Overview and Neurobiology of Attention-Deficit/Hyperactivity Disorder

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Although attention-deficit/hyperactivity disorder (ADHD) impairs millions of people worldwide, both the prevalence and existence of the disorder are being reevaluated at the phenotypic level. To safeguard against overdiagnosis, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), demands that individuals with ADHD have pervasive impairment, that is, impairment in more than 1 setting. However, the appropriateness of the DSM-IV classification of ADHD is also undergoing reevaluation. Like the symptoms of a developmental disability, the symptoms of ADHD must be evaluated in the context of age-based norms; therefore, the current criteria for ADHD, which are not age referenced, may minimize the rate of persistence of ADHD into adulthood. In an effort to better understand the pathophysiology of ADHD, recent research has focused on identifying the etiology of ADHD. These studies have revealed that the disorder is highly heritable and may be associated with neurobiological deficits in the prefrontal cortex and related subcortical systems. Etiologic studies have also identified candidate genes and prenatal and perinatal risk factors for ADHD. As the causes and course of ADHD are better understood, a new generation of medications is being developed for the disorder. Although stimulants are often effective in reducing the symptoms of the disorder, as a class they have limitations such as a lack of 24-hour-a-day coverage, unwanted side effects, potential for abuse, and lessened effectiveness in the context of some comorbidities. Therefore, the treatment characteristics of newer, more selective treatments such as atomoxetine should continue to be explored in ADHD. *(J Clin Psychiatry 2002;63[suppl 12]:3–9)*

Attention-deficit/hyperactivity disorder (ADHD) is present in 3% to 10% of children and 1% to 6% of adults in the United States.[1] This high prevalence, the global impairment caused by the disorder, and its chronicity led the Centers for Disease Control and Prevention (CDC)[2] to identify ADHD as a serious public health problem in 1999. The most likely potential areas of impairment of ADHD in children include academic and social dysfunction and skill deficits. As children with ADHD mature, academic failures may lead to demoralization and poor self-esteem. Other risks include high rates of injuries, cigarette smoking, and substance use. In a subgroup, a risk of delinquency exists. Adults with persistent ADHD experience dysfunctions in occupational and vocational performance, continued social impairments, and higher rates of motor vehicle accidents.

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Like all other psychiatric disorders, ADHD is a disorder for which there is no objective test. However, in recent years, research has made substantial advances in identifying the biological basis of ADHD. As the causes and course of ADHD are better understood, newer and more selective medications are being developed for the disorder.

PREVALENCE AND PERSISTENCE OF ADHD

Many studies[3–10] of the worldwide prevalence of ADHD in children document that the prevalence is between 3% and 9%. Differences in the rates of ADHD (Table 1) among countries are usually methodological artifacts of the criteria used to define the disorder. In studies that followed up children who met criteria for hyperactivity and/or attention deficits, rates of persistence into adolescence and adulthood range from 8% to 85% (Table 2). Early studies,[18,20,21] which used less formalized entry criteria that stressed hyperkinesis, as did the *Diagnostic and Statistical Manual of Mental Disorders*, Second Edition (DSM-II),[24] have the lowest rates of persistence, while more recent studies[16,19] show fairly high rates of ADHD during follow-up. The changing terminology of ADHD, from hyperkinetic reaction of childhood in DSM-II[24] to attention-deficit disorder in DSM-III[25] to ADHD in DSM-III-R[26] and DSM-IV,[27] has reflected the changes in the conceptualization of the

Table 1. Worldwide Prevalence of ADHD in School-Age Children[a]

Study	Region	Criteria	Prevalence (%)
Anderson et al, 1987[3]	New Zealand	DSM-III	6.7
Andres et al, 1995[4]	Spain	DSM-III-R	8.0
Baumgaertel et al, 1995[5]	Germany	DSM-III	9.6
Bird et al, 1988[12]	Puerto Rico	DSM-III	9.5–16.1
Buitelaar and Kooij, 2000[6]	Netherlands	DSM-IV	7.8
Esser et al, 1990[7]	London, England	DSM-III-R	1.7
Esser et al, 1990[7]	Manheim, Germany	DSM-III-R	4.2
Pellham et al, 1992[13]	United States	DSM-III-R	2.5–4.0
Rohde et al, 1999[8]	Brazil	DSM-IV	5.8
Schaffer et al, 1996[9]	United States	DSM-III-R	4.1
Szatmari, 1989[10]	Ontario, Canada	DSM-III	6.3

[a]Adapted with permission from Goldman et al.[11] Abbreviation: DSM = *Diagnostic and Statistical Manual of Mental Disorders*.

fundamental characteristics of this disorder. On the basis of the DSM-III-R criteria, more than 50% of patients no longer meet the full diagnostic criteria by age 20.[28] With the DSM-IV childhood criteria—that is, 6 of 9 of either hyperactive or inattentive symptoms—the rate of persistence is similar.[29] Although the DSM-IV includes the diagnosis of attention-deficit/hyperactivity disorder in partial remission for patients who have symptoms that cause functional impairment but are too few to meet the full diagnostic criteria, the DSM-IV continues to treat ADHD as a traditional psychiatric disorder with a single set of symptoms that characterize the disorder across the life span. Moreover, because adults in the normal population have fewer ADHD symptoms with age, Murphy and Barkley[30] have proposed that the DSM-IV criteria are too stringent for adults.

Barkley[31] has argued that ADHD more closely resembles a developmental disability such as mental retardation or dyslexia than a traditional psychiatric disorder. Because individuals with developmental disabilities experience delays in the rate at which a trait develops, not absolute losses of function, developmental disabilities are diagnosed on the basis of age-referenced criteria. Therefore, ADHD, if viewed as a developmental disability, should be diagnosed relative to characteristics of the individual's age group. Barkley et al.[29] compared diagnoses of ADHD using DSM criteria with those using developmental disorder criteria. He demonstrated that, depending on which model was applied, there was a difference in the persistence of ADHD into adulthood. When strict DSM-IV criteria were used, 58% of children with ADHD had the disorder by age 21. When developmentally referenced criteria and reports by others about the individual were used, the rate of persistence to adulthood was 66%.

How the rate of persistence of ADHD is judged also depends on the definition of remission. The mood disorder literature has a long tradition of examining subthreshold conditions and their relationship to functionality. For example, individuals with mania who no longer meet full criteria are nevertheless often not fully socially functional. In studies on mania, Keck and colleagues[32] have described syndromal, symptomatic, and functional remission. Biederman and colleagues[28] have shown that, if these definitions of remission are used for ADHD, about 60% of individuals with childhood-onset ADHD no longer meet full diagnostic criteria for ADHD, i.e., have achieved syndromal remission, at age 20 years (Figure 1). Another 30% may not meet full diagnostic criteria but continue to have enough symptoms to have an impairing subthreshold condition, i.e., have achieved symptomatic remission. However, when remission of ADHD is defined as functional improvement to the point of having fewer than 5 symptoms and a score greater than 60 on the Global Assessment of Functioning Scale,[28] only 10% are found to be free of ADHD-associated functional impairment.

DIFFERENTIAL DIAGNOSIS OF ADHD

ADHD is a distinct disorder; impairments characteristic of ADHD are present in the absence of comorbid conditions. However, conditions such as conduct disorder, oppositional defiant disorder, major depressive disorder, bipolar disorder, anxiety disorders, substance-related disorders, and learning disabilities may mimic or, more commonly, coexist with ADHD. Before making the diagnosis of ADHD, physicians should collect reports from more than one source (e.g., teachers and parents), review school records, interview the individual, and conduct medical, psychological, and educational tests.[33] A patient's history and examination can determine whether the individual's seeming inattention or impulsivity is caused by a visual or auditory impairment. Other medical conditions, especially endocrine disorders such as hypothyroidism and hyperthyroidism, can have symptoms similar to those of ADHD but are rare in children. Because ADHD begins in childhood, this disorder's onset typically predates thyroid abnormalities, which generally occur later in life. Sleep disorders should also be ruled out as the cause of attention problems before the diagnosis of ADHD is made. During the individual's assessment, physicians should also determine whether the use of a medication, illegal substance, or alcohol is causing the symptoms of inattention, hyperactivity, or impulsivity.

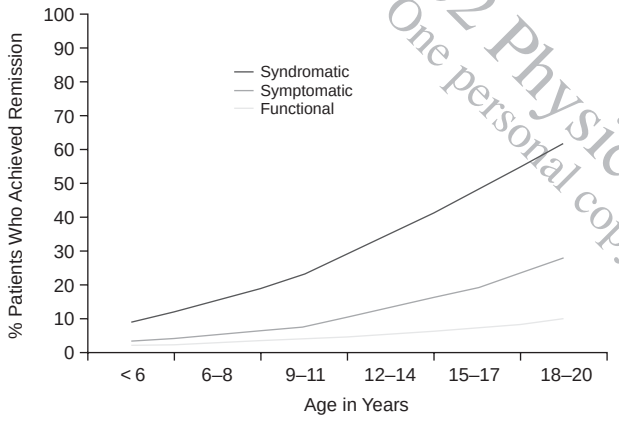
Other mental disorders can cause impairments in social and occupational functioning similar to those associated with ADHD. However, these disorders can be distinguished from ADHD because they have additional symptoms and because ADHD exists in states in which these other disorders are absent. Individuals with conduct disorder differ from those with ADHD by exhibiting persistent antisocial behavior such as lying, cheating, and stealing. Individuals with oppositional defiant disorder

Table 2. Rates of Persistence of Attention-Deficit/Hyperactivity Disorder in Follow-Up Studies[a]

Study	Population (N)	Criteria at Entry	Criteria at Follow-Up	Time to Follow-Up (y)	Mean Age at Follow-Up (y)	Prevalence (%)
Barkley et al, 1990[14]	123	Hyperactivity scales	DSM-IV ADHD	8	14.9	72
Borland and Heckman, 1976[15]	20	Hyperactivity scales	Hyperactivity scales[b]	20–25	30.4	10
Biederman et al, 1996[16]	128	DSM-III-R ADHD	DSM-III-R ADHD	4	14.5	85
Cantwell and Baker, 1987[17]	202	DSM-III ADD	DSM-III ADD	3–4	9.0	33
Gittelman et al, 1985[18]	101	DSM-II hyperkinetic reaction of childhood	DSM-III ADD-H	9	18.3	31
Hart et al, 1995[19]	106	DSM-III-R ADHD	DSM-III-R ADHD	4	10.4	77
Mannuzza et al, 1991[20]	101	DSM-II hyperkinetic reaction of childhood	ADD	8–14	18.5	43
Mannuzza et al, 1993[21]	91	DSM-II hyperkinetic reaction of childhood	DSM-III-R ADHD	13–19	25.5	8
Offord et al, 1992[22]	48	DSM-III ADD	DSM-III ADD	4	NA	34[c]
Weiss et al, 1985[23]	61	Hyperactivity scales	Hyperactivity scales[d]	15	25.1	36

[a]Abbreviations: ADD = attention deficit disorder, ADD-H = attention deficit disorder with hyperactivity, ADHD = attention-deficit/hyperactivity disorder, DSM = *Diagnostic and Statistical Manual of Mental Disorders*, NA = not available.
[b]At least 6 symptoms of hyperactivity.
[c]Weighted data were used.
[d]At least 1 moderately or severely disabling symptom.

Figure 1. Age-Specific Prevalence of the Remission of DSM-III-R Attention-Deficit/Hyperactivity Disorder[a]



[a]Reprinted with permission from Biederman et al.[28] Abbreviation: DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition Revised.

often are easily annoyed and exhibit hostile, defiant, spiteful, and negativistic behaviors. Like individuals with ADHD, those with major depressive disorder may show signs of inattention and become easily upset. However, they must have also experienced at least 2 weeks of depressed mood or loss of interest or pleasure in most activities, and they complain of easy fatigue and loss of energy, not hyperactivity. Mild or fluctuant cases of bipolar disorder, especially in children, can be difficult to distinguish from ADHD, but children with substantial bipolar disorder have clear mood impairments, including elation, grandiosity, severe irritability and anger, a decreased need for sleep, hypersexuality, and racing thoughts.[34] In anxiety disorders, hyperactive behaviors such as fidgeting and inattentive behaviors such as off-task behaviors are accompanied by persistent fears and worries.

The impairment of adaptive functioning in mental retardation is more severe than the social, academic, and occupational impairment associated with ADHD and occurs with an impairment of general intellectual functioning (i.e., an intelligence quotient [IQ] ≤ 75). Like individuals with ADHD, those with pervasive developmental disorders such as autism and Asperger's disorder may exhibit hyperactivity or fidgeting and impaired social, academic, and occupational functioning. However, individuals with pervasive developmental disorders also exhibit a severe disinterest or inability to participate in social interaction or limited and stereotyped behavior, interests, and activities. Although, like ADHD, learning disorders may impair academic or occupational functioning, these disorders, which are frequently comorbid with ADHD, are characterized by a specific learning impairment as evidenced by a significant discrepancy between individuals' performance on a standardized test in reading, mathematics, or written expression and their education and intelligence.

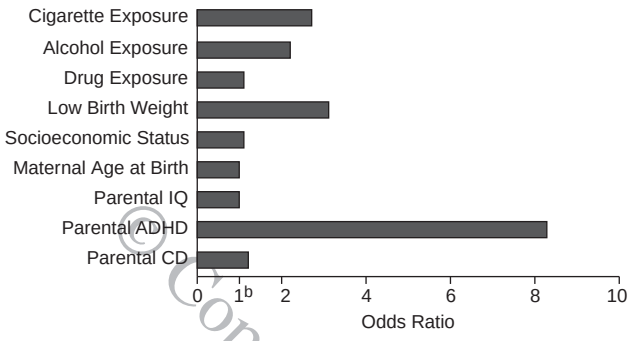
ETIOLOGY OF ADHD

No single etiology has been identified for ADHD, and findings are consistent with a multifactorial hypothesis. Indeed, all neuropsychiatric conditions are thought to be caused by a complex combination of environmental, genetic, and biological factors. Therefore, the proposed etiologies related to prenatal and perinatal risk factors, genetics, and neurobiological deficits may all contribute to the pathophysiology of ADHD in different individuals.

Prenatal and Perinatal Risk Factors

Mick and colleagues[35] used odds ratios, in which 1 is neutral, to examine risk factors for ADHD in siblings (Figure 2). To distinguish whether each of these factors independently contributes to the risk of developing ADHD,

Figure 2. Results From a Logistic Regression Model of Odds Ratios for Prenatal and Perinatal Risk Factors for Attention-Deficit/Hyperactivity Disorder Versus Controls[a]



[a]Data from Mick et al.[35] Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, IQ = intelligence quotient.
[b]1 is neutral.

they used a mathematical model to separate each factor. For example, individuals with ADHD often use alcohol and/or cigarettes; therefore, one could suppose that having a parent with ADHD may contribute to the identification of exposure to alcohol and cigarettes in utero as risk factors for developing ADHD. However, with their analysis, Mick et al. found that, independent of whether a parent has ADHD, exposure to cigarettes or alcohol in utero is a specific teratogen for ADHD that, like low weight at birth, increases the risk of developing ADHD 2- to 3-fold. Parental ADHD, the genetic factor, increased the risk of developing this condition 8-fold. Brain injuries that occur in utero also contributed to the risk of developing ADHD. Socioeconomic status, the mother's age at the time of the child's birth, and parental IQ contributed little to either the risk of developing or protection from the disorder.

Heritability

Studies of dizygotic and monozygotic twins who have grown up in the same environment have been examined to determine the heritability of ADHD (Table 3). A heritability of 0 means that there is no genetic input, and a heritability of 1 means that the characteristic or disorder is completely determined by genetics. Because the identical twins have the same genes and the fraternal twins share only one half of their genes, these studies help to determine the genetic versus the environmental contribution. The mean heritability of ADHD from these studies is approximately 0.75, which means that about 75% of the etiologic contribution to this disorder is genetic. Therefore, ADHD is more attributable to genetic factors than are depression (0.39 heritability),[45] generalized anxiety disorder (0.32 heritability),[46] breast cancer (0.27 heritability),[47] and asthma (0.39 heritability).[48]

One reason for the variation in the heritability of ADHD in these studies is that they used different numbers of items to calculate heritability, from 2 or 3 items from the Rutter A scale to all 14–18 items in the ADHD criteria of various DSM editions. Generally, the studies that used more items showed a higher heritability than did the studies that used only 2 or 3 items. If corrected for unreliability on the basis of the type of scale and number of items used in each of these studies, the heritability of ADHD might be even higher than 0.75.

Candidate Genes

Once the extent of the genetic contribution to ADHD had been revealed, researchers began trying to identify the candidate genes. The association between ADHD and several genes, including those regulating dopamine, norepinephrine, serotonin, γ-aminobutyric acid (GABA), and androgens, has been studied.[49] While some studies[50] have not found an association between any of these genes and ADHD, [51] most did.

The gene association that has been most widely confirmed is the 7-repeat allele of the D_4 dopamine receptor gene (*DRD4*7*).[52,53] *DRD4*7* is a defective gene found in about 30% of the general population and about 50% to 60% of the population with ADHD.[54] Multiple replication of a specific amino acid sequence in *DRD4*7* has been related to a deficiency in translating the dopaminergic signal to the second messenger system. Specifically, there is an incomplete coupling of the receptor to the guanine nucleotide complex in the third cytoplasmic loop of the protein.[54] Other research[55] on the D_4 receptor has shown that, in addition to dopamine, both epinephrine and norepinephrine are agonists at *DRD4*7*. Therefore, medications that affect either of these catecholamines could also affect this dopaminergic system.

Model of Executive Dysfunctions

The change in the nosology from hyperactivity early in the 20th century to ADHD by the early 1980s paralleled the shift in thinking from the belief that this disorder was caused by primarily bad behavior to the hypothesis that the disorder represents a cognitive brain problem that results in associated maladaptive behavior. Now we have a more sophisticated model of the brain dysfunctions that lead to problems with attention, impulsivity, and hyperactivity.

Barkley[56] proposed a model of executive dysfunctions located in the prefrontal cortex that explains the cognitive and behavioral deficits associated with ADHD. Barkley's model comprises 5 major executive functions that enable individuals to recognize and control their actions to achieve a goal: response inhibition, nonverbal working memory, verbal working memory, self-regulation of emotion and motivation, and reconstitution. Response inhibition delays and interrupts responses and controls interference to allow individuals to control verbal and motor impulses. Nonverbal working memory enables a person to have a sense of the past and future and a cognitive

Table 3. Average Genetic Contribution of Attention-Deficit/Hyperactivity Disorder From Studies of Twins Between the Ages of 4 and 16 Years[a]

Study	Twin Pairs (N)	Diagnosis	Measure	Heritability
Eaves et al, 1997[37]	1355	Hyperactivity	Mothers' completion of Rutter A scale	0.60–0.80
Edelbrock et al, 1995[38]	181	Attention problems	Parents' completion of CBCL	0.66
Gillis et al, 1992[39]	74	DSM-III-R ADHD	Structured interviews with parents using DICA	0.91
Gjone et al, 1996[40]	915	Attention problems	Mothers' completion of CBCL	0.73–0.79
Hudziak et al, 2000[41]	492	Attention problems	Parents' completion of CBCL	0.60–0.68
Levy et al, 1997[42]	1634	DSM-III-R ADHD	DSM-III-R–based maternal rating scale	0.75–0.91
Sherman et al, 1997[43]	288	DSM-III ADD-H and DSM-III-R ADHD	Teacher rating form of MTFS and structured maternal interviews using DICA-R	0.73–0.89
Thapar et al, 1995[44]	281	Hyperactivity	Mothers' completion of Rutter A scale	0.88

[a]Adapted with permission from Thapar et al.[36] Abbreviations: CBCL = Child Behavior Checklist, DICA = Diagnostic Interview for Children and Adolescents, DSM = Diagnostic and Statistical Manual of Mental Disorders, MTFS = Minnesota Twin Family Study.

awareness of self. Verbal working memory gives people the ability to internalize receptive and expressive language for self-questioning, self-description, and establishing rules for behavior. Together, the nonverbal and verbal working memories provide the ability for reading comprehension and moral conduct. Through internalizing visual and verbal stimuli, the 2 working memories also lead to the development of the self-regulation of emotion and motivation, which provides individuals the ability to control their emotions and the motivation and persistence necessary to meet their goals. The last major executive function, reconstitution, is a form of play that allows people to analyze the experiences in their working memories to synthesize new responses, which they accept or reject based on the likelihood that the response can help them to achieve their goal. Barkley has proposed that, of these 5 executive functions, response inhibition is most obviously deficient in individuals with ADHD and that this deficit may lead to the impairments observed in the psychological and social abilities associated with the other 4 executive functions.

Brain Imaging

Neurologic differences have been documented in the brains of individuals with and without ADHD through structural and functional magnetic resonance imaging (fMRI). The circuits that control attention are smaller and less active in individuals with ADHD than in controls.[57] These circuits include the parts of the prefrontal cortex that control working memory, alerting, and response inhibition. Because these areas are also rich in catecholamine receptors, the belief that norepinephrine and dopamine are prominently involved in ADHD comes from not only medication and neurotransmitter studies but also studies of the affected brain areas.

Bush and colleagues[58] found differences in the function of the cognitive division of the anterior cingulate cortex in the brains of individuals with ADHD and controls without ADHD. In their study, unmedicated adults with ADHD and adults without ADHD were given the Counting Stroop test, a variation of the Color Stroop, which measures response inhibition. During the Counting Stroop task, a set of 1 to 4 identical words appear on a screen, and subjects are told to identify the number of words on the screen by pressing 1 of 4 buttons, which, from left to right, represent the numbers 1–4. The neutral trials consist of sets of identical common animal names, while the interference trials include sets of identical number words that do not correspond with the number of words appearing on the screen. For example, the word *2* will appear in sets of only 1, 3, or 4. While subjects performed the Counting Stroop, fMRI measured the blood flow in their brains, specifically in the cingulate cortex, to determine which areas were being used during the task.

Metabolism increased in the area of the brain that was used while the task was being performed and diminished when the task was stopped. During a 4-minute span, subjects completed 30-second blocks of alternating neutral and interference trials, each of which contained 20 sets of words. This replication showed that the activity performed during the Counting Stroop is a distinct function that is controlled by a distinct part of the brain. According to the analysis of subjects' reaction times, adults with ADHD took longer to perform the task than the controls. The results of the fMRI showed that the 2 groups also activated different parts of the brain to complete the task. While adult controls activated the cognitive division of the anterior cingulate cortex during the task, adults with ADHD activated a fronto-striato-insular-thalamic network. The use of ancillary areas of the brain by individuals with ADHD demonstrates that, while the brain may compensate for its deficits, these compensations are not perfect and correlate with inefficient processing.[58]

NEED FOR NEW TREATMENTS

While stimulants, the traditional medications for ADHD, are remarkably effective in the treatment of this disorder, their use has some limitations. For example, ADHD lasts 24 hours per day, but we lack 24-hour-per-day treatments. Immediate-release formulations of stimu-

lants must be taken in repeated doses throughout the day. The extended-release formulations of the stimulants are effective for 8 to 12 hours. While these longer acting formulations have been a major advance in our pharmacotherapeutic armamentarium, additional strategies must be employed to cover longer periods. In addition, stimulants have the potential for abuse and may not be optimal in several comorbid conditions such as tic disorders.

Because of stimulants' limitations, a number of alternative medications have been explored in ADHD. Tricyclic antidepressants (TCAs), which affect norepinephrine, may be efficacious in ADHD, but their action is not selective. The effects of TCAs on other neurotransmitter systems can cause side effects such as dry mouth, constipation, sedation, weight gain, changes in blood pressure, and delays in cardiac conduction and repolarization. Selective serotonin reuptake inhibitors (SSRIs) have also been explored as a possible treatment for ADHD, but they have shown no evidence of efficacy. Although antihypertensive medications may help with symptoms of ADHD, these drugs are complicated to use in children because they may be sedating and may cause hypertension if they are abruptly discontinued. Recently, researchers have explored the efficacy of the investigative nonstimulant atomoxetine in the treatment of ADHD. Atomoxetine, which was initially examined under the name tomoxetine as an antidepressant, may be efficacious in ADHD[59] and appears to be a potent and specific norepinephrine reuptake inhibitor.[60]

CONCLUSION

Developmentally sensitive, age-appropriate criteria would help clinicians to more accurately diagnose ADHD in both children and adults. As studies provide more insight into the genetic, environmental, and neurobiological causes of this disorder, the effects of medications on ADHD may be better understood. Expanded medication options will help physicians to choose the most effective and safest treatment for their patients with ADHD, thereby increasing effective therapy and reducing the wide range of ADHD-associated impairments.

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, atomoxetine is not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

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