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31.6 Attention Deficit/Hyperactivity Disorder

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Disorders (DSM5) has made several changes to the diagnostic criteria of ADHD in youth and in adults. Whereas in the past, ADHD symptoms had to be present by age 7 years, in DSM-5, “several inattentive or hyperactive-impulsive symptoms” must be present by age 12 years. Previously, there were two subtypes: Inattentive and Hyperactive/Impulsive type. In DSM-5, however, subtypes have been replaced by the following three specifiers, which essentially denote the same groups: (1) combined presentation, (2) predominantly inattentive presentation, and (3) predominantly hyperactive/impulsive presentation. Additional changes in DSM-5 include permitting a comorbid ADHD and autism spectrum diagnosis to be made. Finally, in DSM-5, for adolescents 17 years and older and for adults, only five symptoms, rather than six symptoms of either inattention or hyperactivity and impulsivity are required. In addition, to reflect the developmental differences in ADHD across the life span, examples of symptoms have been added to the DSM-5 criteria for ADHD. To confirm a diagnosis of ADHD, impairment from inattention and/or hyperactivity and impulsivity must be present in at least two settings and interfere with developmentally appropriate social or academic functioning. For current DSM-5 changes see

Table 31.6-1. Table 31.6-1 DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

ADHD has historically been described in the literature using different terminology. In the early 1900s, impulsive, disinhibited, and hyperactive children—many of whom also

had neurological damage due to encephalitis—were grouped under the label hyperactive syndrome. In the 1960s, a heterogeneous group of children with poor coordination, learning disabilities, and emotional lability, but without specific neurological disorders, were described as having “minimal brain damage”; however, over time, it became clear that this was an inappropriate term. Many hypotheses have been suggested to explain ADHD symptoms including theories of abnormal arousal and poor ability to modulate emotions. This theory was initially supported by the observation that stimulant medications increased sustained attention and improved focus. ADHD is one of the most well-researched childhood psychiatric disorders with strong evidence-based treatments. Epidemiology Rates of ADHD have been reported to be 7 to 8 percent in prepubertal elementary school children. Epidemiologic studies suggest that ADHD occurs in about 5 percent of youth including children and adolescents, and about 2.5 percent of adults. The rate of ADHD in parents and siblings of children with ADHD is 2 to 8 times greater than in the general population. ADHD is more prevalent in boys than in girls, with the ratio ranging from 2:1 to as high as 9:1. First-degree biological relatives (e.g., siblings of probands with ADHD) are at high risk for developing ADHD as well as other psychiatric disorders, including disruptive behavior disorders, anxiety disorders, and depressive disorders. Siblings of children with ADHD are also at higher risk than the general population for learning disorders and academic difficulties. The parents of children with ADHD show an increased incidence of substance use disorders. Symptoms of ADHD are often present by age 3 years, but unless they are very severe, the diagnosis is frequently not made until the child is in kindergarten, or elementary school, when teacher information is available comparing the index child peers of the same age. Etiology Data suggest that the etiology of ADHD is largely genetic, with a heritability of approximately 75 percent. ADHD symptoms are the product of complex interactions of neuroanatomical and neurochemical systems evidenced by data from twin and adoption family genetic studies, dopamine transport gene studies, neuroimaging studies, and neurotransmitter data. Most children with ADHD have no evidence of gross structural damage in the central nervous system (CNS). In some cases, contributory factors for ADHD may include

prenatal toxic exposures, prematurity, and prenatal mechanical insult to the fetal nervous system. Food additives, colorings, preservatives, and sugar have been proposed as possible contributing causes of hyperactive behavior; however, studies have not confirmed these theories. Neither artificial food coloring nor sugar have been established as causes of ADHD. There is no clear evidence that omega-3 fatty acids are beneficial in the treatment of ADHD. Genetic Factors. Evidence for a significant genetic contribution to ADHD has emerged from family studies, which reveal an increased concordance in monozygotic

compared to dizygotic twins, as well as a marked increased risk of 2 to 8 times for siblings as well as parents of an ADHD child, compared to the general population. Clinically, one sibling may have predominantly impulsivity/hyperactivity symptoms and others may have predominantly inattention symptoms. Up to 70 percent of children with ADHD meet criteria for a comorbid psychiatric disorder, including learning disorders, anxiety disorders, mood disorder conduct disorders, and substance use disorders. Several hypotheses of the mode of transmission of ADHD have been proposed, including a sex-linked hypothesis, which would explain the significantly increased rates of ADHD in males. Other theories have focused on a model of interaction of multiple genes that produces the various symptoms of ADHD. Numerous investigations continue to identify specific genes involved in ADHD. Cook and colleagues have found an association of the dopamine transporter gene (DAT1) with ADHD, although data from other research groups have not confirmed that result. Family studies and populationbased studies have found an association between the dopamine 4 receptor seven-repeat allele gene (DRD4) gene and ADHD. Most molecular research on ADHD has focused on genes that influence the metabolism or action of dopamine. Continued investigation is necessary to clarify the complex relationships between multiple interactive genes and the emergence of ADHD. Neurochemical Factors. Many neurotransmitters are postulated to be associated with ADHD symptoms; however, dopamine is a major focus of clinical investigation, and the prefrontal cortex has been implicated based on its role in attention and regulation of impulse control. Animal studies have shown that other brain regions such as locus ceruleus, which consists predominantly of noradrenergic neurons, also play a major role in attention. The noradrenergic system includes the central system (originating in the locus ceruleus) and the peripheral sympathetic system. Dysfunction in peripheral epinephrine, which causes the hormone to accumulate peripherally, may potentially feed back to the central system and “reset” the locus ceruleus to a lower level. In part, hypotheses regarding the neurochemistry of ADHD have arisen from the predictable effect of medications. Simulants, known to be the most effective medications in the treatment of ADHD, affect both dopamine and norepinephrine, leading to neurotransmitter hypotheses that may include dysfunction in both the adrenergic and dopaminergic systems. Stimulants increase catecholamine concentrations by promoting their release and blocking their uptake. Neurophysiological Factors. EEG studies in ADHD children and adolescents over the last several decades have found evidence of increased theta activity, especially in the frontal regions. Further studies of youth with ADHD have provided data showing elevated beta activity in their electroencephalography (EEG) studies. Clarke and colleagues, studying EEG findings in children and adolescents over the last two decades found that those ADHD children with combined type of ADHD were the ones who showed significantly elevated beta activity on EEG, and further studies indicate that these youth also tend to show increased mood lability and temper tantrums. Current

investigation of EEG in youth with ADHD have identified behavioral symptom clusters among children with similar EEG profiles. Neuroanatomical Aspects. Researchers have hypothesized

networks within the brain for promoting components of attention including focusing, sustaining attention, and shifting attention. They describe neuroanatomical correlations for the superior and temporal cortices with focusing attention; external parietal and corpus striatal regions with motor executive functions; the hippocampus with encoding of memory traces; and the prefrontal cortex with shifting from one stimulus to another. Further hypotheses suggest that the brainstem, which contains the reticular thalamic nuclei function, is involved in sustained attention. A review of magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computerized tomography (SPECT) suggests that populations of children with ADHD show evidence of both decreased volume and decreased activity in prefrontal regions, anterior cingulated, globus pallidus, caudate, thalamus, and cerebellum. PET scans have also shown that female adolescents with ADHD have globally lower glucose metabolism than both control female and male adolescents without ADHD. One theory postulates that the frontal lobes in children with ADHD do not adequately inhibit lower brain structures, an effect leading to disinhibition. Developmental Factors. Higher rates of ADHD are present in children who were born prematurely and whose mothers were observed to have maternal infection during pregnancy. Perinatal insult to the brain during early infancy caused by infection, inflammation, and trauma may, in some cases, be contributing factors in the emergence of ADHD symptoms. Children with ADHD have been observed to exhibit nonfocal (soft) neurological signs at higher rates than those in the general population. Reports in the literature indicate that September is a peak month for births of children with ADHD with and without comorbid learning disorders. The implication is that prenatal exposure to winter infections during the first trimester may contribute to the emergence of ADHD symptoms in some susceptible children. Psychosocial Factors. Severe chronic abuse, maltreatment, and neglect are associated with certain behavioral symptoms that overlap with ADHD including poor attention and poor impulse control. Predisposing factors may include the child’s temperament and genetic–familial factors. Diagnosis The principal signs of inattention, impulsivity, and hyperactivity may be elicited on the basis of a detailed history of a child’s early developmental patterns along with direct observation of the child, especially in situations that require sustained attention. Hyperactivity may be more severe in some situations (e.g., school) and less marked in others (e.g., one-on-one interviews), and may be less obvious in pleasant structured

activities (sports). The diagnosis of ADHD requires persistent, impairing symptoms of either hyperactivity/impulsivity or inattention in at least two different settings. For example, most children with ADHD have symptoms in school and at home. The diagnostic criteria for ADHD are outlined in Table 31.6-1. Distinguishing features of ADHD are short attention span and high levels of distractibility for chronological age and developmental level. In school, children with ADHD often exhibit difficulties following instructions and require increased individualized attention from teachers. At home, children with ADHD frequently have difficulty complying with their parents’ directions and may need to be asked multiple times to complete relatively simple tasks. Children with ADHD typically act impulsively, are emotionally labile, explosive, lack focus, and are irritable. Children for whom hyperactivity is a predominant feature are more likely to be referred for treatment earlier than are children whose primarily symptoms are attention deficit. Children with the combined inattentive and hyperactive-impulsive symptoms of ADHD, or predominantly hyperactive-impulsive symptoms of ADHD, are more apt to have a stable diagnosis over time and to exhibit comorbid conduct disorder than those children with inattentive ADHD. Specific learning disorders in the areas of reading, arithmetic, language, and writing occur frequently in association with ADHD. Global developmental assessment must be considered to rule out other sources of

inattention. School history and teachers' reports are critical in evaluating whether a child's difficulties in learning and school behavior are caused primarily by inattention or compromised understanding of the academic material. In addition to intellectual limitations, poor performance in school may result from maturational problems, social rejection, mood disorders, anxiety, or poor self-esteem due to learning disorders. Assessment of social relationships with siblings, peers, and adults, and engagement in free and structured activities may yield valuable diagnostic clues to the presence of ADHD. The mental status examination in a given child with ADHD who is aware of his or her impairment may reflect a demoralized or depressed mood; however, thought disorder or impaired reality testing is not expected. A child with ADHD may exhibit distractibility and perseveration and signs of visual-perceptual, auditory-perceptual, or languagebased learning disorders. A neurological examination may reveal visual, motor, perceptual, or auditory discriminatory immaturity or impairments without overt signs of visual or auditory disorders. Children with ADHD often have problems with motor coordination and difficulty copying age-appropriate figures, rapid alternating movements, right–left discrimination, ambidexterity, reflex asymmetries, and a variety of subtle nonfocal neurological signs (soft signs). If there are indications of possible absence spells, clinicians should obtain a neurological consultation and an EEG to rule out seizure disorders. A child with an unrecognized temporal lobe seizure focus may have behavior disturbances, which can resemble those of ADHD. Clinical Features

ADHD can have its onset in infancy, although it is rarely recognized until a child is at least toddler age. More commonly, infants with ADHD are active in the crib, sleep little, and cry a great deal. In school, children with ADHD may attack a test rapidly, but may answer only the first two questions. They may be unable to wait to be called on in school and may respond before everyone else. At home, they cannot be put off for even a minute. Impulsiveness and an inability to delay gratification are characteristic. Children with ADHD are often susceptible to accidents. The most cited characteristics of children with ADHD, in order of frequency, are hyperactivity, attention deficit (short attention span, distractibility, perseveration, failure to finish tasks, inattention, poor concentration), impulsivity (action before thought, abrupt shifts in activity, lack of organization, jumping up in class), memory and thinking deficits, specific learning disabilities, and speech and hearing deficits. Associated features often include perceptual motor impairment, emotional lability, and developmental coordination disorder. A significant percent of children with ADHD show behavioral symptoms of aggression and defiance. School difficulties, both learning and behavioral, commonly exist with ADHD. Comorbid communication disorders or learning disorders that hamper the acquisition, retention, and display of knowledge complicate the course of ADHD. Justin was a 9-year-old African American adopted boy who was referred for an evaluation by his 4th grade teacher, who informed his adoptive parents that she was unable to manage Justin's impulsive and aggressive behaviors in the classroom. Justin was attending public school and was in a regular classroom with two resource room periods per day to help him with reading and math. Justin also received speech therapy once a week. Justin had been referred in the past for psychiatric evaluation, but his adoptive parents were opposed to medication so they did not follow through. Justin's adoptive parents knew very little about his biological family other than that his biological mother was known to be a polydrug abuser and was currently incarcerated. Justin was adopted as an infant and his pediatrician had told his adoptive parents that Justin was entirely healthy at birth. However, ever since kindergarten, Justin's teachers had complained that Justin did "not seem to listen," had "poor concentration," and was unable to stay in his seat. Because Justin was an engaging and cute child, his teachers in kindergarten and first grade made accommodations for

him in their classrooms despite their complaints. When Justin entered the 2nd grade, however, it became clear that he was struggling with reading and writing, and an individualized educational program (IEP) evaluation was initiated. Justin was provided with resource room periods for remediation during the school day, but Justin continued to have additional problems getting along with his peers during lunch, and even at recess. Justin was often found arguing or fighting with other children who said that he did not know the rules of their games. Justin became angry when he was criticized by his peers and would often push his

classmates. At home, Justin's adoptive parents were becoming more and more frustrated with Justin because he seemed to take hours to do a few math problems, and was unable to write a paragraph without a lot of help. Justin would become easily annoyed when frustrated with himself and then run around the house in a silly and disruptive manner. Justin was a good-hearted child who seemed to get along best with children who were younger than he was. Justin did not seem to make any close friends among his classmates, and the teachers indicated that Justin's peers sometimes avoided him because he was too rough during play and he did not follow the rules of their games. Justin had a difficult time waiting his turn and he became easily provoked when he was reprimanded. Consequently, Justin became alienated and often bullied by his classmates. Justin was aware that he was not able to keep up with the classwork, and he told his adoptive parents that he was just "stupid." Although Justin acted in a rambunctious and impulsive manner, he also appeared sad, and one day after a fight with several peers, he told his adoptive parents that he was going to "kill" himself. At this point, Justin's parents became worried and decided that Justin's teacher was right, and they would seek a psychiatric evaluation for Justin. During the initial evaluation with a child and adolescent psychiatrist, Justin was found to be a well-developed, cute, and active child, who appeared distracted and fidgety and somewhat sad. When asked about it, Justin said that he wanted to do "better" in school but that nobody liked him, he was failing his classes, and that he didn't like doing homework. He denied suicidal thoughts and reported that he had only said that to his parents because he was angry at his peers. Justin admitted that it was very difficult for him to understand his school work and impossible to complete his assignments. During the evaluation, several parent and teacher rating scales were obtained. These included The Child Behavior Checklist, and the SNAP Rating Scale. Justin's teacher and parents endorsed similar symptoms including poor organization, inability to follow directions, being forgetful in daily activities, impulsivity, with several episodes of running into the street without looking, blurting things out in the classroom without raising his hand, and recurrent fights with peers. Justin was observed to look dejected in school when he was excluded from play activities by peers, and sullen or angry at home when he was asked to read or do homework. Based on the clinical history, the rating scales and teacher's report, a diagnosis of Attention-Deficit/Hyperactivity Disorder, with the DSM-5 specifier of combined presentation, was made. In addition, Justin was noted to have a mood disorder with depressed mood, which did not qualify for a major depression. A treatment plan was suggested including a behavioral plan allowing Justin to receive rewards for effort on his homework along with a trial of a stimulant medication. After an extensive medical history was obtained and a recent physical examination by his pediatrician did not reveal any systemic illnesses, an EEG was decided upon, mainly because it was not possible to obtain a full medical and cardiac history due to an absence of early medical records, and his adoptive parents did not have access to his birth and neonatal medical records. After obtaining a normal EEG, Justin was started on a trial dose of a short-acting stimulant, methylphenidate (Ritalin) at 10 mg, to determine if

he could tolerate a stimulant without any unexpected sensitivities. Justin had no adverse effects and was shortly switched to the long-acting stimulant Concerta, 36 mg which would last between 10 and 12 hours. Justin became more vigilant in class and seemed to be less restless and more focused, and his teacher reported that he was not getting out of his seat as often, although he continued to blurt out in class when he was not called on, and he continued to have difficulty following directions and forgetting things. Because Justin was not experiencing any adverse effects and was still displaying some ADHD symptoms, his Concerta was increased to 54 mg per day. At this dose both his teacher and parents noticed a marked improvement in his ability to sit and finish his classwork and homework. However, he began to have significant problems with insomnia, and was becoming fatigued from not being able to fall asleep until about 2 a.m. on a nightly basis. The child and adolescent psychiatrist and Justin's parents discussed two options to address the insomnia. One was to add a dose of short-acting clonidine in the evenings to cause a calming effect along with some sedative properties, and the other was to initiate a trial of Daytrana, the methylphenidate transdermal patch, which could be applied to deliver a similar dose of methylphenidate throughout the day, and the patch could be removed at approximately 4 pm or 5 pm to determine which produced the desired effect for the target symptoms for the most optimal amount of time. Because the Daytrana patch may deliver medication for an hour or so after its removal, Justin would need to try several different removal times to find the optimal treatment time. Justin's family and his child psychiatrist determined that it would be the best next step for Justin to try the Daytrana patch rather than add an additional medication to treat his insomnia. Justin was tried on the Daytrana transdermal 20 mg patch and found that if it was removed by 5 p.m., he was able to fall asleep within 30 to 45 minutes after getting into bed. Despite some mild erythema around the site of the patch, Justin experienced no other side effects and was glad that he did not have to take pills each morning. It was determined by Justin's parents, teachers, and child and adolescent psychiatrist that Justin's ADHD symptoms were now under much improved control. Justin began to receive better grades and his self-esteem was noticeably increased. However, Justin still had difficulties with peers and felt that he wasn't making as many friends as he wanted. Justin's child psychiatrist suggested that Justin be placed in a weekly social skills group that was led by a psychologist who had experience with group interventions for children with ADHD. This was arranged, and although Justin, at first, did not want to attend, after a few sessions, in which Justin was praised for appropriate interactions with peers within his group, Justin decided that he liked the group, and over time, even invited a few of his peers from the group to his home to play. The combination of the medication and the social skills group resulted in a significant improvement in Justin's ADHD symptoms as well as in the quality of his relationships with peers and even his family. (Adapted from Greenhill LL, Hechtman LI. Attention-Deficit/Hyperactivity Disorder In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia:

Lippincott Williams & Wilkins; 2009:3571.) Pathology and Laboratory Examination A child being evaluated for ADHD should receive a comprehensive psychiatric and medical history. Prenatal, perinatal, and toddler information should be included in the history. Complications of mother's pregnancy should also be obtained. Medical problems that may produce symptoms overlapping with ADHD include petit mal epilepsy, hearing and visual impairments, thyroid abnormalities, and hypoglycemia. A thorough cardiac history should be taken, including an investigation of the lifetime history of syncope, family history of sudden death, and a cardiac examination of the child. Although it is reasonable to obtain an electrocardiography (ECG) study prior to treatment, if any cardiac risk

factors are present, a cardiology consultation and examination are warranted. No specific laboratory measures are pathognomonic of ADHD. A continuous performance task, a computerized task in which a child is asked to press a button each time a particular sequence of letters or numbers is flashed on a screen, is not specifically a useful diagnostic tool for ADHD; however, it may be useful in comparing a child's performance before and after medication treatment, particularly at different doses. Children with poor attention tend to make errors of omission—that is, they fail to press the button when the sequence has flashed. Impulsivity is often manifested by errors of commission, in which an impulsive child cannot resist pushing the button, even when the desired sequence has not yet appeared on the screen. Differential Diagnosis A temperamental constellation of high activity level and short attention span, in the normal range for the child's age, and without impairment, should be ruled out. Differentiating these temperamental characteristics from the cardinal symptoms of ADHD before the age of 3 years is difficult, mainly because of the overlapping features of a normally immature nervous system and the emerging signs of visual-motorperceptual impairments frequently seen in ADHD. Anxiety in a child needs to be evaluated. Anxiety can accompany ADHD as a symptom or comorbid disorder, and anxiety can manifest with overactivity and easy distractibility. It is not uncommon for a child with ADHD to become demoralized or, in some cases, to develop depressive symptoms in reaction to persistent frustration with academic difficulties and resulting low self-esteem. Mania and ADHD share many core features, such as excessive verbalization, motoric hyperactivity, and high levels of distractibility. In addition, in children with mania, irritability seems to be more common than euphoria. Although mania and ADHD can coexist, children with bipolar I disorder exhibit more waxing and waning of symptoms than those with ADHD. Recent follow-up data for children who met the criteria for ADHD and subsequently developed bipolar disorder suggest that certain clinical features occurring during the course of ADHD predict future mania. Children with ADHD who had developed bipolar I disorder at 4year follow-up had a greater co-occurrence of additional disorders and a greater family

history of bipolar disorders and other mood disorders than children without bipolar disorder. Frequently, oppositional defiant disorder, or conduct disorder and ADHD may coexist, and when that occurs, both disorders are diagnosed. Specific learning disorders of various kinds must also be distinguished from ADHD; a child may be unable to read or do mathematics because of a learning disorder, rather than because of inattention. ADHD often coexists with one or more learning problems, including deficits in reading, mathematics or written expression. Course and Prognosis The course of ADHD is variable. Symptoms have been shown to persist into adolescence in 60 to 85 percent of cases, and into adult life in approximately 60 percent of cases. The remaining 40 percent of cases may remit at puberty, or in early adulthood. In some cases, the hyperactivity may disappear, but the decreased attention span and impulsecontrol problems persist. Overactivity is usually the first symptom to remit, and distractibility is the last. ADHD does not usually remit during middle childhood. Persistence is predicted by a family history of the disorder, negative life events, and comorbidity with conduct symptoms, depression, and anxiety disorders. When remission occurs, it is usually between the ages of 12 and 20. Remission can be accompanied by a productive adolescence and adult life, satisfying interpersonal relationships, and few significant sequelae. Most patients with the disorder, however, undergo partial remission and are vulnerable to antisocial behavior, substance use disorders, and mood disorders. Learning problems often continue throughout life. In about 60 percent of cases, some symptoms persist into adulthood. Those who persist with the disorder may show diminished hyperactivity but remain impulsive and

accident-prone. Although the educational attainments of people with ADHD as a group are lower than those of people without ADHD, early employment histories do not differ from those of people with similar educations. Children with ADHD whose symptoms persist into adolescence are at higher risk for developing conduct disorder. Children with both ADHD and conduct disorder are also at risk for developing substance use disorders. The development of substance abuse disorders among ADHD youth in adolescence appears to be more related to the presence of conduct disorder rather than to ADHD. Most children with ADHD have some social difficulties. Socially dysfunctional children with ADHD have significantly higher rates of comorbid psychiatric disorders, and experience more problems with behavior in school as well as with peers and family members. Overall, the outcome of ADHD in childhood seems to be related to the degree of persistent comorbid psychopathology, especially conduct disorder, social disability, and chaotic family factors. Optimal outcomes may be promoted by ameliorating children's social functioning, diminishing aggression, and improving family situations as early as possible.

Treatment Pharmacotherapy. Pharmacologic treatment is considered the first line of treatment for ADHD. Central nervous system stimulants are the first choice of agents in that they have been shown to have the greatest efficacy with generally mild tolerable side effects. Stimulants are contraindicated in children, adolescents, and adults with known cardiac risks and abnormalities. In medically healthy youth, however, excellent safety records are documented for short- and sustained-release preparations of methylphenidate (Ritalin, Ritalin-SR, Concerta, Metadate CD, Metadate ER), dextroamphetamine (Dexedrine, Dexedrine spansules, Vyvanse), and dextroamphetamine and amphetamine salt combinations (Adderall, Adderall XR). Newer preparations of methylphenidate, include Methylin, a chewable form of methylphenidate; Daytrana, a methylphenidate patch; and dexmethylphenidate, the denantiomer (Focalin), and its longer acting form Focalin XR. These newer preparations aim to maximize the target effects and minimize the adverse effects in individuals with ADHD who obtain partial response from methylphenidate or whose dose was limited by side effects. Vyvanse (lisdexamfetamine dimesylate) is a pro-drug of dextroamphetamine, which requires intestinal metabolism in order to reach its active form. Vyvanse is approved by the U.S. Food and Drug Administration (FDA) for children 6 years and older. Vyvanse, inactive until it is metabolized, is a less likely agent to have risks of abuse or overdose. It has side effects and efficacy similar to the other forms of amphetamines used in the treatment of ADHD. Current strategies favor once a day sustained-release stimulant preparations for their convenience and diminished rebound side effects. Advantages of the sustained-release preparations for children are that one dose in the morning will sustain the effects all day, and the child is no longer required to interrupt his or her school day, as well as the physiologic advantage that the medication is sustained at an approximately even level in the body throughout the day so that periods of rebound and irritability are avoided. Table 31.6-2 contains comparative information on the above medications. Table 31.6-2 Stimulant Medications in the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)

Nonstimulant medications approved by the FDA in the treatment of ADHD include atomoxetine (Strattera), a norepinephrine uptake inhibitor. Unlike the stimulants, Strattera carries with it a black box warning for potential increases in suicidal thoughts or behaviors and requires children with ADHD to be monitored for these symptoms, similarly to children who are administered antidepressants. A-agonists including clonidine (Catapres) and guanfacine (Tenex) have also been found to be effective in treating ADHD. The FDA has recently approved the extended-release forms

of clonidine (Kapvay) and the extended release form of guanfacine (Intuniv) for the treatment of ADHD in children 6 years and older. Antidepressants, such as bupropion (Wellbutrin, Wellbutrin SR), have been used with variable success in the treatment of ADHD. (Table 31.6-3 contains comparative information on the nonstimulant medications and Table 31.6-4 indicates FDA-approved ages for ADHD medications.) Table 31.6-3 Nonstimulant Medications for Attention-Deficit/Hyperactivity Disorder (ADHD)

Table 31.6-4 FDA Approval for ADHD Medications

STIMULANT MEDICATIONS. Methylphenidate and amphetamine preparations are dopamine agonists; however, the precise mechanism of the stimulant's central action remains unknown. Methylphenidate preparations have been shown to be highly effective in up to three fourths of children with ADHD, with relatively few adverse effects. Concerta, the 10- to 12-hour extended-release OROS (osmotic controlled-release extended delivery system) form of methylphenidate, is administered once daily in the morning and is effective during school hours as well as after school during the afternoon and early evening. Both shorter forms of methylphenidate and Concerta have similar common adverse effects including headaches, stomachaches, nausea, and insomnia. Some children experience a rebound effect, in which they become mildly irritable and appear to be slightly hyperactive for a brief period when the medication wears off. In children with a history of motor tics, some observations must be made as, in some cases, methylphenidate can exacerbate the tics, whereas in other children the tics are unaffected or even improved. Because tics wax and wane, it is important to observe their patterns over some time. Another common concern about use of methylphenidate preparations over long periods is potential growth suppression. During periods of use, methylphenidate is associated with slightly decreased rates of growth, and if used over

many years continuously without any drug holidays growth suppression of about several centimeters has been noted. When given "drug holidays" on weekends or summers, children tend to eat more and also make up the growth. The methylphenidate products have been shown to improve ADHD children's scores on tasks of vigilance, such as on math calculation tests, the continuous performance task, and paired associations. Daytrana, a transdermal delivery system designed to release methylphenidate continuously on application of the patch to the skin, has been developed and approved for use in children and adolescents. Advantages of Daytrana include an alternative for children who have difficulties swallowing pills, and that the patch can individualize how many hours per day a given child with ADHD is receiving medication. This is important because a child with ADHD who needs the medication in the late afternoons to do homework but develops insomnia if the medication is still present after dinner, is able to remove the patch at the desired time. Thus, an individualized delivery time may be provided for each child by virtue of how many hours the patch is left on the skin. This is in contrast to oral sustained-release forms of methylphenidate, such as Concerta, in which the release time continues for 12 hours after the pill is swallowed. A double-blind randomized study in children with ADHD who wore the methylphenidate patch for 12 hours at a time, showed efficacy of the patch preparation doses ranging from patches delivering 0.45 mg per hour to 1.8 mg per hour of methylphenidate. The effectiveness of the patch reached a plateau without much further improvement as dose was increased, but intensive behavioral interventions were also being administered. A delay in the onset of the transdermal medication effect was approximately an hour. Side effects were similar to

oral preparations of methylphenidate. Approximately half of the children exhibited at least minor erythematous reactions to the patch; however, these side effects are usually well tolerated by children on the patch. Dextroamphetamine and dextroamphetamine/amphetamine salt combinations are usually the second drugs of choice when methylphenidate is not effective. Vyvanse is advantageous because it is inactive until it is metabolized. NONSTIMULANT MEDICATIONS. Atomoxetine HCl (Strattera) is a norepinephrine uptake inhibitor approved by the FDA for the treatment of ADHD in children age 6 years and older. The mechanism of action is not well understood, but it is believed to involve selective inhibition of presynaptic norepinephrine transporter. Atomoxetine is well absorbed by the gastrointestinal tract, and maximal plasma levels are reached in 1 to 2 hours after ingestion. It has been shown to be effective for inattention as well as impulsivity in children and in adults with ADHD. Its half-life is approximately 5 hours and it is usually administered twice daily. Most common side effects include diminished appetite, abdominal discomfort, dizziness, and irritability. In some cases, increases in blood pressure and heart rate have been reported. Atomoxetine is metabolized by the cytochrome P450 (CYP) 2D6 hepatic enzyme system. A small fraction of the population are poor metabolizers of CYP 2D6–metabolized drugs and, for those individuals, plasma concentrations of the drug may rise as much as fivefold for a given dose of medication. Drugs that inhibit CYP 2D6, including fluoxetine, paroxetine, and quinidine, may lead to

increased plasma levels of this medication. Despite its short half-life, atomoxetine has been shown in a recent study to be effective in reducing symptoms of ADHD in children during the school day when administered once daily. Another recent study of a combination of atomoxetine alone and combined with fluoxetine in the treatment of 127 children with ADHD and symptoms of anxiety or depression suggested that atomoxetine alone can lead to improvements in mood and anxiety. Children who received combined atomoxetine and fluoxetine experienced greater increases in blood pressure and pulse than those who were treated with atomoxetine only. α-Agonists, short-acting, and the extended-release forms of clonidine hydrochloride (Kapvay) and Guanfacine (Intuniv) are FDA approved for the treatment of ADHD in children and adolescents from 6 to 7 years of age. Kapvay, a centrally acting α-2adrenergic receptor agonist is believed to exert its effect on the prefrontal cortex, although the mechanism of action is unknown. Kapvay is available in 0.1 mg and 0.2 mg tablets, and is generally used twice daily, once in the morning and once at night, to provide a round-the-clock effect. Kapvay is initiated at 0.1 mg at bedtime and can be increased in increments of 0.1 mg at weekly intervals. The maximal dose recommended is 0.2 mg twice daily. Kapvay is not used interchangeably with the short-acting clonidine. Because Kapvay is an antihypertensive agent, it causes a decrease in blood pressure and heart rate. These vital signs must be monitored in patients, especially during initiation and titration of the dose. Common side effects include somnolence, headache, upper abdominal pain, and fatigue. When Kapvay is tapered, it is recommended to taper no more than 0.1 mg every 3 to 7 days. Intuniv, the extended release preparation of guanfacine, is a once-a-day medication for children between 6 and 17 years of age, available in 1 mg, 2 mg, 3 mg, and 4 mg tabs. Intuniv is a tablet that is swallowed whole, and should be taken with water, milk or other liquids; it is not recommended to take Intuniv with a high-fat meal. Intuniv is typically initiated as a 1 mg tab daily and titrated by 1 mg per day at 1-week intervals. The maximum dose approved is 4 mg per day. As a monotherapy, improvement in ADHD symptoms have been found to occur at 0.05 to 0.08 mg/kg once daily. As an adjunctive treatment, optimal doses are reported to range from 0.05 to 0.12 mg/kg/day. Common side effects for Intuniv include somnolence, sedation, fatigue, nausea, hypotension, insomnia, and dizziness.

Heart rate and blood pressure must be monitored as in Kapvay. When discontinuing Intuniv, a gradual taper decreasing by 1 mg every 3 to 7 days is recommended. α-Adrenergic agents including the short- and extended-release preparations of guanfacine and clonidine are sometimes preferred treatments in children with ADHD and comorbid tic disorders that have been exacerbated while the patient was taking stimulants. Bupropion has been shown to be somewhat effective for some children and adolescents in the treatment of ADHD. One multisite, double-blind, placebo-controlled study found a positive result regarding the efficacy of bupropion. No further studies have compared bupropion with other stimulants. The risk of seizure development while on this drug is increased when using doses of greater than 400 mg per day. Few data confirm the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the

treatment of ADHD, but due to the frequency of comorbid depression and anxiety with ADHD, in cases of comorbidity, the SSRIs are likely to be considered at least in conjunction with a stimulant. Tricyclic drugs are not recommended in the treatment of ADHD due to potential cardiac arrhythmia effects. The reports of sudden death in at least four children with ADHD who were being treated with desipramine (Norpramin, Pertofrane) have made the tricyclic antidepressants an unlikely choice. Antipsychotics are occasionally introduced to treat refractory severely hyperactive children and adolescents who are significantly dysfunctional. Antipsychotics are generally not chosen in the treatment of ADHD due to the risks of tardive dyskinesia, withdrawal dyskinesia, neuroleptic malignant syndrome, and weight gain. Modafinil (Provigil), another type of CNS stimulant, originally developed to reduce daytime sleepiness in patients with narcolepsy, has been tried clinically in the treatment of adults with ADHD. Only one randomized, double-blind, placebo-controlled study of the efficacy and safety of modafinil film-coated tablets in approximately 250 adolescents with ADHD showed that 48 percent of those on active treatment were rated as “much” or “very much” improved compared with 17 percent of patients receiving placebo. The dosage range was from 170 to 425 mg administered once daily, titrated to optimal doses based on efficacy and tolerability. Modafinil failed to receive FDA approval based on a Stevens-Johnson skin rash that occurred in a patient during the trial. The most common side effects included insomnia, headache, and decreased appetite. Venlafaxine has been tried in clinical practice, especially for children and adolescents with combinations of ADHD and depression or anxiety features. No clear empirical evidence supports the use of venlafaxine in the treatment of ADHD. One open-label report of reboxetine, a selective norepinephrine reuptake inhibitor in 31 children and adolescents with ADHD who were resistant to methylphenidate treatment suggested that this agent may have efficacy. In this open trial, reboxetine was initiated and maintained at 4 mg per day. Most common side effects included drowsiness, sedation, and gastrointestinal symptoms. Reboxetine and other new agents in this class await controlled studies to further evaluate their potential efficacy. TREATMENT OF CNS STIMULANT SIDE EFFECTS. CNS stimulants are generally well tolerated, and current consensus is that once a day dosing is preferable for convenience and to minimize rebound side effects. Long-term tolerability of once-daily mixed amphetamine salts has shown mild side effects, most commonly decreased appetite, insomnia, and headache. A variety of strategies have been suggested for children and/or adolescents with ADHD who respond favorably to methylphenidate, but for whom insomnia has become a significant problem. Clinical strategies to manage insomnia include use of diphenhydramine (25 to 75 mg), low dose of trazodone (25 to 50 mg), or the addition of an α-adrenergic agent, such as guanfacine. In some cases, insomnia may attenuate on its own after several months of treatment.

Monitoring Pharmacological Treatment STIMULANTS. Stimulant medications have adrenergic effects and cause moderate increases in blood pressure and pulse rate. At baseline, the most recent American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters recommend the following workup before starting use of stimulant medications: physical examination, blood pressure, pulse, weight, and height. It is recommended that children and adolescents being treated with stimulants have their height, weight, blood pressure, and pulse checked on a quarterly basis and have a physical examination annually. Monitoring starts with the initiation of medication. Because school performance is most markedly affected, special attention and effort should be given to establishing and maintaining a close collaborative working relationship with a child's school personnel. In most patients, stimulants reduce overactivity, distractibility, impulsiveness, explosiveness, and irritability. No evidence indicates that medications directly improve any existing impairments in learning, although, when the attention deficits diminish, children can learn more effectively. In addition, medication can improve self-esteem when children are no longer constantly reprimanded for their behavior. Children treated with medications should be taught the purpose of the medication and given the opportunity to describe any side effects that they may be experiencing. Psychosocial Interventions. Psychosocial interventions for children with ADHD include psychoeducation, academic organization skills remediation, parent training, behavior modification in the classroom and at home, cognitive behavioral therapy (CBT), and social skills training. Social skills groups, behavioral training for parents of children with ADHD, and behavioral interventions at school and at home have been studied alone and in combination with medication management for ADHD. Evaluation and treatment of coexisting learning disorders or additional psychiatric disorders is important. When children are helped to structure their environment, their anxiety diminishes. It is beneficial for parents and teachers to work together to develop a concrete set of expectations for the child and a system of rewards for the child when the expectations are met. A common goal of therapy is to help parents of children with ADHD recognize and promote the notion that, although the child may not "voluntarily" exhibit symptoms of ADHD, he or she is still capable of being responsible for meeting reasonable expectations. Parents should also be helped to recognize that, despite their child's difficulties, every child faces the normal tasks of maturation, including significant building of self-esteem when he or she develops a sense of mastery. Therefore, children with ADHD do not benefit from being exempted from the requirements, expectations, and planning applicable to other children. Parental training is an integral part of the psychotherapeutic interventions for ADHD. Most parental training is based on helping parents develop usable behavioral interventions with positive reinforcement that target

both social and academic behaviors. Group therapy aimed at both refining social skills and increasing self-esteem and a sense of success may be very useful for children with ADHD who have great difficulty functioning in group settings, especially in school. A recent year-long group therapy intervention in a clinical setting for boys with the disorder described the goals as helping the boys improve skills in game playing and feeling a sense of mastery with peers. The boys were first asked to do a task that was fun, in pairs, and then were gradually asked to do projects in a group. They were directed in following instructions, waiting, and paying attention, and were praised for successful cooperation. MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD (MTA STUDY) The National Institute of Mental Health (NIMH)–supported Multimodal Treatment Study of Children with ADHD (The MTA Cooperative Group, 1999) was a 14-month–long randomized clinical trial involving six clinical sites comparing four treatment strategies. More than 500 children diagnosed

with DSM-IV ADHD, combined type, were randomly assigned to (1) systematic medication management utilizing an initial placebocontrolled titration and t.i.d. dosing 7 days per week and monthly 30-minute clinic visits, (2) behavior therapy consisting of 27 sessions of group parent training, eight individual parent sessions, an 8-week summer treatment program, 12 weeks of classroom administered behavior therapy with a half-time aide, and 10 teacher consultation sessions, (3) a combination of medication and behavior therapy, or (4) usual community care. All groups showed improvement over baseline; however, a combination of medication management and behavior therapy led to greater reduction in symptoms in children with ADHD alone or ADHD and Oppositional Defiant Disorder than behavior therapy alone or community care. The combination treatment had significantly better outcomes for those children with ADHD and anxiety and/or mood disorders compared to behavioral treatment and community care. Combined treatment but not medication management was superior for improvement in oppositional and aggressive symptoms, anxiety and mood symptoms, teacher rated social skills, parent– child relationships, and reading achievement. Furthermore, mean dose of medication per day was less in the combination group than in the medication-only management group. Results A follow-up of the MTA sample at 6 and 8 years revealed that the clinical presentation of the disorder, including severity of ADHD, comorbid conduct disturbance, and intellect were stronger predictors of later functioning than the type of treatment received in childhood during the 14-month study period. Although treatment-related improvements for the children who participated in the MTA study are maintained as long as treatment continues, the differential treatment efficacy appeared to be lost at approximately the 3-

year mark. Overall, the evidence suggests that medication and psychosocial interventions for the combined type of ADHD in childhood provides the broadest benefit in functioning for this population. This is especially pertinent in view of the comorbidity of learning disorders, anxiety, mood disorders, and other disruptive behavior disorders that occur in children with ADHD. UNSPECIFIED ATTENTION-DEFICIT/HYPERACTIVITY DISORDER The DSM-5 includes Unspecified ADHD as a category for disturbances of inattention or hyperactivity that cause impairment, but do not meet the full criteria for ADHD. ADULT MANIFESTATIONS OF ADHD ADHD was historically believed to be a childhood condition resulting in delayed development of impulse control that would be generally outgrown by adolescence. In the last few decades many more adults with ADHD have been identified, diagnosed, and successfully treated. Longitudinal follow-up has shown that up to 60 percent of children with ADHD have persistent impairment from symptoms into adulthood. Genetic studies, brain imaging, and neurocognitive and pharmacological studies in adults with ADHD have replicated findings demonstrated in children with ADHD. Increased public awareness and treatment studies within the last decade have led to widespread acceptance of the need for diagnosis and treatment of adults with ADHD. Epidemiology Among adults, evidence suggests an approximate 4 percent prevalence of ADHD in the population. ADHD in adulthood is generally diagnosed by self-report, given the lack of school information and observer information available; therefore, it is more difficult to make an accurate diagnosis. Etiology Currently, ADHD is believed to be largely transmitted genetically, and increasing evidence supports this hypothesis, including the genetic studies, twin studies, and family studies outlined in the child and adolescent ADHD section. Brain imaging studies have obtained data suggesting that adults with ADHD exhibit decreased prefrontal glucose metabolism on PET compared with adults without ADHD. It is unclear whether these data reflect the presence of the disorder or a secondary effect of having ADHD over a period of time. Further studies using SPECT have revealed increased dopamine transporter (DAT) binding

densities in the striatum of the brain in samples of adults with ADHD. This finding may be understood within the context of treatment for ADHD, in that standard stimulant treatment for ADHD, such as methylphenidate, acts to block DAT activity, possibly leading to a normalization of the striatal brain region in individuals with ADHD.

Diagnosis and Clinical Features The clinical phenomenology of ADHD features inattention and manifestations of impulsivity prevailing as the core of this disorder. A leading figure in the development of criteria for adult manifestations of ADHD is Paul Wender, from the University of Utah, who began his work on adult ADHD in the 1970s. Wender developed criteria that could be applied to adults (Table 31.6-5). They included a retrospective diagnosis of ADHD in childhood, and evidence of current impairment from ADHD symptoms in adulthood. Furthermore, evidence exists of several additional symptoms that are typical of adult behavior as opposed to childhood behaviors. Table 31.6-5 Utah Criteria for Adult Attention-Deficit/Hyperactivity Disorder (ADHD) In adults, residual signs of the disorder include impulsivity and attention deficit (e.g., difficulty in organizing and completing work, inability to concentrate, increased distractibility, and sudden decision-making without thought of the consequences). Many people with the disorder have a secondary depressive disorder associated with low selfesteem related to their impaired performance and which affects both occupational and social functioning. Brett was a 26-year-old man convinced by his new wife to seek an evaluation for his distractibility, forgetfulness, and “not listening” after a minor traffic accident. After consulting his mother, Brett reported that in grade school, he was often “in trouble” for talking out of turn, and his mother recalled teachers’ reports that Brett often made careless mistakes on tests, forgot his assignments, and had great difficulty sitting still. Although as a young child he was considered gifted intellectually, when he got to the third grade his grades were only average, and he seemed more interested in getting his work done quickly than correctly. Brett was talkative and loud and

enjoyed sports, although he was not particularly talented at them. Nevertheless, Brett had acquaintances and superficial friends because he was likeable, funny, and even entertaining. Brett had no idea what he wanted to do when he grew up, and during his senior year in high school, he neglected to finish any of his college applications on time, and ended up attending a community college part-time. During the two years after high school, Brett held down a series of jobs only briefly, including a construction job, a waiter position in a restaurant, and a Fed-Ex driver, and then decided that he wanted to become an actor. Brett went on a series of auditions, but found that he would become distracted and did poorly remembering his lines and even spaced out during readings. Despite that, he was chosen for one commercial. Brett reported that he had never had problems with abuse of drugs or alcohol, and he occasionally drank beer socially. During his evaluation with a child and adolescent psychiatrist, Brett disclosed that his greatest difficulties were with tasks that seemed boring to him. He had difficulty maintaining his attention, was easily distracted, felt restless most of the time, and became frustrated when he was expected to sit still for long periods of time. Brett endorsed 6 inattentive and 5 hyperactive/impulsive symptoms on a DSM ADHD Checklist of current symptoms. Brett met the diagnostic criteria for Adult ADHD, combined type, with a probable onset in childhood. Brett’s medical history was negative for all major illnesses, and neither he nor his parents had a history of cardiac abnormalities. He took no prescribed medications. After discussing the situation with his psychiatrist and his wife, Brett decided that he would like to try a stimulant medication. A trial of a once-a-day extended-release formulation of a stimulant medication was selected: Adderall XR 10 mg. At his first follow-up visit, a

week later, Brett reported that he felt a slight effect from this medication but it was not enough to improve his functioning, so Brett and his psychiatrist agreed that he would increase his dose to 20 mg per day. At his next follow-up appointment, Brett reported that he had noticed significant improvement in his ability to focus, concentrate, and remember his lines in auditions. In fact, he had just received a small part in an upcoming movie. Brett and his wife were both thrilled with the results, and Brett continued to return monthly for follow up visits. (Adapted from McGough J. Adult manifestations of attention-deficit/hyperactivity disorder. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:3577.) Differential Diagnosis A diagnosis of ADHD is likely when symptoms of inattention and impulsivity are described by adults as a life-long problem, not as episodic events. The overlap of ADHD and hypomania, bipolar II disorder, and cyclothymia is controversial and difficult to sort out retrospectively. Clear-cut histories of discrete episodes of hypomania and mania, with or without periods of depression, are suggestive of a mood disorder rather than a clinical picture of ADHD; however, ADHD may have predated the emergence of a mood

disorder in some individuals. In such a case, ADHD and bipolar disorder may be diagnosed comorbidly. Adults with an early history of chronic school difficulties related to paying attention, activity level, and impulsive behavior are generally diagnosed with ADHD, even when a mood disorder occurs later in life. Anxiety disorders can coexist with ADHD, and are less difficult than hypomania to distinguish from it. Course and Prognosis The prevalence of ADHD diminishes over time, although at least half of children and adolescents may have the disorder into adulthood. Many children initially diagnosed with ADHD, combined type, exhibit fewer impulsive-hyperactive symptoms as they get older and, by the time they are adults, will meet criteria for ADHD, inattentive type. As with children, adults with ADHD demonstrate higher rates of learning disorders, anxiety disorders, mood disorders, and substance use disorder compared with the general population. Treatment Treatment of ADHD in adults targets pharmacotherapy, mainly long-acting stimulants, similar to that used with children and adolescents with ADHD. In adults, only the longacting stimulants are FDA approved in the treatment of ADHD. Signs of a positive response are an increased attention span, decreased impulsiveness, and improved mood. Psychopharmacological therapy may be needed indefinitely. Clinicians should use standard ways to monitor drug response and patient compliance. REFERENCES Antshel KM, Hargrave TM, Simonescu M, Kaul P, Hendricks K, Faraone SV. Advances in understanding and treating ADHD. BMC Medicine. 2011;9:7. Clarke AR, Barry RJ, Dupuy FE, Heckel LD, McCarthy R, Selikowitz M, Johnstone SJ. Behavioural differences between EEG-defined subgroups of children with Attention-Deficit/Hyperactivity Disorder. Clin Neurophysiol. 2011;122:1333– 1341. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX. Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. Am J Psychiatry. 2012;169:1038–1055. Elbe D, MacBride A, Reddy D. Focus on lisdexamfetamine: A review of its use in child and adolescent psychiatry. J Can Acad Child Adolesc Psychiatry. 2010;19:303–314. Greenhill, LL, Hechtman, L. Attention-deficit disorders. In: Sadock BJ, Sadock VA, & Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia. Lippincott Williams & Wilkins; 2009:3560. Hammerness PG, Perrin JM, Shelley-Abrahamson R, Wilens TE. Cardiovascular risk of stimulant treatment in pediatric attention-deficit/hyperactivity disorder: Update and clinical recommendations. J Am Acad Child Adolesc Psych. 2011;50:978–990. Hechtman L. Comorbidity and neuroimaging in attention-deficit hyperactivity disorder. Can J Psychiatry. 2009;54:649– 650. Kratochvil CJ, Lake M, Pliszka SR, Walkup JT. Pharmacologic management of treatment-induced insomnia in ADHD. J Am

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