

# ADHD and Comorbidity in Childhood

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In recent years, evidence has been accumulating regarding high levels of comorbidity between attention-deficit/hyperactivity disorder (ADHD) and a number of disorders, including mood and anxiety disorders and conduct disorder. Thus, ADHD is most likely a group of conditions, rather than a single homogeneous clinical entity, with potentially different etiologic and modifying risk factors and different outcomes. Follow-up studies of children with ADHD indicate that subgroups of subjects with ADHD and comorbid disorders have a poorer outcome as evidenced by significantly greater social, emotional, and psychological difficulties. Investigation of these issues should help to clarify the etiology, course, and outcome of ADHD. *(J Clin Psychiatry 2006;67[suppl 8]:27-31)*

During the past decade, epidemiologic studies have documented high rates of concurrent psychiatric and learning disorders among individuals with attention-deficit/hyperactivity disorder (ADHD).<sup>1,2</sup> Most commonly, comorbidity with ADHD in youth includes oppositional, conduct, mood, and anxiety disorders.<sup>3-6</sup>

## Mood Disorders

Juvenile mood disorders are commonly classified as bipolar based on the presence of mania and as unipolar, depressed based on the absence of mania. In addition, there is the category of dysthymia, defined by low-grade, chronic depression. However, mania and depression may co-occur (dysphoric mania) and fluctuate from subsyndromal to fulminate expression. Juvenile mood disorders tend to be chronic as compared to the more episodic nature typical of adult mood disorders.<sup>7</sup>

Major depression in a child may be apparent from a sad or irritable mood or a persistent loss of interest or pleasure in favorite activities. Other signs and symptoms include physiologic disturbances, such as changes in appetite and weight, abnormal sleep patterns, psychomotor abnormalities, fatigue, and diminished ability to think, as well as feelings of worthlessness or guilt and suicidal preoccupation. Some depressed states are severe and include psychotic symptoms. Associated features of depression in children include school difficulties, school refusal, withdrawal, somatic complaints, negativism, aggression, and

antisocial behavior. Conduct disorder and substance abuse commonly co-occur with depression in older children and adolescents. Dysthymia is well described in children, adolescents, and adults. It is the best predictor of future episodes of depression as well as long-term psychosocial difficulty.<sup>8</sup>

An unusual feature of childhood depression is the high rate of conversion to mania. Several studies have reported that an ultimate manic outcome occurs in 20% to 50% of children first diagnosed as unipolar.<sup>9,10</sup> The best predictors of the switch to mania are a family history of mania, acute onset, psychomotor retardation, mood-congruent psychosis, and poor or hypomanic response to antidepressants.<sup>10</sup>

Classical mania in adults is characterized by euphoria, elation, grandiosity, and increased energy. The condition may progress to delusions with these same grandiose features or even frank paranoia. However, in many adults and most children, mania is more commonly manifested by extreme irritability or explosive mood with associated poor psychosocial functioning that is often devastating to the patient and family. In milder conditions, additional symptoms include unmodulated high energy, such as decreased sleep, overtalkativeness, racing thoughts, or increased goal-directed activity (social, work, school, sexual), or an associated manifestation of markedly poor judgment, such as thrill-seeking or reckless activities. It is often difficult to differentiate juvenile mania from ADHD, conduct disorder, depression, and psychotic disorders because of overlapping developmental features. In addition, these disorders commonly co-occur with childhood mania. The clinical course of juvenile mania is frequently chronic and commonly mixed with co-occurring manic and depressive features. In adolescent-onset mania, one may obtain a clearer picture of childhood-onset disorders such as ADHD, in which symptoms may precede the first manic episode by many years.

Unlike ADHD, which has an onset before age 7 years and maintains a consistent presence over time, major de-

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pression and mania evidence a rate of onset that increases with age. Major depression is estimated to affect 0.3% of preschoolers, 1% to 2% of elementary-age children, and 5% of adolescents.<sup>11</sup> While the lifetime prevalence of mania is estimated to be 1%, 15% to 30% have an onset by age 19 years.<sup>12</sup> Family genetic studies of depression and mania reveal that the risk of these mood disorders in family members of individuals with either major depression or mania increases inversely with earlier age at onset.<sup>13</sup>

Attention-deficit/hyperactivity disorder and mood disorders have been found to co-occur in 15% to 75% of cases in both epidemiologic and clinical samples of children and adolescents.<sup>3</sup> Studies of high-risk children of parents with mood disorders have found high rates of ADHD in these children,<sup>14</sup> and family studies of ADHD children have found a significantly higher rate of mood disorders in children with ADHD and in their first-degree relatives compared with healthy control children and their first-degree relatives.<sup>15</sup>

The comorbidity between mood disorders and ADHD is not an artifact of psychiatric referral. This overlap appears in epidemiologic studies<sup>16</sup> as well as non-psychiatrically referred studies. Jensen and colleagues<sup>17</sup> compared 47 pediatrically referred children with ADHD (treated by pediatricians for ADHD) with a matched psychiatric sample and controls. Thirty-eight percent (N = 18/47) of the pediatrically referred children with ADHD were diagnosed with comorbid depression. Clinician- and parent-endorsed rating scale scores of depression were equally as high in the ADHD children as in the children in a comparison psychiatric clinic. The authors concluded that clinicians might underappreciate the high rate of clinically significant depression in children with ADHD unless there was a systematic assessment of mood symptoms.

In several prospective studies, our group at Massachusetts General Hospital examined rates of depression in children with ADHD.<sup>18</sup> At 4-year follow up, lifetime rates of comorbid depression in children with ADHD increased from 29% at baseline to 45% at an average age of 15 years. A baseline diagnosis of major depression predicted lower psychosocial functioning, a higher rate of hospitalization, and impairments in interpersonal and family functioning. If not recognized and attended to, the combination of depressive symptoms and ADHD may lead to high morbidity and disability with a poor long-term prognosis and, perhaps, increased mortality.

Despite heightened interest in childhood mania, the condition remains controversial. One potential source of diagnostic confusion in prepubertal mania is the symptomatic overlap with ADHD. The symptoms of distractibility, impulsivity, hyperactivity, and emotional lability are characteristic of both ADHD and mania. There are developmental variations in the expression of mania. The past literature on mania in adults emphasized a pathognomonic euphoric mood. However, current evidence in adults docu-

ments a common mood disturbance similar to that found in manic children that may be better characterized as extremely irritable, with "affective storms" or prolonged and aggressive temper outbursts.<sup>19</sup> Although tantrums are common among children with ADHD, the type of irritability observed in our prepubertal manic children was very severe, including explosive reactions with persistent violence to persons and property.<sup>20</sup> Additionally, the behavior associated with childhood-onset mania tends to be chronic and continuous rather than episodic and acute, as was the classical description of the adult disorder.<sup>21</sup> In the absence of euphoria, clinicians may incorrectly attribute irritability in a child to psychosocial factors or conduct disorder rather than to mania. The differential diagnosis of very difficult children with ADHD and mood features should include the possibility of mania.

In our follow-up study of children with ADHD,<sup>5</sup> mania was detected in 11% of children at baseline (mean age = 11 years) and in 12% at 4-year follow-up (lifetime rate at follow-up = 23%). In contrast, rates of mania in controls were appropriately low (0% at baseline and 1.8% at follow-up). Children with ADHD and comorbid mania at either baseline or follow-up assessment had other correlates expected in mania including additional psychopathology, psychiatric hospitalization, severely impaired psychosocial functioning, and a greater family history of mood disorders. Our family-genetic data suggest that the comorbid condition of ADHD plus mania may be a distinct nosologic entity.<sup>18</sup>

### Anxiety Disorders

Anxiety symptoms are generally expressed in 4 domains: cognitive, affective, physical, and behavioral.<sup>22</sup> Cognitive elements may range from rumination and vigilant apprehension to catastrophic thinking such as the anticipation of great embarrassment or threat to life. Behavioral features may include agitation, tantrums, attention-seeking, overdependence, and rituals. Many of these symptoms may be misinterpreted because of overlap with ADHD. Childhood anxiety disorders are often not suspected in an overactive child, just as ADHD is often not assessed in inhibited children. When present, both contribute to social, behavioral, and academic dysfunction. In addition, anxiety may be associated with intense intrapsychic suffering.

Childhood anxiety disorders are relatively common disorders that bear striking similarities to the adult anxiety disorders and, in many cases, persist into adult life. The DSM-IV recognizes 2 diagnoses as childhood anxiety disorders: separation anxiety disorder and selective mutism. In fact, adult anxiety syndromes commonly emerge and can be diagnosed in childhood and adolescence.<sup>22,23</sup> These include panic disorder with and without agoraphobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and the atypical anxiety disorders termed anxiety disorders not

otherwise specified. Only recently has the literature documented that the diagnosis of panic disorder can be made in juveniles. A recent study reported high rates of both panic disorder (6%) and agoraphobia (15%) in psychiatrically referred children and adolescents (N = 424).<sup>24</sup> Further, this study<sup>24</sup> and a study of children with obsessive-compulsive disorder<sup>25</sup> both reported high rates of comorbid mood and other anxiety disorders as well as high rates of ADHD and other disruptive behavior disorders in these children.

A comorbid association between ADHD and anxiety disorders of approximately 25% has been found in epidemiologic and clinical samples of children with anxiety disorders and children with ADHD.<sup>3</sup> Investigators have also noted higher rates of ADHD in children of parents with anxiety disorders than in children of comparison groups. Lahey et al.<sup>26</sup> noted that children with the DSM-III diagnosis of attention deficit disorder without hyperactivity had higher rates of anxiety disorders than those with hyperactivity. Rutter<sup>27</sup> has noted that anxiety problems in childhood or adolescence can signal considerable impairment in later adult functioning. Thus, having both ADHD and anxiety disorders may substantially worsen the outcome of children with both disorders.

As with depression, the comorbidity of anxiety and ADHD is not an artifact of psychiatric referral. In the controlled study of 47 pediatrically referred children with ADHD by Jensen and colleagues,<sup>17</sup> 28% (N = 13/47) of the pediatrically referred children with ADHD were diagnosed with comorbid anxiety. Similarly, in the Massachusetts General Hospital sample of psychiatrically and pediatrically referred boys with ADHD (140 children with ADHD and 120 healthy controls),<sup>28</sup> we also examined rates of anxiety. Children with ADHD had higher rates of agoraphobia, overanxious disorder, simple phobia, and separation anxiety disorder at baseline and higher rates of these same disorders as well as others (social phobia and obsessive-compulsive disorder) at 4-year follow-up. We defined a category of multiple anxieties as having 2 or more anxiety disorders to index the severity of comorbid anxiety. Using this definition, we detected higher lifetime rates of multiple anxiety disorders in ADHD children at baseline (27%; mean age = 11 years) and at 4-year follow-up (35%). In contrast, lifetime rates of multiple anxiety disorders in controls were appropriately low (5% at baseline and 9% at follow-up). Children with ADHD and comorbid anxiety disorder at either baseline or follow-up assessment had other correlates expected in anxiety including additional psychopathology, increased psychiatric treatment, more impaired psychosocial functioning, and a greater family history of anxiety disorders.

### **Oppositional Defiant Disorder and Conduct Disorder**

Attention-deficit/hyperactivity disorder and oppositional defiant disorder/conduct disorder have been found

to co-occur in 30% to 50% of cases in both epidemiologic and clinical samples.<sup>3</sup> Oppositional defiant disorder is characterized by a pattern of negativistic, hostile, and defiant behavior.<sup>29</sup> In contrast, conduct disorder is a more severe disorder of habitual rule breaking defined by a pattern of aggression, destruction, lying, stealing, or truancy. The typical onset of both disorders is prepubertal; hence, careful early diagnosis may be crucial for timely treatment to prevent chronicity or progressive escalation into social failure and/or delinquency.

There is increasing evidence that ADHD and conduct disorder represent related but independent dimensions. In follow-up studies,<sup>30</sup> childhood aggression, with or without ADHD, has been associated with delinquency and antisocial behaviors in adolescence, but ADHD alone has not. Several studies have suggested, however, that conduct disorder is more severe and persistent in the context of ADHD. A review of the literature by Hinshaw and colleagues<sup>31</sup> concluded that children with ADHD plus conduct disorder have an earlier age at onset of conduct disorder, are more aggressive, and have more persistent conduct disorder than other children with conduct disorder alone. These differences in children with and without ADHD may explain why, although conduct disorder is a necessary precursor for adult antisocial personality disorder, only 30% to 40% of children with conduct disorder appear to progress to this outcome.<sup>29</sup> It is possible that ADHD children with comorbid conduct disorder represent this "poor outcome" subgroup.

A recent follow-up study of children with ADHD confirmed that the overlap of conduct disorder and oppositional defiant disorder was asymmetric.<sup>32</sup> While conduct disorder was almost always comorbid with and was preceded by oppositional defiant disorder, oppositional defiant disorder at baseline was a weak predictor of new onset of conduct disorder at follow-up into midadolescence 4 years later. In addition, while conduct disorder was a strong predictor of substance abuse at follow-up, oppositional defiant disorder without conduct disorder was not. These findings further support the notion that oppositional defiant disorder does not necessarily progress to conduct disorder and does not share the poor outcome of conduct disorder.

In terms of severity of the clinical picture, the available data suggest that children with ADHD and oppositional defiant disorder may form an intermediate subgroup between those who have ADHD alone and those with ADHD plus conduct disorder. For example, Faraone et al.<sup>33</sup> showed that, whereas ADHD children with oppositional disorder had a higher rate of school dysfunction than those with ADHD alone, this rate was lower than that of the ADHD plus conduct disorder subgroup. These findings are consistent with the hypothesis that oppositional defiant disorder may be a subsyndromal manifestation of conduct disorder.

### **Cognitive Performance and Learning Disabilities**

Studies have consistently shown that children with ADHD perform more poorly in school than do controls, as evidenced by more grade repetitions, poorer grades in academic subjects, more placement in special classes, and more tutoring.<sup>34-40</sup> Findings also indicate that children with ADHD perform more poorly than controls on standard measures of intelligence and achievement.<sup>41</sup>

Although children with ADHD may show learning disabilities, these 2 disorders are not mutually inclusive.<sup>42</sup> A widely variable overlap between ADHD and learning disabilities has been reported in the literature.<sup>3,39</sup> The reported degree of overlap ranges from as low as 10%<sup>43,44</sup> to as high as 92%.<sup>34</sup> This variability is most likely due to differences in selection criteria, sampling, and measurement instruments, as well as inconsistencies in the criteria used to define both ADHD and learning disabilities in different studies.<sup>39,45,46</sup> Faraone et al.<sup>35</sup> found that the neuropsychological impairments of their ADHD sample were due to the ADHD syndrome itself and not to other psychiatric comorbidity. Among subjects with ADHD, comorbid conduct, major depressive, and anxiety disorders predicted placement in special classes but not tutoring, repeated grades, or learning disabilities. Psychiatric comorbidity also had limited influence on Wechsler Intelligence Scale for Children-Revised (WISC-R) scores.

Faraone et al.<sup>35</sup> reported family-genetic data that suggested that ADHD and learning disorders are etiologically independent but co-occur due to nonrandom mating. The results were not compatible with the idea that ADHD and learning disabilities are manifestations of a single disorder or with the hypothesis that patients with ADHD plus learning disabilities are ADHD children who develop learning disabilities secondary to the symptomatology of ADHD. These conclusions are also supported by twin studies.<sup>47</sup>

### **Developmental Disorders**

As coded in DSM-IV, this class of disorders includes mental retardation (Axis II), pervasive developmental disorders (autistic and autistic-like disorders), and the specific developmental disorders (learning disabilities). The specific developmental disorders (learning disabilities) represent a mixed group of cognitive dysfunctions in the context of no overall intelligence deficit and adequate educational opportunities.

Children with mental retardation and pervasive developmental disorders often have psychiatric disorders and behavioral problems, including hyperactive, aggressive, distractible, and self-abusive behaviors. They also often manifest multiple neurologic abnormalities.

### **Tic Disorders**

The presence of a tic disorder may not contribute additional dysfunction to children with ADHD beyond the distractions and social impairments directly attributable to

the movements or vocalizations themselves. Recent studies have reported limited consequences of this comorbidity in youth with ADHD.<sup>48,49</sup>

In the aforementioned prospective follow-up study of boys with ADHD,<sup>49</sup> we systematically evaluated the impact of tic disorders on the course and outcome of ADHD, attending to issues of additional comorbidity and therapeutics. Tic disorders were overrepresented in boys with ADHD when compared with controls. Attention-deficit/hyperactivity disorder and tic disorders appeared to be independent in course: in contrast to low rates of ADHD remission, tic disorders mostly remitted. In striking contrast to the severe consequences of other disorders such as conduct, mood, and anxiety, tic disorders had little impact on the course of ADHD. Specifically, tic disorders had little impact on rates of other comorbid disorders and indices of psychosocial function in multiple domains (school, cognitive, social, and family). These findings suggest that comorbidity with a tic disorder has a limited impact on ADHD outcome.

### **Substance Use Disorders**

Combined data from retrospective accounts of adults and prospective observations of youth indicate that juveniles with ADHD are at increased risk for cigarette smoking and substance abuse during adolescence. In particular, youth with ADHD and bipolar or conduct disorder are at risk for very early cigarette use and substance use disorder (i.e., < 16 years of age), whereas the typical age of risk for the onset of substance abuse accounted for by ADHD itself is probably between 17 to 22 years of age.<sup>50</sup> Recent work suggests that youth with ADHD disproportionately become involved with cigarettes, alcohol, and then illicit drugs.<sup>51,52</sup> Adolescents and adults with ADHD become addicted to cigarette smoking at twice the rate of individuals without ADHD. Moreover, substance abusers with ADHD tend to prefer the class of drugs over alcohol with no evidence of a preference for specific types of drugs.<sup>53</sup> Data indicate that cocaine and stimulant abuse are not overrepresented in ADHD; in fact, as is the case in abusers without ADHD, marijuana continues to be the most commonly abused agent among untreated patients.<sup>53</sup> Individuals with ADHD, independent of comorbidity, tend to maintain their addiction longer compared to their peers without ADHD.<sup>54</sup>

### **Summary**

While ADHD is characterized by behavioral symptoms of inattention, hyperactivity, and impulsivity, often other symptoms co-occur. In many instances, these other symptoms are part of comorbid disorders that modify the course and outcome of individuals with ADHD.

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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