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Attention-Deficit/ Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood behavioral disorder. Over the past two decades, our ability to diagnose and effectively treat ADHD has improved significantly, and we are now able to help children who would otherwise have long suffered without assistance. Children affected by ADHD more often than not suffer coexisting conditions, such as learning disorders and behavioral difficulties, that are equally if not more disruptive to their healthy development.

CLINICAL PRESENTATION

Throughout the first half of the past century, ADHD was thought to be the result of developmental problems in utero, and the diagnosis given to extremely hyperactive and impulsive children was *minimal brain damage*. As studies of affected children grew, it was recognized that these children were not technically brain damaged and that the concept of minimal brain damage, therefore, was in error. From approximately 1950 to 1970, children with severe hyperactivity and impulsivity were instead considered to suffer from a purely hyperkinetic or hyperactivity syndrome. *DSM-II* (American Psychiatric Association, 1968) recognized a diagnosis similar to what we now view as ADHD for the first time and labeled it within the psychiatric lexicon as the "hyperkinetic reaction of childhood."

During the 1970s, over 200 peer-reviewed publications brought to the forefront a frequently co-occurring symptom of children who suffered

impairing hyperactivity and impulsivity, namely inattention. Based on this wealth of new scientific data, the entire concept of the disorder was reconsidered from one of hyperactivity to one of inattention by the time *DSM-III* (American Psychiatric Association, 1980) was published. The new diagnosis, "Attention Deficit Disorder (with or without symptoms of hyperactivity)," reflected this change. Attention deficit now became the cornerstone or sine qua non of the diagnosis itself. As researchers learned during the following decade that these three symptoms are most commonly intertwined and present in some combined fashion, attention deficit disorder (ADD) was once again renamed with the publication of *DSM-III-R* (American Psychiatric Association, 1987), this time as ADHD, with a series of mixed criteria. The diagnosis was now based on the presence of at least 8 of 14 symptoms, which could constitute a variety or intermingling of difficulties including hyperactivity, impulsivity, and inattention. With the publication of *DSM-IV* (American Psychiatric Association, 1994), the diagnosis became "ADHD (predominantly inattentive type, hyperactive/impulsive type, or combined type)," and it has remained essentially the same in *DSM-5* (American Psychiatric Association, 2013) with one small exception. *DSM-IV* mandated that some symptoms be present before age 7, whereas *DSM-5* now requires that several symptoms be present prior to age 12. As our understanding of the disorder has grown, so has our ability to diagnose it more accurately, which is reflected in each successive version of the *DSM* (Barkley, 1998).

Children diagnosed with ADHD can present clinically in myriad ways. The most easily recognizable children are remarkably physically active and almost always viewed by others as disruptive and extremely impulsive. Many of these children are falsely believed to be willfully dismissive of others' needs and desires, and as a result they are increasingly ostracized as they age. Preschool children are particularly forgiving of their peers' idiosyncrasies, but with age children become less forgiving, especially when one of them is always moving too quickly from topic to topic, rarely able to stay focused in a school or extracurricular activity, and distracting for others to be around. As a result, we commonly see affected children who have not been treated by their school-age years struggling with their self-esteem, as other children simply do not want to learn and play with them. Such social isolation, however, only compounds the feelings that these children already have about themselves, as they indeed also wonder why they cannot focus, stay seated, and control their impulses like their peers.

Another type of child affected by ADHD is simply inattentive but not generally hyperactive or impulsive. This child typically does better with peers but will also soon be filled with self-doubt as to why he can-

not stay focused like his friends, be attentive on the ball field, and complete his schoolwork in the allotted time. As parents and teachers make fruitless but genuine efforts to help this child with his schoolwork (often employing tutors at home and special assistance at school), they become increasingly frustrated with his apparent lack of drive and determination. None of this dissatisfaction goes unnoticed by the child, who begins to view himself as an academic failure, incapable of succeeding in school and often with friends. After years of disappointment, he, just like the child affected by hyperactivity and impulsivity, is likely to lose faith in himself, undermine his own academic and social progress, and despair for his future.

ETIOLOGY

The etiology of ADHD is not clear, but research increasingly points to the cause of the disorder as neurological with limited environmental influence. Numerous brain structures have been implicated in some fashion, including the dorsolateral prefrontal cortex, the dorsal anterior cingulate cortex, the striatum, and the parietal cortex. Imaging studies have demonstrated that the caudate nucleus and globus pallidus (striatum), which contain a high density of dopamine receptors, are smaller in children affected by ADHD than in control groups. This research has also demonstrated that children with ADHD have smaller posterior brain regions (e.g., the occipital lobes), particularly in areas that coordinate the activities of multiple brain regions, such as the rostrum and splenium of the corpus callosum and the cerebellar vermis. Furthermore, we are now convinced that children with ADHD have smaller brain volumes in virtually all regions. Total cerebral volume, including cortical white and gray matter, is smaller by about 3%, and cerebellar volume is smaller by about 3.5%. These volumetric abnormalities persist with age, except those found within the caudate nucleus. There appear to be no gender differences, and the volumetric findings correlate with the severity of ADHD symptoms. Importantly, children who are unmedicated for ADHD show roughly the same differences in brain volume abnormalities as children who have been medicated or treated for ADHD, suggesting that the medication itself is not responsible for these changes (Castellanos et al., 2002).

Research has also begun to demonstrate that children suffering from ADHD have decreased cortical thickening in the anterior cingulate cortex, a key region involved in cognitive control (Makris et al., 2007). Some studies have found that children with a worse clinical outcome have a thinner left medial prefrontal cortex at baseline than children

with a better outcome (Shaw et al., 2006). Taken as a whole, these studies increasingly point to neurological abnormalities in children diagnosed with ADHD.

Another potential cause of ADHD lies within the genetic code, and there are a number of genes that have been found to date to be associated with the disorder. Rare mutations in the human thyroid receptor beta gene on Chromosome 3 have resulted in symptoms suggestive of ADHD and are found in those with a general resistance to thyroid hormone (Hauser et al., 1993). The dopamine transporter gene on Chromosome 5 has also been implicated as a possible genetic cause of ADHD (Gill, Daly, Heron, Hawi, & Fitzgerald, 1997). When the dopamine presynaptic transporter (DAT), which is coded by Chromosome 5, is somewhat overly active and reabsorbs too much dopamine, the postsynaptic neuron cannot be fed adequate amounts of the neurotransmitter, which may result in an inability to maintain focus and attention (see Figure 3.1). Lastly, the dopamine receptor D4 gene on Chromosome 11 and the dopamine receptor D5 gene on Chromosome 4 have also been implicated, such that malfunction of these genes on the postsynaptic receptor does not allow transmission of dopamine (Swanson et al., 1998; see Figure 3.2). Malfunction at Chromosome 5, 11, or 4 and the resulting impairments at the dopamine transporter gene or D4 or D5 receptors would support the monoamine hypothesis of ADHD, that is, that a deficiency of dopamine and norepinephrine leads to clinical findings of ADHD. A number of other genes that code for enzymes that impact dopamine and norepinephrine, such as catechol-O-methyltransferase, monoamine oxidase, and tyrosine hydroxylase, have variably shown a modest association with ADHD (J. Eisenberg et al., 1999; Ernst et al., 1999; Hawi et al., 2001; Jiang et al., 2003; Lawson et al., 2003; Payton et al., 2001).

ADHD is a familial illness. Family studies have repeatedly demonstrated that a sibling's risk of having the disorder is two to five times greater than the general population risk. The parents are also at risk, and there is a three- to five-times-greater likelihood that if a child is affected, a parent is also affected. Twin studies have shown that ADHD is highly genetically bound. Monozygotes (identical twins) have about an 80% risk of suffering ADHD if the identical sibling is affected. ADHD is more tightly genetically bound among monozygotes than breast cancer, asthma, and schizophrenia (Faraone, 2000; Hemminki & Mutanen, 2001; Nikolas & Burt, 2010; Palmer et al., 2001).

A number of environmental factors with almost certain neurobiological impact are also likely to be implicated in the etiology of ADHD. Children with low birth weight, for example, are more likely to suffer ADHD symptoms as they age. The same is true for children who suf-

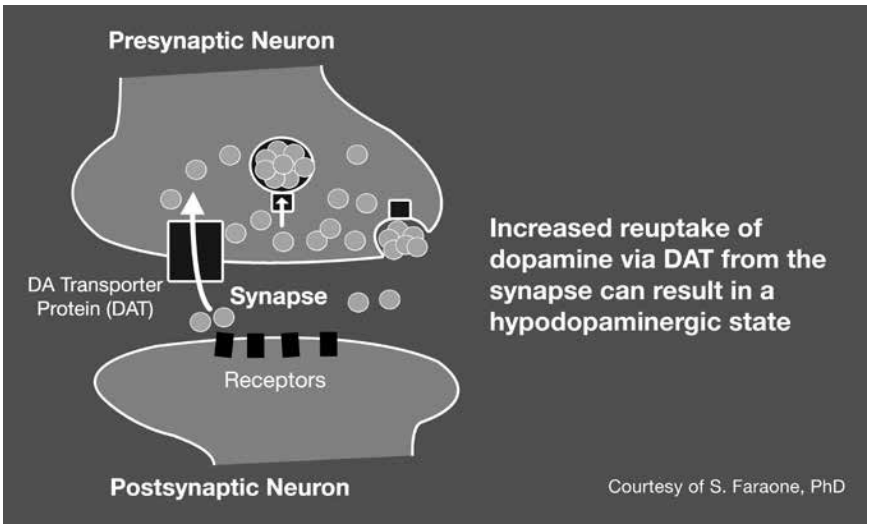

Figure 3.1 Significance of DAT dysfunction.

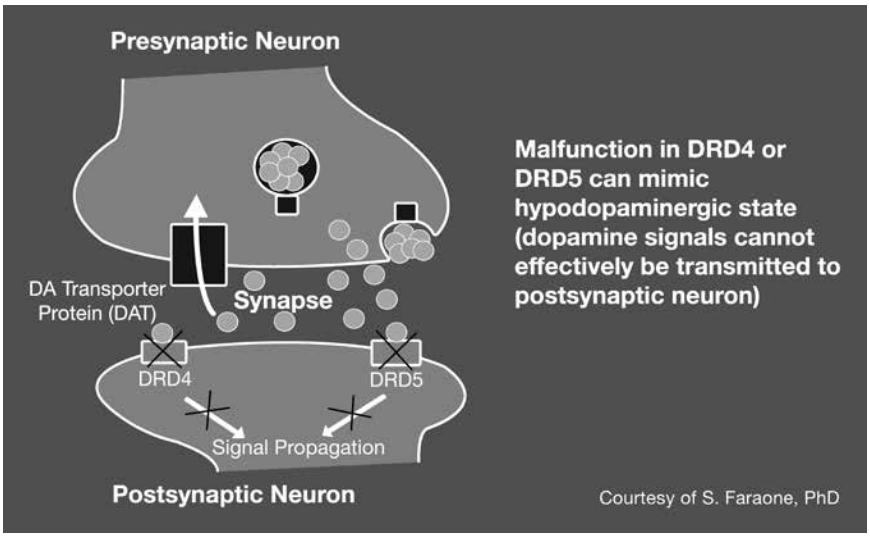

Figure 3.2 Significance of DRD4 or DRD5 dysfunction.

fer traumatic brain injury or experience excessive perinatal stress, whose mothers smoked during pregnancy, or who face severe early deprivation. The precise reasons for these findings are not clear, yet they appear to be more than simply correlational. Rather, it is likely that infants and children who face such environmental circumstances in conjunction with a

genetic risk or predisposition suffer subsequent developmental and neurobiological damage, resulting in symptoms of inattention, hyperactivity, and impulsivity (Nigg & Casey, 2005; Nigg, Nikolas, & Burt, 2010).

Another area that has received much attention in recent years is the role of pesticides, toxins, and diet in the etiology of ADHD. Organophosphate pesticides have been studied minimally in relation to ADHD, with mixed and as yet unimpressive results. Among the industrial exposures, polychlorinated biphenyls (PCBs) and lead are both known to impair working memory, cognitive flexibility, and response inhibition, all characteristics of individuals affected by ADHD. It is plausible, and some studies have suggested but not yet proven, that these toxins could have a role in the development of ADHD. Certainly, there is adequate evidence to suggest that limiting early childhood exposure to these toxins is wise. Although it is clear that severe nutritional deficiency can result in neurodevelopmental impairment, it is not at all clear that mild to moderate deficiencies of various nutrients can lead to ADHD. Zinc, magnesium, iron, and polyunsaturated fatty acids have, perhaps, been studied to the greatest extent, but even here the data are insufficient to correlate cause and effect. Iron deficiency in particular is an attractive etiological hypothesis for ADHD, as iron is necessary in the processing of dopamine, one of the major neurotransmitters responsible for our ability to focus, sit still, and pay attention (Cortese, Angriman, Lecendreux, & Konofal, 2012; Thapar, Cooper, Eyre, & Langley, 2013). Food additives, such as colorings and preservatives, have been suggested as a cause of ADHD since Feingold prescribed a diet free of salicylates and synthetic colors and flavors (Feingold, 1975). To date, however, there is little data to suggest that food colorings and preservatives cause or aggravate ADHD, although one meta-analysis, with significant limitations, did find that approximately one third of children with ADHD may show symptom improvement with a dietary intervention limiting colors and preservatives and that up to 8% of children may experience symptoms of ADHD that are due to food coloring (Nigg, Lewis, Edinger, & Falk, 2012). Finally, there is virtually no convincing evidence linking dietary sugar intake with ADHD (Hoover & Milich, 1994; Millichap & Yee, 2012; Wolraich, Milich, Stumbo, & Schultz, 1985; Wolraich et al., 1994).

EPIDEMIOLOGY

Approximately 1 in 20, or 5%, of children worldwide are affected by ADHD. International research has demonstrated that between 3% and 9% of schoolchildren are affected, although in some studies the percent-

age of affected children is far greater (Goldman, Genel, Bezman, & Slanetz, 1998; Merikangas, He, Burstein, et al., 2010b). A recent random-digit-dialing telephone survey of nearly 96,000 parents in the United States, for example, found that 11% of children aged 4 to 17 years have been given a diagnosis of ADHD, up from 7.8% in 2003, an increase of 42%. Furthermore, 6.1% of children are currently being given a prescription medication for the treatment of ADHD, up from 4.8% in 2007, an increase of 27%, but nearly 20% of affected children are not receiving either medication or counseling (Visser et al., 2013). As with virtually all neurobehavioral disorders of childhood, males are more commonly affected than females. In the past, when ADHD was viewed largely as a disorder of hyperactivity and impulsivity, the vast majority of patients diagnosed were male. However, our current understanding of ADHD as not only a hyperkinetic disorder but also a disorder of inattention has led us to study females more carefully. We now understand that the likelihood of boys and girls being affected is much less discrepant than we had previously thought, such that we now believe males are probably affected only about twice as often as females. Girls typically but not always show less hyperactivity, exhibit fewer conduct problems and externalizing behaviors, demonstrate symptoms a bit later than boys, and are more often to be "politely inattentive" and not as overtly disruptive as boys.

Interestingly, we sometimes see a sex paradox with ADHD. That is, since girls are less often afflicted by ADHD, when they do demonstrate observable impairment, it may appear as clinically more severe than that of the average boy with ADHD (Loeber & Kennan, 1994). The sex paradox in ADHD is consistent with other multifactorial or polygenic conditions (e.g., disorders where numerous factors or genes are acting as combined causal agents). In other words, since girls are less commonly affected by ADHD on a population level, it takes a greater accumulation of vulnerability and risk factors for them to develop the disorder. Even more striking is the fact that girls with ADHD tend to have more functional impairment than boys with ADHD, such as an increased risk of depression, suicide, and eating disorders (J. Gershon, 2002; Mikami, Hinshaw, Patterson, & Lee, 2008). Furthermore, girls with ADHD, particularly the inattentive subtype, have been shown to be bullied more often, to have worse peer relationships, and to be more negatively affected in academics than boys with ADHD (Elkins, Malone, Keyes, Iacono, & McGue, 2011).

Over 80% of children with ADHD demonstrate some sort of psychopathology as adults. Over half and perhaps as many as two thirds continue to struggle with ADHD, but other impairments, such as mood, anxiety, and learning disorders, commonly persist or develop (Cantwell, 1996). Furthermore, adults with ADHD face more problems maintaining

employment, an increase in sexual and reproductive risks, an increase in motor vehicle accidents and traffic violations, an increase in substance abuse, and a higher accident rate than those not affected by ADHD (Barkley, Murphy, & Kwasnik, 1996; Biederman, Petty, et al., 2008; Biederman, Wilens, Mick, Faraone, & Spencer, 1998). This increase in risk translates into higher associated medical costs and more outpatient medical care, inpatient hospitalizations, and emergency room visits for those with ADHD (Leibson, Katusic, Barbaresi, Ransom, & O'Brien, 2001).

Parents commonly ask about the risk of substance abuse among children who are treated for ADHD with stimulants. After much investigation, we now recognize that individuals with ADHD have a greater risk of substance abuse than the general population. In one longitudinal study, the hazard of developing any substance use disorder or alcohol dependence during the 10-year period was approximately 1.5 times greater among those with ADHD than among the general population, and even higher hazard rates were found for drug dependence (hazard ratio = 2.7) and cigarette smoking (hazard ratio = 2.4; Wilens et al., 2011). However, the data clearly show that children and adolescents with ADHD who are treated with stimulants are no more likely to become abusers of alcohol, tobacco, and illicit drugs than untreated youth with ADHD (Humphreys, Eng, & Lee, 2013). In fact, some studies have even found that those treated with stimulants for ADHD have lower rates of substance abuse than untreated adolescents who suffer ADHD, in addition to a host of other benefits (Wilens et al., 2008). In one study of 370 children with ADHD over 18 years, prescription stimulant treatment was associated with improved academic success, such as reading achievement, decreased absenteeism, and a decreased likelihood of grade retention (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007). Another 10-year prospective study found that those treated for ADHD with stimulants had lower subsequent rates of depression, conduct disorder, oppositional defiant disorder, and anxiety disorders, in addition to lower rates of grade retention, than children with ADHD who never received stimulant treatment (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009).

Primary care practitioners treat the vast majority of ADHD. ADHD-related outpatient visits to primary care practitioners increased from 1.6 million to 4.2 million between 1990 and 1993, along with an increase in the use of stimulant medications to treat the disorder (Swanson, Lerner, & Williams, 1995). Between 1991 and 2000, the annual production of methylphenidate rose by 740% in the United States. Production of amphetamine increased 25 times during this same time period (Diller, 2002). From 2000 to 2010, the number of physician outpatient visits in which ADHD was diagnosed increased by 66%, from 6.2 to 10.4 million visits.

Although pediatricians and family physicians continue to diagnose and treat most cases of ADHD, an increasing number of children and adolescents are being treated by psychiatrists, totaling 36% in 2010 (Garfield et al., 2012). The reasons for the increase in specialty care are unclear, particularly as the number of ADHD cases has continued to rise sharply while the number of specialists has risen only modestly. One reasonable hypothesis is that parents and practitioners are becoming increasingly aware of the potential hazards of prescription treatment for ADHD and prefer a specialist to be at the helm. A similar shift toward specialist care has been found in the case of antidepressants, where safety concerns have mounted and regulatory agencies have provided stricter recommendations for treatment of children and adolescents (Libby et al., 2007).

Although we find ADHD present within every culture studied, the United States uses the vast majority of stimulants. In 2000, America utilized 80% of the world's stimulants, while most other industrialized countries used about 10% the amount the United States used (Diller, 2002). Canada uses stimulants at about 50% of the U.S. rate. Hawaii has the lowest per-capita use of methylphenidate by a factor of about five. High stimulant utilization areas are found mostly in the eastern United States near college campuses and clinics that specialize in the diagnosis and treatment of ADHD (U.S. Drug Enforcement Agency, 2000). In 2008, approximately 2.8 million children and adolescents in the United States—3.5% of all youth in the United States—received a stimulant medication for ADHD, and sales of medications used to treat ADHD have now risen to over $4 billion from $759 million in the year 2000 (Food and Drug Administration, 2006; Scheffler, Hinshaw, Modrek, & Levine, 2007; Tcacik, 2011; Zuvekas & Vitiello, 2012). Finally, the Drug Enforcement Agency, which limits the amount of commercially manufactured amphetamine produced each year, has allowed increasing volumes to be produced in recent decades in line with the increased demand—in 1990, that number was 417 kg; in 2000, it was 9,007 kg; and in 2012, it was 25,300 kg (Kent, 2013).

Concurrent with an increase in the diagnosis and treatment of ADHD in children, adults have also been recognized to suffer from ADHD. The use of medications in adults increased 90% between 2002 and 2005, and the use of medications to treat ADHD in adults aged 20 to 44 rose 19% in 2005 alone. That same year, an estimated 1.7 million adults aged 20 to 64 years and 3.3 million children under 19 took a medication for ADHD (Okie, 2006).

With all of the increase in treatment, we would be remiss if we did not ask ourselves why the diagnosis has appeared more frequently in recent years. There are numerous possible explanations. Perhaps the most

evident reason is that physicians and allied professionals are much better at recognizing ADHD today than they were in the past. Increasingly, not only child and adolescent psychiatrists but also neurologists, pediatricians, and primary care practitioners, including primary care physicians, nurse practitioners, and physicians' assistants, are being trained in the identification and treatment of ADHD.

Many wonder whether an increase in scholastic demands also accounts for some of the growth we have witnessed in the diagnosis and treatment of ADHD. This suspicion is impossible to fully substantiate, but many argue convincingly that the increased reliance on standardized testing within our schools and the consequent increase in focus required for students to perform on standardized exams has led to increasing parental anxiety about school performance and a greater likelihood that they will have their children evaluated for ADHD. As a result of the No Child Left Behind federal legislation, schools and teachers are also under increasing pressure for their students to perform well on standardized tests in order to maintain necessary funding. Parent and teacher pressure and a visit to a physician for an evaluation will not, in and of themselves, result in a diagnosis of ADHD, but we must also not forget the recent changes to our health care system (e.g., the influence of managed care), which have left physicians and therapists with less time to complete an evaluation and to arrive at a proper diagnosis. In addition, the availability of an increasing number of medications for the treatment of ADHD and the influence of the pharmaceutical industry on physicians have, no doubt, fostered an increase in the treatment of this disorder.

Finally, the 1991 amendments to the Individuals with Disability Education Act (IDEA) may have also inadvertently supported an increase in the diagnosis and treatment of ADHD by establishing the category of "other health impaired" (OHI). The OHI categorization now allows children with ADHD to receive special education services, whereas heretofore only children with a recognized learning disorder were given such supports. Consequently, a child with ADHD who is suffering academically can now also receive special assistance at school. While entirely justifiable and reasonable, the addition of OHI to the IDEA may have encouraged some parents and teachers to more readily identify ADHD in children who may have been left to struggle in silence in the not-too-distant past.

CLINICAL COURSE

The symptom of ADHD most often first reported is hyperactivity. In some cases mothers report that even in utero the child was active and

kicking from nearly the moment of conception. More commonly, however, parents note a gradual onset of symptoms during the primary years. Parents will often report that by 2, 3, or 4 years of age, their children appeared very active and constantly "on the go." As children age and are able to make more choices for themselves, impulsivity is more easily spotted. As children age into their teen years, hyperactivity and impulsivity diminish in most cases. By midadolescence and into adulthood, it is much less common to experience proper hyperactivity, although some degree may remain and be described now as a sense of internal restlessness. Inattention, for those who are affected by this type alone or by combined-type ADHD, commonly persists to some degree well into adulthood, but often diminishes at least somewhat over time.

The natural history of ADHD is understood in general terms to follow the "rule of thirds," such that approximately one third of children demonstrate significant symptom resolution and are not terribly bothered in adulthood, about one third of children continue to experience inattention into adulthood, and about one third of children continue to experience symptoms in all domains (hyperactivity, impulsivity, and inattention) and to suffer other related difficulties, such as oppositional defiance, severe conduct-disordered behavior, excessively poor academic achievement, substance abuse, and perhaps even some antisocial traits as adults. Although one third of children appear to generally outgrow their ADHD, the majority of children affected by ADHD appear to maintain the diagnosis into adulthood, with the strongest predictor of a poor prognosis being prepubertal aggression (Cantwell, 1996).

Studies of specific age-related changes in children with ADHD indicate that preschool children, ages 3 to 5 years, are often identified as having hyperactive and impulsive symptoms. By school age, 6 to 12 years, children are often noted to suffer from a combination of symptoms (or inattentive symptoms alone in the case of inattentive type only). By adolescence, 13 to 18 years, youths complain of inattention, often with some restlessness and impulsivity, and adults likewise often complain of inattention with periodic restlessness and impulsivity.

DIAGNOSIS

Given the high prevalence of ADHD, it is not common to mistake the combined symptoms of hyperactivity, inattention, and impulsivity for another disorder. However, many other possible explanations for these symptoms (a.k.a. the "differential diagnosis") exist, including mood and psychotic disorders, anxiety disorders, learning disorders, intellectual

disability and borderline intellectual functioning, oppositional defiant and conduct disorders, autism spectrum disorders, substance use disorders, and various personality disorders. Symptoms of hypervigilance and impulsivity are also sometimes found among children who have been physically or sexually abused or subjected to excessively harsh parenting. Finally, there are a number of general medical illnesses that can also result in a clinical picture that appears to be something like ADHD, including seizure disorders, chronic otitis media, hyperthyroidism, sleep apnea, various drug-induced inattentional syndromes, head injury, hepatic illness, toxic exposures, and narcolepsy.

DSM-5 diagnostic criteria for ADHD include two general symptom categories: (a) inattention and (b) hyperactivity and impulsivity. *DSM-5* demands that six of nine symptoms, in either or both domains, be present to meet diagnostic criteria. In addition to general inattention, symptoms within the inattentive domain include making careless mistakes, having difficulty following instructions and listening to others, being forgetful and poorly organized, losing things necessary for school or other required activities, being easily distracted, and avoiding tasks that require sustained focus. Within the hyperactive domain, symptoms include being always on the go and having great difficulty settling down, being extremely talkative, having difficulty quietly engaging in play or relaxing activities, having difficulty remaining seated for extended periods of time, being fidgety, and running or climbing about in locations where it is not appropriate to do so (e.g., the classroom, jumping on the furniture at home). Impulsive symptoms include blurting out responses to questions before they have been fully stated, having difficulty waiting one's turn, and interrupting and intruding on others. The *DSM* also demands that a series of so-called functional criteria be met for an individual to qualify for the diagnosis: The symptoms must have persisted for at least six months; at least some symptoms must have existed before 12 years of age; there must be impairment in two or more settings (home, school, church, ball field, etc.); and there must be social, academic, or occupational impairment (American Psychiatric Association, 2013).

Many parents ask about having their child "tested" for ADHD. As yet, there is no single test to identify ADHD. Assessing *DSM-5* symptoms to determine the degree of impairment is, at this time, the most useful measure of ADHD. The clinician must be careful, however, because ADHD should never be diagnosed in a one-to-one setting. Many, and perhaps most, children affected by ADHD are able to focus and contain their behavior when attention is focused solely on them, such as during a school tutorial, during a visit with a physician or therapist, or while playing video games. During these moments, all attention is focused entirely

on the child, who is getting feedback to every statement, movement, and nuance. Rather, it is during shared or group activities, or when a child must wait his or her turn, that the symptoms of ADHD are most clearly evident. Consequently, the observations of not only the clinician, but also the parents, grandparents, or other caregivers; schoolteachers; coaches; Sunday school teacher; and so forth are vital in establishing a diagnosis.

Although there is no "test" to establish the diagnosis of ADHD, neuropsychological testing is often useful in measuring symptom severity. As would be expected, most children with ADHD have significant impairments in executive functioning, including their ability to maintain attentional vigilance, utilize working memory effectively, plan, organize, and inhibit impulsive responses. Neuropsychological testing of children with ADHD typically identifies impairment in spatial working memory, planning ability and ability with mazes, stop-task response suppression, and naming speed. Perhaps the most popular neuropsychological tests for ADHD are the continuous performance tasks. These instruments require a child to stay focused on a computerized task, such as pressing the space bar each time a certain letter or number appears on the screen, while the pace of the stimuli is varied and distractions are purposely added in. The tests, which include the Test of Variables of Attention (TOVA), the Conners' Continuous Performance Test (CPT), and the Intermediate Visual and Auditory Continuous Performance Test (IVA), are sometimes useful for monitoring symptoms and the changes that occur over time and with treatment (Nigg et al., 2005). However useful they may sometimes be, it is important to recognize that neuropsychological tests have not been found to be reliable diagnostic tools for ADHD.

The diagnosis of ADHD is multifactorial and relies on a thorough clinical interview, collateral interviews with individuals who see the child in numerous settings, an early age of onset of at least some symptoms, and symptoms in more than one setting. The clinical interview should include a diagnostic assessment of the primary complaint and a review of other possible explanations for the observed symptoms. More specifically, the clinician should assess not only inattention, hyperactivity, and impulsivity, but also general behavior (including oppositional and conduct difficulties), mood, anxiety, psychosis, trauma, vocal and motor tics, and substance abuse. A full medical history, including a detailed developmental, family, educational, and social history, should also be assessed.

Because children are often not the best historians and almost universally have trouble describing their symptoms of ADHD and other mental disorders (at least until adolescence), various objective rating scales have been designed for use by parents, teachers, and other collateral informants to help identify symptoms. Some of the better-known

rating scales for ADHD include the Swanson, Nolan, and Pelham Questionnaire (SNAP) for parents and teachers; the Conners scales for teachers, parents, and affected adults; the ADHD Rating Scale (ADHD-RS); the Vanderbilt ADHD rating scales for parents and teachers, and the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) for teachers. These rating scales are readily available as freeware or for purchase on the Internet.

Some individual practitioners will engage in a treatment trial with medication in order to establish or confirm the diagnosis. This approach is not advised, as the risk of adverse effects is not insignificant. Furthermore, many individuals, perhaps most, without ADHD will show some degree of improvement in their attention and focus, along with a decrease in impulsivity and general activity level, when treated with a stimulant medication. When an individual is affected by ADHD, however, the degree of improvement seen with treatment is remarkable and much greater than that typically seen by individuals who are unaffected. Although reliable indicators are not available, according to parent reports children with ADHD will commonly show greater than 50% improvement in their symptoms of inattention, hyperactivity, and impulsivity, whereas individuals unaffected by ADHD may show only small increases of 10% to 15% improvement in their ability to focus and pay attention.

Other practitioners will employ a placebo trial before initiating treatment with a stimulant. While placebo responses in many areas of medicine are high, they are moderate in ADHD (approximately 30%) but not sustained, thereby only further prolonging the effort at establishing a proper diagnosis (Sandler, Glesne, & Geller, 2008). Consequently, this method is also not recommended.

Approximately two thirds of children with ADHD present with one or more coexisting or comorbid psychiatric disorders (Biederman et al., 1996; Spencer, Biederman, & Wilens, 2000). The percentage of children with ADHD comorbid with another diagnosis varies greatly by study, but there is no denying that comorbidities remain a major concern for most children with ADHD. Anxiety disorders, behavioral disturbances such as oppositional defiant disorder and conduct disorder, mood disorders, tics, and learning disorders are extremely common comorbidities among children with ADHD.

TREATMENT

Treatment for ADHD typically involves three primary considerations: (a) medication; (b) behavioral therapy; and (c) educational support. The

Multimodal Treatment Assessment (MTA) Study of 1999 as well as numerous other studies have clearly demonstrated that medication is the most effective and reliable treatment for children suffering from the core symptoms of ADHD (MTA Cooperative Group, 1999). Although more recent iterations of organizational skills training have shown promise (see below), behavioral treatments have never demonstrated the efficacy that medications have for the primary symptom domains of ADHD (i.e., inattention, hyperactivity, and impulsivity). Behavioral treatments have, however, proven to be of great utility for commonly related impairments that beset children with ADHD, such as oppositional behavior and defiance. The MTA Study also found that more frequent and higher dosing of stimulant medication, along with increased physician contact (e.g., more frequent visits), leads to better treatment response and improved outcomes for children affected by ADHD.

Stimulants remain the most effective and most commonly employed treatment for ADHD, although a number of other medications are sometimes utilized. In 2010, 87% of outpatient prescriptions given for treatment of ADHD in the United States comprised stimulants, with the remaining 13% comprising alpha-2 agonists, atomoxetine, and antidepressants (Garfield et al., 2012). Although not entirely elucidated, the mechanism of action appears to involve the reuptake inhibition of dopamine and, to a lesser extent, norepinephrine (see Figure 3.3). In addition, stimulants cause an increase in the release of presynaptic norepinephrine and dopamine. Some stimulants are also mild inhibitors of monoamine oxidase (MAO), an enzyme that breaks down norepinephrine and dopamine, thereby leaving more active neurochemical in the synapse for a longer time. Amphetamine, but not methylphenidate, also promotes passive diffusion of norepinephrine and dopamine into the synaptic cleft and promotes the release of norepinephrine from cytoplasmic pools (Wilens & Spencer, 1998).

The response rate to stimulants is remarkably high and far greater than with most psychiatric medications. Regardless of the stimulant selected, typically 70% of children and adolescents with ADHD will respond favorably to the first medication trial (Spencer et al., 1996). If the first stimulant attempt is not effective, the second stimulant trial will usually pick up an additional 10% to 15% of individuals, such that 85% of those affected by ADHD will show statistically significant symptom improvement by the time they have tried two stimulants (Elia, Borcherding, Rapoport, & Keysor, 1991). This degree of efficacy is rarely found with treatments in any medical discipline. As implied, there is no significant difference in response rates when looking at large populations of youth treated with amphetamine, methylphenidate, or any of their

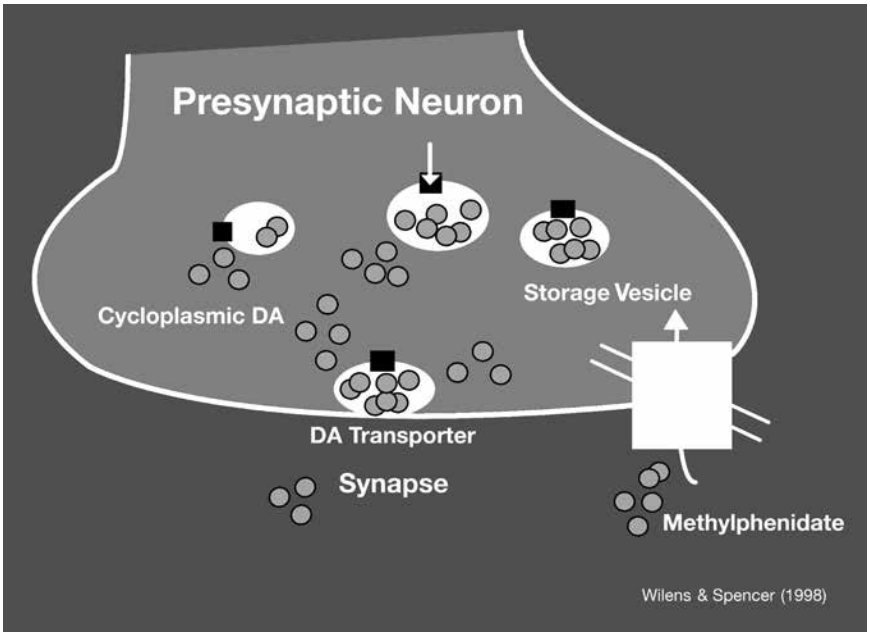

Figure 3.3 Probable mechanism of action of methylphenidate. Methylphenidate blocks the reuptake of dopamine into the presynaptic neuron, thereby increasing the amount of dopamine within the synapse that is free to interact with the postsynaptic neuron.

derivatives, and numerous studies have demonstrated efficacy for these treatments in preschool children, school-age children, adolescents, and adults, although preschool children tend to show a less robust treatment effect (Arnold, 2000; Greenhill et al., 2006).

Historically, children and adults with ADHD were treated with immediate-release medications that were dosed numerous times throughout the day to maintain effect. The first long-acting stimulant medications for the treatment of ADHD were designed to result in a steady blood level of stimulant throughout the day. These medications, however, such as Ritalin SR and Metadate ER, were found to be ineffective for many patients. We now realize that maintaining a steady blood level of a stimulant throughout the day does not effectively treat ADHD beyond a few hours for most individuals due to tachyphylaxis or the fact that the body's response to stimulants diminishes rapidly. Consequently, the blood level of a stimulant must be steadily increased throughout the day to maintain a continued response. Over the past decade, numerous long-acting medications have been developed that take advantage of our

increasing knowledge of how these medications must be dosed (Swanson et al., 2003).

It is important to note that this method of treatment does not result in addiction or any habit-forming effect of the medication. Rather, because all individuals respond to the benefits of stimulants for only about as long as the half-life of the drug (presumably because of tachyphylaxis), another dose of the medication must be delivered at approximately every half-life to maintain clinical response. (See the Appendix for a thorough discussion of psychopharmacology, including drug half-lives.) As the half-life of methylphenidate is about two and a half to four hours and the half-life of amphetamine is about four to six hours, these medications must be dosed at those intervals if a sustained clinical response is to be achieved. The newer long-acting medications, such as Concerta, Adderall XR, Focalin XR, Metadate CD, Ritalin LA, Vyvanse, Daytrana, and Quillivant XR, take advantage of our understanding of tachyphylaxis, and by various mechanisms they increase the blood level of stimulant throughout the day, mirroring the effects of dosing an immediate-release medication numerous times throughout the day, thereby resulting in continual efficacy (see Figure 3.4).

Although doses vary considerably, the average dose of methylphenidate in the United States is typically about 30 mg per day and that of

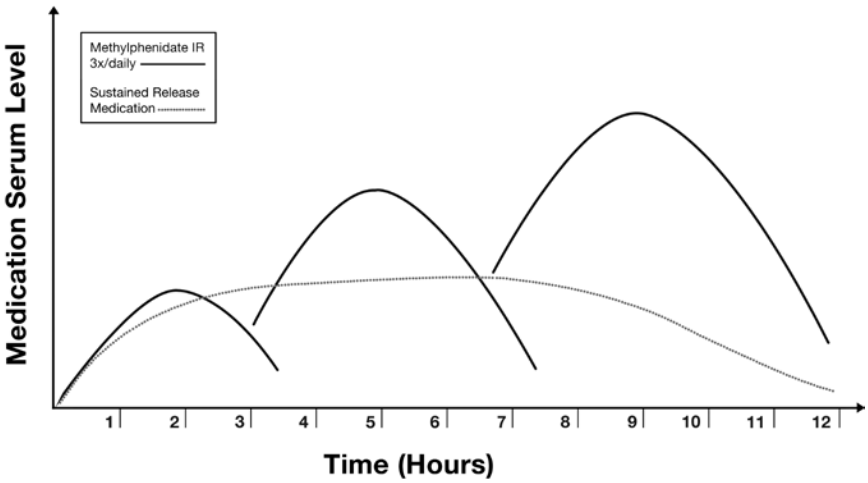

Figure 3.4 Tachyphylaxis and stimulant dosing. The use of a sustained-release medication (or one that maintains a steady blood level of stimulant throughout the day) does not result in an increase in blood levels and therefore is not effective after the first few hours of treatment. In contrast, repeated dosing of immediate-release medications does lead to increasing blood levels throughout the day and is the model for the newer and successful long-acting stimulant medications.

amphetamine about 20 mg per day. Body weight was historically utilized to determine the most effective dose for a given patient. Approximately 1 mg/kg per day for methylphenidate and 0.6 mg/kg per day for amphetamine were the generally accepted values. However, we now realize that weight-based dosing is rarely accurate, as children, adolescents, and adults may require far lower or far higher doses, depending upon idiosyncratic features that have yet to be elucidated (Rapport & Denney, 1997). Consequently, we currently dose these medications to clinical response, lowering the dose or changing the medication if side effects develop.

In many cases children do not adequately benefit from stimulants because they are not properly dosed for a sufficient time. Compounding this problem is the fact that many practitioners are not comfortable prescribing stimulants and will therefore provide only a low dose, which will generally not result in notable benefit. For these reasons, practitioners are now often advised to follow a forced-dosage titration when starting a stimulant medication in a child diagnosed with ADHD. A forced-dosage titration takes place over a relatively short time and relies on increasing the dose every week or two until clinical benefit is achieved. For a child taking immediate-release methylphenidate, the practitioner may begin the dose at 5 mg three times a day for the first week, advance the dose to 10 mg three times a day for the second week, and advance the dose still further to 15 mg three times a day for the third week. A more conservative approach may involve dosing at 5 mg, then 7.5 mg, then 10 mg weekly. As long as rating scales are utilized during this period by the parents and teachers and side effects are well monitored by the family, the practitioner will typically know within three weeks if methylphenidate is helpful for this child.

Utilizing a long-acting methylphenidate product for the same child—Concerta, for example—the practitioner may prescribe 18-mg tablets in the morning for the first week, 36-mg tablets in the morning for the second week, and 54-mg tablets in the morning for the third week. If at any point significant side effects are encountered, the family is instructed to call the practitioner, stop the medication, and seek clarification on how to proceed. For a child prescribed Adderall XR, a long-acting amphetamine, a dose of 10 mg per day may be utilized for the first week, 20 mg for the second week, and 30 mg for the third week. Again, if impairing side effects are encountered, the family should contact the practitioner and clarify whether or not to continue.

The starting stimulant dosage and weekly increases are determined by the practitioner's clinical experience and perception of symptom severity. Although we do not rely on weight-based dosing any longer, sometimes practitioners will initiate treatment with some consideration

of the child's weight. For example, a practitioner may start a child of 25 kg on a forced-dosage titration of Concerta of 18 mg for the first week, 27 mg for the second week, and 36 mg for the third week; while a child of 50 kg may be dosed at 18 mg for the first week, 36 mg for the second week, and 54 mg for the third week. Although this method is an imprecise science, as long as the child's caregivers understand the potential side effects of treatment, dosage increases in this fashion result in the most rapid assessment of medication efficacy.

Side effects of stimulants are common but rarely significant and insurmountable. The four most common difficulties are nausea, headaches, insomnia, decreased appetite. Other less frequent side effects include the unmasking of motor and vocal tics, anxiety, hypertension, tachycardia, diaphoresis (sweating), tremors, and even psychosis. Insomnia and appetite suppression are generally the most distressing side effects for patients and can be so bothersome that the medication dose may need to be decreased or the medication itself changed. On some occasions, additional medication may be necessary to address these side effects. Relative contraindications to the use of stimulants include hypertension, symptomatic cardiovascular disease, glaucoma, hyperthyroidism, severe Tourette's syndrome, significant drug abuse, and psychosis. Depending on the nature and severity of these difficulties, the practitioner may decide to treat with stimulants or alternative medications (see below).

There have been increasing popular concerns about the cardiac safety of stimulants, and a number of patient advocacy groups and physicians have suggested that caution is demanded of those prescribing stimulants (Biederman, Spencer, Wilens, Prince, & Faraone, 2006). This issue has been explored in great detail by the American Academy of Child and Adolescent Psychiatry (AACAP), American Academy of Pediatrics (AAP) and the American Heart Association (AHA), among others, and it has been clearly determined that children with heart conditions have a higher incidence of ADHD than the general population (Vetter et al., 2008). It is also clear that, although rare, cardiovascular events (e.g., hypertension, arrhythmias, cerebrovascular disease) are more common in stimulant users than in those who do not use stimulants, and in a nationwide study in Denmark of over 700,000 individuals followed for nearly 10 years, such occurrences were twice as likely among those using stimulants, particularly those with significant risk factors such as preexisting diabetes or cardiovascular disease, and those taking high doses of the stimulant (Dalsgaard, Kvist, Leckman, Nielsen, & Simonsen, 2014).

Current recommendations endorsed by these leading medical specialty organizations include the following: First, it is advised that all children who are diagnosed with ADHD be carefully evaluated for heart

conditions prior to treatment. Second, the most important features of this assessment are a patient and family cardiovascular history along with a physical examination focused on cardiovascular risk factors. Acquiring an electrocardiogram (ECG) or echocardiogram is not mandatory or advised for all patients. However, it is recognized that obtaining an ECG or echocardiogram is reasonable if risk factors are identified, including a history of chest pain, dizziness, syncope (fainting), exercise intolerance, shortness of breath or a family history of sudden cardiac death in an individual under 40 years of age. Finally, treatment of patients with ADHD should not be withheld because an ECG is not performed unless further cardiac investigations are indicated. It is important to note that medications that treat ADHD have not been shown to cause heart conditions, nor have they been demonstrated to cause sudden cardiac death. However, stimulant medications that treat ADHD almost always result in modest increases in heart rate and blood pressure. While these side effects are not usually considered dangerous, blood pressure, heart rate, and cardiovascular symptoms should be monitored regularly in patients treated for ADHD. Most importantly, our best data indicate that there is no association between stimulant use in children and adolescents with ADHD and sudden cardiac death, myocardial infarction, stroke, or ventricular arrhythmia (Winterstein, 2013). The recommendations for cardiac monitoring prior to starting a stimulant medication in a child or adolescent, as put forth by the American Academy of Pediatrics and endorsed by the AACAP, Society for Developmental and Behavioral Pediatrics, and National Initiative for Children's Healthcare Quality, among others, appear in Figure 3.5.

The standard of care for treatment with stimulants includes the measurement of vital signs (e.g., blood pressure and heart rate) as well as a cardiac exam and a full family history. As previously discussed, the identification of cardiac concerns suggests the need for an ECG and a pediatric cardiology referral for possible echocardiogram prior to treatment. During treatment, height and weight measurements should be performed annually at a minimum and compared to published norms for age. If height for age decreases by more than one standard deviation while the patient is on treatment with stimulants, referral to a pediatric endocrinologist to evaluate possible growth hormone deficiency or hypothyroidism should be considered. Blood pressure and heart rate should be evaluated at least twice annually as well as prior and subsequent to any dosage increase. If the patient's medical history is unremarkable, laboratory and neurological testing are not indicated. Psychological and neuropsychological testing are not mandatory and should be performed only if the patient's history suggests general low cognitive ability or low

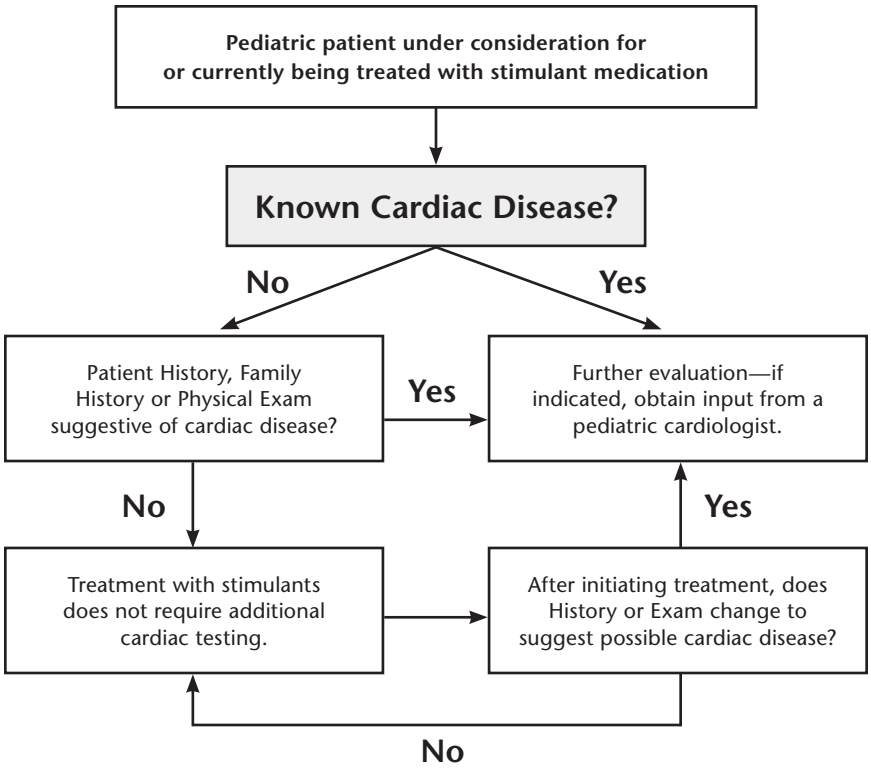

Figure 3.5 Cardiac evaluation of children and adolescents receiving or being considered for stimulant medications. Source: Perrin, Friedman, Knilans, American Academy of Pediatrics Black Box Working Group, and American Academy of Pediatrics Section on Cardiology and Cardiac Surgery (2008).

achievement in language or mathematics relative to his or her intellectual functioning (AACAP Work Group on Stimulant Medications, 2002).

There are numerous pros and cons to the use of stimulants for the treatment of ADHD. As previously noted, stimulants are highly effective and have been utilized successfully for many years. However, their use results in a limited duration of action, and there are sometimes significant side effects and occasionally contraindications. Consequently, a variety of other medications have been developed for the treatment of ADHD.

Many children, perhaps over half of those who initiate treatment with a stimulant, may develop a transient motor tic (e.g., a repetitive, rhythmic motor movement, such as eye blinking or nose wrinkling; Borcherding, Keysor, Rapoport, Elia, & Amass, 1990; Tannock, Schachar, & Logan, 1995). Most tics diminish with time and are not a cause for

great concern by the child or family (see Chapter 9). At this time, it is not clear that stimulants cause tics, although they may "unmask" them or make them more evident. The comorbidity or co-occurrence of tics in individuals with ADHD, whether or not they have been treated with stimulants, is quite high and generally noted at between 10% and 15%. Historically, it was believed that stimulants caused motor and vocal tics. We now realize that stimulants actually improve tics in many cases, so our understanding is not quite as simplistic as it once was (Gadow, Sverd, Sprafkin, Nolan, & Ezor, 1995).

For children who develop tics while taking stimulants, a slight decrease in the stimulant dose or a discontinuation or change of stimulant is often effective. At other times we are able to use habit reversal therapy, a behavioral therapy targeted directly at tics (see Chapter 9). If the tics are severe, we may consider other medications, such as atomoxetine (Strattera) for the treatment of ADHD, which may be less likely to cause tics, or alpha-2 agonists, such as clonidine (Catapres) or guanfacine (Tenex), or even antipsychotic medications. The mechanism of action of alpha-2 agonists is much less clear but may involve decreasing activity in the locus coeruleus noradrenergic cell bodies to improve attentional arousal and cognitive processes (Pliszka, McCracken, & Maas, 1996). Although alpha 2-agonists are frequently employed in children and adolescents, only the long-acting ones, Intuniv (extended-release guanfacine) and Kapvay (extended-release clonidine) are FDA approved for the treatment of ADHD; otherwise, the sole FDA indication for these medications is hypertension in adults.

More commonly, alpha-2 agonists have been utilized to decrease residual hyperactivity, impulsivity, and aggression, and to treat insomnia and treatment-emergent motor and vocal tics. Dosages of clonidine (Catapres) have typically been 0.1 to 0.3 mg per day and dosages of guanfacine (Tenex) have typically been 1 to 3 mg per day, although these dosages are sometimes doubled. In terms of the long-acting preparations, dosages of clonidine (Kapvay) are generally 0.1 to 0.4 mg per day, divided into morning and evening doses, and dosages of guanfacine (Intuniv) are generally 1 to 4 mg per day, given once daily. A routine physical examination and the assessment of vital signs should be performed prior to initiation of treatment. Contraindications to the use of alpha-2 agonists include coronary artery disease and impaired liver and renal function. Side effects most commonly include rebound hypertension and tachycardia, hypotension, sedation, dizziness, constipation, headache, and fatigue. When initiating treatment with an alpha-2 agonist, we generally begin with late afternoon or evening dosing and titrate toward the morning. With a child who is successfully utilizing a stimulant for the treatment

of ADHD but suffering insomnia or late-afternoon rebound hyperactivity, we may begin with 0.05 mg (half a tablet) of clonidine (Catapres) or 0.5 mg (half a tablet) of guanfacine (Tenex) an hour before bedtime. This treatment may allow the child to relax, become less agitated and aggressive, and sleep better through the night. If the child continues to have afternoon difficulties after three or four days of this evening dose, we may add another dose of the same amount around 3 or 4 p.m. when he or she comes home from school. Should disruptivity, aggression, agitation, or tics persist, we may add yet a third dose toward the morning after three or four more days. If the initial dose is not sufficient, we may increase the dose to a full tablet, 0.1 mg of clonidine or 1 mg of guanfacine, in the evening, afternoon, and morning, using the same dosage titration.

Monitoring blood pressure is important, but the use of ECGs is not routinely necessary unless there is suspicion of cardiac concerns or impairment. Alpha-2 agonists have been shown to effectively reduce hyperactivity and impulsivity, both with and without methylphenidate, and in more recent studies they have even been found to improve inattention, although to a much lesser extent than stimulants (Biederman, Melmed, et al., 2008; Sallee et al., 2008; Tourette's Syndrome Study Group, 2002). For the treatment of ADHD, alpha-2 agonists are much less effective than stimulants.

Combining a stimulant with an alpha-2 agonist is a common and effective strategy for children with ADHD who also struggle with behavioral rebound in the afternoon, motor or vocal tics, comorbid aggression, or insomnia (Hazel & Stuart, 2003). A small number of physicians remain hesitant to prescribe these medications in conjunction with each other because of four reported deaths of children who were prescribed both methylphenidate and clonidine. In each of these cases, however, there were extenuating circumstances that better accounted for the death—an overdose of medication, an unrelated surgery, a history of syncope, and preexisting damage to the heart valves. At this time the Food and Drug Administration (FDA) places no limitations on the combined use of these medications and posts no advisories against their conjoint use. In addition, neither the American Academy of Pediatrics nor the American Academy of Child and Adolescent Psychiatry advises against their combined use nor recommends routine ECG monitoring, presuming there is no cardiac history (AACAP Work Group on Stimulant Medications, 2002).

Atomoxetine (Strattera) is another FDA-approved medication for the treatment of ADHD that works by a novel mechanism. Atomoxetine is a norepinephrine and dopamine reuptake inhibitor at the presynaptic

neuron in the prefrontal cortex. Because atomoxetine does not have any effect on dopamine in the limbic system or striatum, the medication is typically associated with a lower risk of motor and vocal tics and has no abuse potential. Other advantages of atomoxetine include its 24-hour duration of action and the fact that it is not classified as a Schedule II medication by the Drug Enforcement Agency (DEA). As a result, atomoxetine prescriptions can be called in to pharmacies, and refills can be given on prescriptions. Unfortunately, however, it is quite clear to most practitioners that treatment of ADHD with atomoxetine does not result in as robust a response as treatment with stimulants. This clinical observation has now been confirmed in a series of studies as well (Gibson, Bettinger, Patel, & Crismon, 2006; Mano, Tom-Revzon, Bukstein, & Crismon, 2007; Newcorn et al., 2008). Side effects of atomoxetine most commonly include decreased appetite, dizziness, stomachaches, sedation, and mild changes in blood pressure and heart rate. There have been three reports of liver toxicity, each of which resolved when the medication was discontinued (Bangs et al., 2008), and some adults suffer anticholinergic side effects, such as dry mouth, constipation, urinary retention, and sexual dysfunction, such as decreased libido, erectile disturbance, and anorgasmia. Finally, atomoxetine has been serendipitously found to be effective in the treatment of enuresis, or bed-wetting (see Chapter 18).

The dosage of atomoxetine is entirely weight based. Typical starting dosages are between 0.5 and 1.0 mg/kg/day for up to 1 to 2 weeks; thereafter, the dose can generally be increased to 1.2 to 1.8 mg/kg/day, which is therapeutic for most individuals. Not infrequently, a higher dosage is administered, up to 2 or even 3 mg/kg/day, although studies have not demonstrated any increase in efficacy beyond 1.8 mg/kg/day. For children and adolescents who suffer excessive side effects due to stimulants but who require the efficacy of a stimulant, a common strategy is to combine a therapeutic dose of atomoxetine along with a lower dose of stimulant. Together, these medications sometimes result in therapeutic benefit with a decrease in side effects as compared to a higher dose of the stimulant alone.

There are a number of other treatments that have historically been utilized for the treatment of ADHD and are sometimes still employed for children and adolescents who have severe symptoms that are not adequately treated with stimulants, alpha-2 agonists, or atomoxetine. These medications are also used for the small number of children who cannot tolerate the side effects of stimulants and alpha-2 agonists.

The tricyclic antidepressants, particularly desipramine (Norpramin, Pertofrane), have been successfully employed for the treatment of ADHD. However, their use must be weighed carefully against the cardiac risk of

treating a child with a tricyclic antidepressant due to the possible cardiac arrhythmia that can ensue with their use. Because of their cardiotoxicity, these medications should be prescribed only by an experienced practitioner and must be employed along with routine cardiac monitoring, including ECGs (see Chapter 12).

Bupropion (Wellbutrin) has been demonstrated to be effective in some studies, but the findings have been inconsistent (Conners et al., 1996; Daviss et al., 2001; Jafarinia et al., 2012). This medication is not approved for the treatment of ADHD by the FDA, indicating that the data supporting this treatment are not as yet adequately impressive. Furthermore, practicing clinicians rarely find bupropion to be of great use for the treatment of ADHD. Bupropion may be more of a consideration for a child suffering from comorbid depression and for whom the practitioner cannot ascribe the inattention and lack of focus entirely to ADHD but rather attributes it to some combination of ADHD and major depression. However, bupropion has little data to support its use as an antidepressant for children and adolescents as well (see Chapter 12). Another antidepressant, venlafaxine (Effexor) has shown some contradictory data, suggesting that it may have minimal utility for the treatment of adult ADHD, but it is rarely employed by physicians (Amiri, Farhang, Ghoreishizadeh, Malek, & Mohammadzadeh, 2012; Findling, Greenhill, et al., 2007).

A novel medication for the treatment of narcolepsy and excessive daytime sedation associated with sleep apnea and shift work sleep disorder, modafinil (Provigil), has also shown variable efficacy in the treatment of ADHD. Three randomized, double-blind, placebo-controlled trials at dosages of generally more than 300 mg per day have, however, yielded positive results (Biederman & Pliszka, 2008). Another study compared the performance of 28 children with ADHD on the TOVA after they were each given a one-time dose of either modafinil or methylphenidate, demonstrating no difference in improvement between the two drugs (Goez, Scott, Nevo, Bennett-Back, & Zelnik, 2012). Side effects to modafinil are relatively infrequent and include insomnia, headaches, and decreased appetite; there is also an extremely remote risk of severe dermatologic disorders, such as Stevens-Johnson syndrome.

Three relatively new stimulant formulations have recently arrived on the market. Lisdexamfetamine (Vyvanse) is an amphetamine pro-drug stimulant, which has a 12-hour duration of treatment. Because this medication is a "pro-drug," it is not metabolized to an active stimulant until it is digested. In patients with a history of drug abuse, the treatment has been shown to be less pleasurable and therefore may have utility among those at risk of drug abuse who require treatment for ADHD. Additionally, the methylphenidate patch (Daytrana), which is worn for nine hours

a day, demonstrates 12-hour efficacy for the treatment of ADHD. Finally, an extended-release liquid form of methylphenidate (Quillivant XR) is a useful alternative for children who cannot swallow pills. Each of these various formulations appears to work as well as standard preparations of methylphenidate and amphetamine for the treatment of children and adolescents with ADHD.

As previously noted, behavioral treatments for the core symptoms of ADHD have not generally proven themselves to be effective. Various psychotherapies, including cognitive behavior therapy, parent management training, and social skills training, have not demonstrated consistent efficacy. These treatments are often effective, however, for a variety of common comorbidities, including oppositional defiant disorder and conduct disorder.

Organizational skills training represents a new approach to the behavioral treatment of ADHD. Organizational skills training involves the application of a manualized treatment, which is flexibly applied to individual needs and incorporates meetings with the child and the parents, consultation with teachers, and a focus on practical routines that children can repeatedly employ. Behavioral modification techniques, including rewards and reinforcement, are used to motivate change. Particular areas of focus typically include tracking assignments, organization of the settings in which children study and work, materials management (e.g., collection, storage, and transfer of their schoolwork), time management and scheduling, setting priorities, and planning for both short- and long-term projects. Studies of organizational skills training have identified major improvements in children's ability to organize, manage their time, and plan for tasks, all common problems among children with ADHD (Abikoff et al., 2013). While these treatments appear to be often useful, however, studies have not yet demonstrated their efficacy in the treatment of the core symptoms of ADHD (Langberg, Epstein, & Graham, 2008).

A variety of educational aids, including individual educational plans (IEPs) and various accommodations (e.g., 504 plans), are also often helpful for children with ADHD. These learning supports will be discussed in greater detail in Chapter 5.