of co-morbidity may delineate homogenous subgroups with different aetiological and modifying risk factors, different treatment responses and outcomes.

Problems of diagnosing co-morbidity
Attempts have been made in the past by clinicians to create diagnostic criteria specific for children primarily by extrapolating from the adult literature (Anthony & Scott, 1960; Weinberg & Brumback, 1976). However, there are reasons for doubting the validity of such extrapolation because the clinical picture in childhood may be very different from that in adulthood, early presentation may represent a more severe form of disorder, have a greater effect on development, have a higher genetic loading and a different neurobiological basis. Developmental factors may mediate the presentation of symptoms and adversely affect outcome by interfering with the mastery of important developmental tasks.

To date, there does not exist a consensus between clinicians as to the clinical presentation, making it difficult to disentangle core symptoms of early-onset bipolar disorder from symptoms associated with co-morbid conditions. It may be that in the absence of definitive diagnostic criteria the best we can do is clearly document the clinical presentation and make diagnoses which are viewed as working hypotheses and are reviewed on a regular basis as additional clinical material comes to light. The importance of a positive family history cannot be underestimated and its responsiveness to various medication may guide medication choice in the child. Ultimately, we need to be guided by clinical factors, carefully considering the balance between possible prevention and adverse side-effects from the medication used. Biederman, Klein and colleagues, and
others eloquently debated the pitfalls of misdiagnosis and co-morbidity (Biederman et al., 1998). Such clinical debates are to be welcomed and will keep these diagnostic issues to the fore.

In this article we present a series of four cases in which the diagnosis of ADHD was well established but the children, in addition, developed co-morbid bipolar disorder. This highlights the need to be alert to diagnostic co-morbidity, which arises during the course of managing childhood disorders of behaviour.

**Case 1**

**Background**
JA is a 15-year-old boy with a history from age two of overactive, impulsive and reckless behaviour. By age three his attentional difficulties along with his inability to remain seated and follow nursery routines were noted. From a similar age, he was noted by his mother and aunt to have a significant mood component and was described by his aunt as a ‘Jekyll and Hyde’ personality, alternating between being very polite, approachable and sociable and at other times being very aggressive, irritable and spiteful. These moods continued until his first prolonged depressive episode at the age of 12 lasting three weeks. This consisted of anhedonia, worthlessness, self-injury and constant ruminations about various misdemeanours. A round this time school reports made reference to ‘cycles of behaviour’ documenting good periods lasting a couple of days and observing significant behavioural outbursts being preceded by prodromal irritable periods. At the age of 14 he had three episodes in which he described auditory hallucinations, a male voice instructing him to act in an aggressive and antisocial fashion. He himself reported a number of occasions on which he felt unusually happy, felt very generous and donated many of his possessions, but this mood was not observed by either his residential school or his parents.

**Family history**
There was a significant family history on the paternal side, his father having volatile mood swings, alcohol dependence and a similar history in his uncle, aunt and paternal grandfather.

**Diagnosis**
The diagnosis of ADHD plus major depressive disorder was made and further monitoring was needed to out rule the possibility of a bipolar disorder type II.

**Review**
Upon review some three months later his predominant mood was depressed and he was commenced on an antidepressant medication (Fluoxetine 20 mg). He appeared to respond favourably to this but some four months later an urgent referral was made from his residential school documenting bizarre behaviour, staying up very late at night, being over-talkative, overactive and talking to himself. A diagnosis of drug-induced mania was made and his medication was switched to carbamazepine 100 mg b.d. He remained well for almost one year and re-presented with a two to three-week history of depression that is currently being treated with sertraline 75 mg nocte and carbamazepine 100 mg b.d. His main complaint of inattention and impulsivity persist despite improved mood.

**Clinical issue**
Treatment of his ADHD symptoms in addition to his mood disorder.
Case 2

Background
SB is an 11-year-old girl referred due to behavioural problems at school and volatile mood swings. Her history supported a diagnosis of ADHD with significant attentional problems at school and at clubs, in addition to marked impulsivity and overactivity. She had been described by her mother as a ‘moody’ child, being nice and sociable within the family at times and at other times being disinterested, withdrawn and deliberately provocative, particularly to her younger brother. SB was commenced on imipramine 50 mg (for the treatment of her ADHD symptoms) to good effect. One year later she developed a depressive episode experiencing self-neglect, withdrawal, anhedonia, futility feelings and angry outbursts. Her medication was increased to 100 mg imipramine and this precipitated cycles of two to three days of hypomania interspersed with depression. Carbamazepine was added gradually, increasing to 300 mg b.d. and her antidepressants discontinued.

Family history
There was a family history of ADHD and depression, responsive to imipramine in her mother, a history suggestive of bipolar disorder in her maternal grandmother and a family history of tics.

Diagnosis
A diagnosis of ADHD co-morbid with bipolar disorder type II was made.

Review
A year after she presented with her second depressive episode which was responsive to sertraline 100 mg. Despite many attempts, it was not possible to ask S or her mother to keep a consistent diary as both suffered from significant disorganization and forgetfulness. She remained well on her antidepressants over a five-month period, which was also noted at school, but made a request to discontinue them. With reluctance, her antidepressant medication was stopped and she remained on carbamazepine. Upon review, nine months later, although she was not depressed her mood had certainly become more labile. However, her prominent symptom at that time was concentration difficulties and the need for a medication specifically addressing her ADHD. Methylphenidate (10 mg t.d.s.) was added successfully to treat her attentional problems. Three months later her depression returned, which did not respond to a lowering of her methylphenidate, and sertraline was once again added to her medication regime (50 mg nocte). At three months follow-up she remains well, euthymic and with an improved attentional span.

Clinical issue
Clinically indicated polypharmacy with carbamazepine, methylphenidate and sertraline, its effectiveness and safety, and the difficulty in gathering a detailed history from parent and child.

Case 3

Background
HC is a 13-year-old boy diagnosed with ADHD at the age of eight (symptoms of overactivity, attention difficulties and defiance from age three) and treated successfully with methylphenidate 10 mg bd. On account of increasingly poor adherence to daytime dosage, he was started on clonidine but this had to be discontinued on account of the...
adverse side-effect of depression. Over periods of review it was noted that he had always had a significant mood component where his mood would oscillate between quite high, overactive, tending to sleep less and on other occasions being low in mood, fed up and experiencing futility feelings and anhedonia. Although less specific, the school also documented various crisis points during his schooling but they were unable to attribute these to any mood swings. An attempt was made to document his moods by asking, both mother, HC and the school but this proved impossible.

Family history
There was a family history of rapid cycling, treatment-resistant, bipolar disorder type I in his mother.

Diagnosis
It was difficult to get a history of discrete episodes and therefore the working diagnosis was co-morbid ADHD and cyclothymia.

Review
A trial of sodium valproate was started (as his mother was partially responsive to this) gradually reaching 400 mg b.d. which proved to have a good effect on his mood as noted by both HC and his mother. Methylphenidate was continued on account of his significant attentional difficulties. Adherence to medication became a significant problem and by February 1999 all medication was stopped with a significant deterioration of ADHD symptoms but also the possibility of a hypomanic episode. Despite being aged 13, HC was unable to clarify what his predominant mood was and admitted to fleeting feelings of depression but also feeling quite good, which would occur on many occasions throughout one day. At interview he was clearly overactive, very restless, appeared to have pressure of speech but no flight of ideas.

Clinical issue
The difficulty in gathering a detailed history from parent and child and adherence to medication.

Case 4

Background
JD is a nine-year-old boy referred at age six to consider a diagnosis of ADHD. He was temperamentally difficult and demanding with marked irritability and hyperactivity from age one, and subsequent destructive play and severe behavioural outbursts. These difficulties, in addition to poor concentration and compliance, led to him being excluded from nursery at the age of two and a half.

At the time of presentation J merited a diagnosis of ADHD and oppositional defiant disorder (ODD). Methylphenidate and clonidine both produced a deterioration in behaviour. By age eight, mood variability became more prominent and J had a cyclical pattern of days of relative calm interspersed with days (four to five) of temper outbursts, low frustration tolerance, inappropriate giggling and sleep difficulties. He also experienced days (four to five) on which his predominant mood was low.

Family history
JD's mother developed postnatal depression on top of existing cycles of depression and hypomania. There was a family history in his maternal aunt and grandfather of lithium
responsive bipolar disorder, and depression in a maternal granduncle. One family member had a psychotic depression and another had committed suicide.

Diagnosis
A diagnosis of bipolar disorder co-morbid with ADHD and ODD was considered.

Review
Carbamazepine was started gradually (up to 300 mg b.d.) but JD became significantly depressed with behavioural outbursts leading to hospital admission and the addition of sertraline. This combination had a significant effect on both his ADHD symptoms and his mood severity and frequency.

Clinical issue
Long-term treatment.

Discussion
Each of the clinical cases presented had a diagnosis of ADHD that appeared to have been well substantiated, both from history and school reports, and had been present from a very early age (before age five). However, all four cases had evidence of a significant mood component from an early age, albeit very difficult to define ('moody, lability of mood, severe temper outbursts, erratic moods'). These descriptions were not sufficiently severe or discrete to fit the diagnostic criteria required for a mood disorder. In only one case, case 4, did such a pattern emerge by age eight and was substantiated by observations during a hospital admission. In the other cases described clear-cut depressive and hypomanic episodes developed some years later and it was only then possible to make a confident diagnosis of bipolar disorder type II (hypomania as opposed to mania).

A further difficulty in trying to establish definite diagnosis in these cases was the lack of reliability in recording mood states, either by the young people themselves, due to parental mental illness, or an inability to get detailed information from the school. It was difficult to determine whether the earlier references by the family and others to a significant mood component represented a cyclical mood disorder (or the prodromal stages) as has been suggested by several researchers in the field (Biederman et al., 1996; Geller & Luby, 1997; Kovacks & Pollock, 1995; Sadler, 1952) or the significant mood lability that is present in children with ADHD. Even in the absence of the characteristic episodic presentation it is still possible that the mood swings described represented co-morbid bipolar disorder given the diagnostic confusion surrounding early-onset bipolar disorder.

The accuracy of diagnosis is important as it helps plan treatment and is also predictive in terms of prognosis. ADHD in the absence of bipolar disorder responds favourably to methylphenidate and other second-line treatment approaches. However, when co-morbid with bipolar disorder there is a real possibility that the methylphenidate may worsen the presentation (Koehler-Troy et al., 1986), although this has not been noted by all (Max, Richards, & Hamdan-Allen, 1995). This occurred in case 4, was a real concern in case 1, where the mood stabilizer on its own did not alleviate the ADHD symptoms and the addition of a stimulant was considered, and also in case 3, where both were in fact prescribed. Strober et al. (1999) found that children with mania and ADHD have a poorer response to lithium than children with mania alone. Biederman and colleagues (1998) also found that the treatment of ADHD symptoms with anti-ADHD agents is efficacious only after mood stabilization.
It is unclear whether medication should be continued long-term in order to prevent relapse or whether it should be limited to prevent against possible long-term medication induced adverse educational effects. This was a clinical issue in case 4 where the diagnosis of bipolar disorder was made at age nine. The adult literature suggests that intermittent lithium therapy is worse for outcome than continuous administration and Strober replicated these findings in an adolescent population leading to an argument for long-term maintenance treatment (Strober, Morrell, Lampert, & Burroughs, 1990). Follow-up studies show that the recovery and relapse rate in adolescence is less predictable and lower than in adults (Strober et al., 1995). It is also unclear from the literature, and the cases described, whether suspicion of an emerging bipolar disorder at an earlier stage would lead to earlier treatment and an improved outcome.

Pharmacological treatment needs to be accompanied by age-appropriate psychosocial intervention both with children and their families, on account of the fact that children are often dependant on families both to assist with adherence to medication and also in terms of modulating the expressed emotion in the environment. Negative expressed emotion is associated with poorer outcome in bipolar adults and it is arguable that the same is true for children (Miklowitz, Goldstein, Neuchterlein, Synder, & Mintz, 1988). In case 4, attachment issues were very relevant to both presentation, differential diagnosis and treatment issues and should not be overlooked in the management of children even when there is clear evidence of neuropsychiatric disorders.

The clinical dilemma in these cases was the difficulty in establishing an accurate diagnosis when: (i) presentation may be prodromal, and (ii) both the child and the parents may have diagnoses themselves which make them unreliable historians, i.e. either ADHD, bipolar disorder or other psychotic conditions. It was also clear that treatment with a mood stabilizer on its own did not provide sufficient treatment of attentional difficulties and there was a need to consider a combination of mood stabilizers and ADHD-specific medication (methylphenidate).

The safety record for such a combination therapy is not well established. Children established on mood stabilizers and stimulant medication who subsequently develop depressive episodes pose treatment difficulties. Is the depressed mood due to the stimulant drug, or the emergence of a depressive state, which may need treatment with an antidepressant (as in case 2)?

Summary

Bipolar disorder presenting in early childhood is characterized by a non-episodic, chronic rapid cycling and mixed manic state, which is often co-morbid with other psychiatric diagnosis. Research into pre-pubertal presentation is in its infancy and there is an increasing and urgent need for developmentally relevant diagnostic criteria. A ccurate diagnosis is therefore difficult and there is a real risk of failing to diagnose it in preference for other disorders. This can have a profound effect on the child’s development and treatment response.

The search for biological markers is in its infancy and it is clearly difficult to disentangle any abnormalities found from the effect of subsequent episodes of mental illness or from the effect of concurrent or past medication treatment. It is not known whether there is a neurotoxic risk from either depressive or manic episodes but if this is the case, as it is in adult psychosis, then it is clearly important to treat early and aggressively even sub-syndromal conditions in order to prevent subsequent relapses.
References


