Editorial

Prepubertal Bipolar I Disorder and Bipolar Disorder NOS Are Separable From ADHD

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As reported in the recent National Institute of Mental Health (NIMH) Research Roundtable on Prepubertal Bipolar Disorder,[1] considerable controversy surrounds the definition and prevalence of prepubertal-onset bipolar disorders. Contentious areas included disagreements about diagnostic criteria and differences between presentations of prepubertal bipolar disorder and typical adult-onset mania (i.e., discrete episodes of mania and depression with intervening well periods). Despite these and other ongoing disagreements in the literature, there are data to support an increasing prevalence and younger age at onset of bipolar illness.[2–4] Thus, investigations of prepubertal bipolar disorder and of offspring of bipolar disorder parents are warranted. To facilitate these studies, the NIMH Research Roundtable recommended categorizing prepubertal bipolar disorder as fitting either DSM-IV bipolar I or II disorder or bipolar disorder not otherwise specified (NOS) criteria.

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Although 1-, 2-, and 4-year prospective longitudinal diagnostic validation of prepubertal bipolar I disorder has been demonstrated,[5–7] there are no prospective follow-up studies into adulthood. These outcome studies are needed to demonstrate whether prepubertal bipolar disorder becomes adult bipolar disorder as opposed to other psychiatric syndromes.[1]

COMORBIDITIES

Both the prepubertal and adult-onset types of bipolar illness are confounded by a high prevalence of comorbid Axis I diagnoses. For example, in adults in the Stanley Foundation Bipolar Network, there was an average of 1.7 other diagnoses in this population, and 24% presented with 3 or more comorbid conditions in addition to bipolar illness.[8] These data are consistent with those from epidemiologic surveys that identify alcoholism, substance abuse, and anxiety disorders as particularly prominent in patients with adult bipolar disorder.[9,10]

The mix of comorbidities in prepubertal onset bipolar I or II disorder and bipolar disorder NOS, which often complicates the diagnosis, are somewhat different from those in adults. Comorbid diagnoses in prepubertal bipolar disorder include a high rate of attention-deficit/hyperactivity disorder (ADHD), as well as substantial rates of oppositional defiant disorder, conduct disorder, and anxiety disorders.[11–21] It is not yet known whether comorbid ADHD is a result of overlapping DSM-IV criteria in different diagnostic categories, dual genetic diatheses, a true coexistence of 2 or more disorders, or a developmentally determined child-age manifestation.[22,23]

The statement is often made either directly or by implication that it is difficult to differentiate the diagnosis

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of bipolar disorder from these comorbid conditions, especially ADHD. This assertion, while narrowly correct, may be counterproductive. It may contribute to the already considerable delay in arriving at an appropriate bipolar disorder diagnosis. In children, such a delay may harm the child and family because of inadequate or, even worse, inappropriate treatment. The many readily recognized signs and symptoms that are inconsistent with an ADHD diagnosis, and raise the likelihood of a bipolar disorder diagnosis, are noted below.[24–26]

With respect to the diagnosis of bipolar disorder, consensus exists that there is high comorbidity with ADHD while, inversely, a relatively low incidence of bipolar disorder in the general population of patients with ADHD.[13,27,28] Thus, practitioners should be mindful of the relatively infrequent cases of bipolar disorder that may be misdiagnosed as uncomplicated ADHD. In this regard, there are recently available reliable assessments of DSM-IV mania criteria in prepubertal children that may help identify children with prepubertal bipolar disorder.[24,25,29,30] These data show that the symptoms that best differentiate bipolar disorder from ADHD are elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep, and hypersexuality.[24,29] Hypersexuality occurring in the absence of sexual abuse may also be a useful sign of childhood-onset bipolar illness and, in the context of other aspects of this syndrome, may aid in differentiation from uncomplicated ADHD.[18,24,25,31]

LONGITUDINAL COURSE

The category of prepubertal bipolar I disorder has been validated by reliable assessment; 6-month stability of diagnoses and mania symptoms; 1-, 2-, and 4-year diagnostic outcome; and high familial aggregation of bipolar disorder.[5–7,30,32] These data have demonstrated that prepubertal bipolar I disorder resembles the most severe form of adult-onset mania and includes marked psychosocial impairment.[31] Both prepubertal bipolar I disorder and the most severe presentations of adult-onset mania may be characterized by a chronic course, mixed mania, psychosis, and continuous (ultradian) rapid cycling on a daily basis.[5,6,33] Therefore, one form of prepubertal bipolar I disorder appears to be similar to other familial illnesses in which earlier onset is associated with more severe pathology and greater familial aggregation.[7,34,35]

By contrast to prepubertal bipolar I disorder, the category of bipolar disorder NOS may be helpful when prodromal symptoms are the focus of diagnostic assessment.[36] Subsyndromal symptoms and intermittent presentations of bipolar disorder NOS are especially important for offspring studies. The problem of recognizing intermittent bipolar disorder NOS is very similar to the initial lack of recognition of adult-onset recurrent brief depression described and documented by Angst et al.[37] and Montgomery et al.[38] In recurrent brief depression, irregularly recurring brief periods of severe depression (averaging 3 days in duration and associated with considerable dysfunction and risk of suicide) were not previously recognized or diagnosed because they did not meet the arbitrary 2-week minimum for major depression.

There is wide agreement that children with bipolar disorder NOS presenting with chronic and extreme mood lability, emotionality, and impulsivity (often accompanied by aggression and suicidal or homicidal thoughts and acts) are often extremely difficult to manage.[1,39] This is so even in the most highly integrated and functional family, educational, and psychotherapeutic environments. This degree of impairment and dysfunction, as well as pain and suffering of patient and family, and loss of social and educational opportunities[40] further raise the stakes for arriving as rapidly as possible at the appropriate diagnosis and treatment.

KEY DIFFERENTIATING SYMPTOMS

What are indices of these prepubertal bipolar disorder NOS presentations? One of the earliest manifestations may be frequent and extreme temper tantrums,[39,41,42] sometimes lasting hours and triggered by minor admonishments. Although temper tantrums also occur in other conditions, the full range of other symptoms in the presentation should be considered. Another clue is frequent and extreme periods of mood lability associated with periods of sadness and tearfulness, alternating with periods of irritability, impulsivity, and aggression. Additionally, grandiose delusions and other psychotic manifestations (including the presence of auditory and visual hallucinations) occur in childhood-onset bipolar illness, but do not occur in ADHD.

Suicidal thoughts and acts are also inconsistent with a diagnosis of ADHD. Martha Hellander, Executive Director of the Child and Adolescent Bipolar Foundation, reports that among Web-site–user families who have a child with bipolar disorder, many have observed their child attempting to jump or jumping from a moving vehicle (personal communication, 2003). Data support this observation in that 25% of subjects with prepubertal bipolar I disorder had serious suicidality.[18,24] Particularly if suicidal behavior occurs in the context of expressed suicidal thoughts, it is likely associated with a bipolar diagnosis, with high specificity but low sensitivity; that is, many children with a bipolar diagnosis do not demonstrate suicidal behavior, but if present, suicidality very likely differentiates mood disorder from uncomplicated ADHD, conduct disorder, oppositional defiant disorder, and various anxiety disorder diagnoses. Similarly, homicidal threats or actions in a preadolescent are inconsistent with a diagnosis of ADHD, but are suggestive of a conduct or mood disorder.

Thus, while prepubertal bipolar disorder NOS is often comorbid with ADHD, the two are separable on the basis that uncomplicated ADHD does not present with the symptoms of frequent and extreme mood lability, extended tantrums evidencing poor frustration tolerance, extreme aggression, suicidality, grandiose or self-accusatory delusions, hallucinations, or hypersexuality. The presence of this array of additional signs and symptoms superimposed on an ADHD presentation, particularly in the context of a positive unilineal (1-parent) or, even more compelling, a bilineal (2-parent) family history of bipolar disorder,[40,43–45] helps one to be alert to the diagnosis of prepubertal bipolar disorder NOS.

One important differential diagnostic problem is that many other syndromes, including comorbid ADHD, oppositional defiant disorder, and conduct disorder, also present with prominent aggressive and irritable behaviors. For example, the Research Units on Pediatric Psychopharmacology (RUPP) group[46] reported risperidone treatment for aggressive and irritable behaviors in autism, and Aman et al.[47] reported risperidone treatment for aggression/irritability in subjects with low IQ. Thus, it is important to note the low specificity of aggression/irritability for bipolar disorder, as these behaviors are also highly prevalent symptoms in multiple other child psychiatry disorders.[35]

TREATMENT IMPLICATIONS

Establishing prepubertal bipolar disorder diagnoses appears crucial to a child's ultimate good outcome. This is because treatments for uncomplicated ADHD, such as stimulants and antidepressants, not only are typically ineffective as monotherapy for childhood-onset bipolar illness, but may also exacerbate it,[39,48–52] although not all data are supportive of this view.[53] In contrast, childhood-onset bipolar disorder is often partially responsive to treatment with lithium, anticonvulsant mood stabilizers such as carbamazepine and valproate,[54] the combination of lithium and valproate,[55] or atypical antipsychotic agents.[56]

Some investigators have observed that once mood stabilization is achieved with one or more of these agents, residual ADHD symptoms, if present, can then be treated with small doses of psychomotor stimulants as adjuncts to the primary mood-stabilizing regimen. Other investigators have observed that usual adjunctive doses of stimulant medications do not worsen the course of prepubertal bipolar I disorder.[5,6,53]

Practitioners are faced with the dilemma of how to treat prepubertal bipolar disorder given the paucity of data on the efficacy or effectiveness of antimanic drugs in prepubertal children. Conservatively, it may be prudent to avoid antidepressants in children who have or are suspected of having bipolar disorder, especially if there is a family history of bipolar disorder. In addition, children diagnosed with bipolar disorder should be observed for the potential occurrence of worsening mania symptoms.

RECOGNITION BY PRACTITIONERS

We write this editorial as an attempt to extend the consensus statements in the NIMH Research Roundtable toward a general strategy for treatment based on an emerging but incomplete database. Most importantly, we believe that it is crucial to highlight these diagnostic issues and further assist practitioners who prescribe psychopharmacologic treatments for uncomplicated ADHD. Particularly in the context of a positive family history for bipolar disorder, the failure to arrive at an appropriate diagnosis of bipolar disorder in the face of the range of symptoms noted that are unusual in or atypical of ADHD could have considerable adverse consequences for the child and the child's family.

As the field coalesces around an emerging literature on agreed-upon severity of dysfunction accompanying bipolar I, II, and NOS presentations in children, it is of great importance that families themselves, as well as school authorities, psychologists, social workers, pediatricians, family physicians, and child and adult psychiatrists, actively consider these bipolar diagnoses rather than reserving them only as diagnoses of last resort, after such children have failed to respond to or worsened on a long series of clinical trials with stimulants and antidepressants in the absence of a mood stabilizer.

CAVEATS

It is important to balance differential diagnostic approaches to avoid both over- and underdiagnosis of child bipolar disorder. No one wants children to be given a lifelong diagnosis that is commonly treated with major psychotropic medications unless there is reasonable certainty of the diagnosis. As noted above, however, underdiagnosis may occur if bipolar disorder is not considered as part of the differential diagnosis of children who present with complicated symptoms that include ADHD or aggression/irritability.[20] As described above, aggression/irritability problems are frequent reasons for referral across multiple child psychiatry diagnoses, as evidenced by several recent studies.[46,47] Moreover, Kim-Cohen et al.[57] reported that 20% to 60% of young adults with various adult psychiatric diagnoses had an aggression/irritability diagnosis in childhood.

Thus, to avoid overdiagnosis of bipolar disorder based on aggression/irritability symptoms, it may be useful to consider symptoms that best differentiate bipolar disorder from ADHD (elated mood, grandiosity, flight of ideas/racing thoughts, decreased sleep need), especially the cardinal symptoms of elated mood and grandiosity.[24–26] Data

to support this "cardinal" symptom approach are also available from the ongoing multisite Treatment of Early Age Mania (TEAM) study at 6 major academic centers (B.G., unpublished data, 2004). To enter the TEAM protocol, cardinal symptoms were *not* required as an inclusion criterion. Nevertheless, 100% of TEAM subjects had either elated mood or grandiosity, and over 90% had both. In this regard, a recent report[58] supported the idea that diagnosis of child bipolar disorder is best made when children are also interviewed separately from their parents, to avoid missing the substantial mania symptoms that are given only by the children. Although it has been suggested anecdotally that aggressive and irritable behaviors in children with bipolar disorder have different characteristics from aggression/irritability observed in other child psychiatry diagnoses, there are not yet data to support this speculation.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), lithium (Eskalith, Lithobid, and others), risperidone (Risperdal).

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