56 Attention Deficit–Hyperactivity Disorder

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Attention deficit–hyperactivity disorder (ADHD) has been described as the most common neurobehavioral disorder in childhood.[1] Prevailing opinion characterizes ADHD as a disorder of executive function attributable to abnormal dopamine transmission in the frontal lobes and frontostriatal circuitry. In large part, this concept is based on the clinical efficacy of medications affecting catecholamine transmission in these regions.

The first reference to behavior now associated with ADHD was by George Still in 1902, who referred to a deficit of "moral control." Within the context of this broad concept, he made the following observation: "A notable feature in many of these cases of moral deficit without general impairment of intellect is a quite abnormal incapacity for sustained attention".[2] In 1947 Strauss and Lehtinen[3] used the term *minimal brain damage syndrome* to describe children with cognitive and behavioral deficits. In 1962 Clements and Peters[4] coined the term *minimal brain dysfunction* to describe functional abnormalities in children in whom brain damage could not be demonstrated. Although widely accepted, this concept came under immediate challenge as including too heterogeneous a group of children.[5] The subsequent emphasis on attention and its neurologic substrate, the frontal lobe and frontostriatal circuitry, represents a refinement of the definition of the condition. This extensive history has not prevented some from questioning whether ADHD actually exists.[6,7]

DIAGNOSIS AND CONTROVERSIES IN THE DIAGNOSIS OF ATTENTION DEFICIT–HYPERACTIVITY DISORDER

ADHD is a clinical diagnosis based on criteria in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)[8] (Box 56-1). Criteria are divided into two lists of symptoms, one for inattention and another for hyperactive-impulsive behavior. Based on the number of items identified, there are three classifications: ADHD/I (primarily inattentive type), ADHD/HI (primarily hyperactive-impulsive type), and ADHD/C (combined type). When the criteria for ADHD were revised for the prior edition of the DSM (DSM-IV),[9] the inclusion of the three subtypes increased the number of females, preschoolers, and adults with ADHD.[10] This resulted in an increase in the prevalence of ADHD from 3% to 5% with the DSM-III-R to about 12%; ADHD/I alone has been estimated to have a prevalence between 5.4% and 9%.[11,12] A study looking at the trends in the diagnosis of ADHD in the United States found that approximately 2 million more children aged 4 to 17 years were diagnosed with ADHD in 2011 compared with 2003, and that two-thirds of those with a current diagnosis of ADHD were taking medication in 2011. The DSM-5 diagnostic criteria, by reducing the number of symptoms required for a diagnosis from six to five for adolescents 17 and older and adults, will inevitably result in an increased incidence of ADHD in those age groups.

Data from the 2014 National Survey of the Diagnosis and Treatment of ADHD and Tourette syndrome (a follow-up to the 2011–2012 National Survey of Children's Health) found that in a representative sample of U.S. children diagnosed with ADHD as of 2011 to 2012, the median age of diagnosis was 7 years, with about one-third of the children diagnosed before age 6. The diagnosis of ADHD was made by pediatricians, general physicians, psychiatrists, neurologists, and psychologists. Children diagnosed under age 6 were more likely to have been diagnosed by a psychiatrist than those over age 6. Behavior rating scales were used for about 90% of the children assessed for ADHD. Neuropsychological testing was performed on more than three-quarters diagnosed before age 6 and nearly two-thirds diagnosed at ages 6 and over. At least one adult outside the family was involved in the diagnostic process for 80% of the children diagnosed with ADHD. "This suggests that one out of five children had a diagnosing provider who relied only on information collected from family members, which is inconsistent with the AAP guideline to collect information from individuals across multiple settings, including outside the home".[13]

Concern has been raised about the overdiagnosis of ADHD, with the potential influence of pharmaceutical manufacturers and the misdiagnosis of normal behavior as pathologic cited as possible causes.[14] The use of a stepped diagnosis, which includes five steps of care before making a definite diagnosis, has been proposed as a means to reduce overdiagnosis without risking undertreatment[15] (Box 56-2). One study found a higher rate of diagnosis in high-income households. The authors hypothesize that "higher rates of ADHD observed in affluent, white families likely represent an effort by these highly educated parents to seek help for their children who may not be fulfilling their expectations for schoolwork".[16] Yet another study comparing the incidence of ADHD diagnoses found a higher frequency of ADHD diagnoses in children from lower socioeconomic levels but a lower rate of medication use in that group.[17] Adding to the problem of possible overdiagnosis the criteria for ADHD have been eased for adolescents and adults. The possibility of college students reporting symptoms of ADHD to gain access to stimulant medications has been a concern, and such malingering, is not easily detected with the current measures used to diagnose ADHD.[18]

The use of the word *often* in the list of symptoms lends an element of subjectivity to this diagnostic schema. Symptom rating scales for parents and teachers have been developed to assist in the ascertainment of diagnostic criteria.[19] The use of broader rating scales, such as the Child Behavior Checklist, provides information regarding the presence of other disorders, such as conduct disorder, oppositional defiant disorder (ODD), and anxiety disorder,[20,21] which may warrant diagnoses other than ADHD.[22] The Yale Children's Inventory was developed to ascertain the presence of attentional deficits and learning disabilities.[23] A comprehensive review of evaluation issues in ADHD concluded that no single test can be used to make the diagnosis and that it is up to the clinician "to choose a battery of measures that satisfies what is, to some degree, an individually determined level of diagnostic certainty".[24] The American Academy of Pediatrics has endorsed the Vanderbilt ADHD rating scales for parents and teachers[25,26] and has provided a complete "toolkit," including a cover letter to teachers and scoring information, on the Internet (see http://www.nichq.org/childrens-health/adhd/resources).

Developmental variability in the presentation of ADHD and the inconsistency of behavior of children with ADHD in different settings and at different times in the same setting add to the diagnostic confusion. In preschool children, in

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BOX 56-1 Diagnostic Criteria for Attention Deficit–Hyperactivity Disorder

DSM-5 CRITERIA FOR ADHD

Attention Deficit–Hyperactivity Disorder

Diagnostic Criteria

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
  1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively and directly affects social and academic/occupational activities:
  Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
    a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
    b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
    c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
    d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
    e. Often has difficult organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
    f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
    g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
    h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
    i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
  2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to

a degree that is inconsistent with developmental level and that negatively and directly affects social and academic/occupational activities:
  Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
    a. Often fidgets with or taps hands or feet or squirms in seat.
    b. Often leaves seat in situations when remaining stead is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
    c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
    d. Often unable to play or engage in leisure activities quietly.
    e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
    f. Often talks excessively.
    g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
    h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
    i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
B. Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

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particular, the prevalence of ADHD-type symptoms[27,28] and the transient nature of such symptoms in many cases[29] make this a difficult diagnosis. Efforts have been made to provide a more objective basis for the diagnosis of ADHD, such as computerized continuous performance tests[30] or tests of variables of attention.[31] However, the correlation of these measures of attention with the behavioral disorder is not sufficient for them to be used as replacements for the application of the behavioral criteria of the DSM.

The motor examination may help distinguish between children with a learning disorder and those with ADHD; it is

best to evaluate a child between the ages of 5 years and the onset of puberty, a period of rapid change in motor development, when quantitative examination of the motor system, such as the Physical and Neurological Examination for Soft Signs (PANESS),[32] may demonstrate evidence of motor disinhibition.[33]

The DSM-5 clinical criteria for diagnosing ADHD (see Box 56-1) list a number of qualifications that are too often ignored, possibly resulting in an incorrect diagnosis.[8] The text explicitly states that for the symptoms to be diagnostically significant, "There is clear evidence that the symptoms interfere with, or

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BOX 56-2 Stepped Diagnostic Approach to Attention Deficit–Hyperactivity Disorder

Step 1: Gather baseline data from more than one source (e.g., school and home). If problems are urgent, recurring, or persistent and specific, go directly to step 6. For other cases, follow steps 2 to 5 first.

Step 2: Look for other explanations of behavioral problems—for example, confrontation problems and agitation may be a result of sleep deprivation, overly challenging schoolwork or workload, or tensions at home or at school.

Step 3: Watchful waiting—assess, monitor, and follow up with no pretense of a definitive diagnosis or active treatment.

Step 4: If problems remain, offer a minimal intervention, such as bibliotherapy (e.g., information brochures) or self-help training for parents of hyperactive children. Avoid the term *ADHD*, and speak in terms of concentration problems, restlessness, or behavioral difficulties.

Step 5: If minimal intervention is not sufficient, provide brief (five or six sessions) counseling using simple techniques to teach new attitudes and coping skills for dealing with hyperactivity and concentration problems.

Step 6: If concentration and behavior problems and impairment persist, more intensive therapy, usually in secondary care, is needed. Refer the patient to a developmental pediatrician or psychiatrist for definite diagnosis and treatment.

(With permission from Attention-deficit/hyperactivity disorder: are we helping or harming? Thomas R, Geoffrey K Mitchell GK, Laura Batstra, BMJ 2013;347:f6172 doi: 10.1136/bmj.f6172)

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reduce the quality of, social, school, or work functioning".[8] Behavior that may not be typical but is not maladaptive does not warrant a diagnosis of ADHD. Similarly, unreasonable expectations of a child at a young age may result in a false diagnosis. The diagnostic criteria are followed by a number of statements regarding the context of the symptoms, for example, "Several symptoms are present in two or more setting, (e.g., at home, school or work; with friends or relatives; in other activities)".[8] This qualification allows for the possibility that a child in an inadequate school environment, perhaps with excessive class size, hostile peers, or inexperienced teachers, may present with findings that are unique to that setting and thus do not represent a disorder of attention. Similarly, a chaotic home environment may explain the child's presentation.

Perhaps most important is the last item, which states: "The symptoms do not happen only during the course of schizophrenia or another psychotic disorder. The symptoms are not better explained by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)".[8] If a child has symptoms that meet the diagnostic criteria for ADHD in the context of these other disorders, treatment should be directed at these other conditions before concluding the child has a disorder of attention. Not addressed in the DSM-5 criteria are studies that have demonstrated that children with specific neurologic disorders can present with symptoms that meet criteria for ADHD but are attributable to the neurologic disorder rather than a primary disorder of attention. A study by Walters and colleagues[34] demonstrated symptoms of impaired attention and hyperactivity in children diagnosed with restless leg syndrome; treatment of the sleep disturbance resolved the so-called ADHD symptoms. A subsequent double-blind study of a dopaminergic therapy in 16 children with restless leg syndrome/periodic limb movements in sleep (RLS/PLMS) and ADHD symptoms found that,

compared with placebo, L-dopa significantly improved RLS/PLMS but not ADHD symptoms. The authors cautioned that the results may have been influenced by the small sample size and baseline differences in the severity of ADHD symptoms.[35] Disordered breathing during sleep has also been found to manifest with symptoms consistent with ADHD.[36,37] A study of snoring in 3-year-olds found parent endorsement ("often" or "always") of irritability and hyperactivity to be significantly higher in the habitual snoring group compared with those without habitual snoring.[38] There are reports of children with focal epileptic discharges having symptoms suggestive of ADHD that resolved when the spike activity was suppressed with antiepileptic drugs.[39,40] Many symptoms of ADHD are prevalent in neurogenetic syndromes as part of the behavioral phenotype.[41]

The recent revision of the DSM criteria for ADHD failed to add neurologic disorders (e.g., sleep disorders, epilepsy, neurogenetic syndromes) to the list of conditions to be excluded before ADHD is diagnosed, which complicates the effort to ascertain the physiologic and genetic underpinnings of ADHD and its optimal treatment.

COEXISTING CONDITIONS

The question of conditions coexisting with ADHD is quite complex. Should a diagnosis of ADHD be reserved for individuals with an isolated disorder of attention, hyperactivity, or impulsivity, with an alternative classification used to describe children who meet DSM-5 criteria for ADHD in the context of other neurodevelopmental problems? Denckla[33] used the term *pseudo-ADHD* to describe children with comorbidities or confounding factors.

In a paper describing a father and son both with orbitofrontal epilepsy and associated attention difficulties and hyperactivity, the term *attention-deficit–hyperactivity syndrome* was used to make a distinction from the specific disorder of ADHD,[42] analogous to the distinction between Parkinson's disease and parkinsonism. It has been proposed that ADHD be divided into subgroups based on the patterns of comorbidity.[43]

The presumption that a response to psychostimulant medication indicates that the underlying problem is ADHD can lead to an erroneous diagnosis. Psychostimulant medications can ameliorate depression,[44] chronic fatigue syndrome,[45] and daytime somnolence caused by sleep disorders[46,47] and enhance normal individuals' cognitive functioning and behavior.[48] A positive response to psychostimulants has no validated diagnostic significance.

NEUROBIOLOGY OF ATTENTION DEFICIT–HYPERACTIVITY DISORDER

It has been proposed that the core deficit in ADHD is impairment of behavioral inhibition, which leads to the other symptoms of ADHD. This model of impaired behavioral inhibition is limited to ADHD/HI and ADHD/C (i.e., those with hyperactive or impulsive symptoms) and excludes children with ADHD/I (i.e., those with inattention only).[49] The observation that overflow movements was the most discriminating finding between hyperactive boys (without learning disabilities) and normal control subjects seems to support the concept of impaired behavioral inhibition.[50] If this formulation is widely accepted, future classifications may call for separate diagnostic entities, such as attention-deficit disorder and behavioral-inhibition disorder. Some investigators have proposed that all three ADHD subtypes can be explained as disorders of attention or executive function (other than response inhibition), with symptoms of hyperactivity and impulsivity

resulting from these impairments.[51-53] Others also distinguish ADHD/HI and ADHD/C from ADHD/I, but they posit that the symptoms of hyperactivity and impulsivity can result from poor inhibitory control or differences in motivational style characterized by delay aversion.[54]

A review of the literature regarding the hypothesis that ADHD represents a primary deficit in executive control defined executive function as comprising "at least four factors: (1) response inhibition and execution, (2) working memory and updating, (3) set-shifting and task-switching and (4) interference control".[55] There were significant differences between children with and without ADHD in performance on tasks assessing executive function. Six of eight studies assessing working memory found impaired working memory in children with ADHD. The most consistent effects were obtained on measures of response inhibition, vigilance, and planning; children with combined and inattentive types of ADHD differed from controls and did not differ from each other, whereas children with hyperactive-impulsive-type ADHD had minimal executive function impairment, suggesting that executive function weaknesses are primarily associated with inattention rather than hyperactivity-impulsivity symptoms. The observation that fewer than half of the children with ADHD had significant impairment of any specific task of executive function, and that the correlation, although significant, tended to be small in magnitude, led the authors to conclude that their findings "do not support the hypothesis that executive functions deficits are the single necessary and sufficient cause of ADHD in all individuals with the disorder. Instead executive function difficulties appear to be one of several important weaknesses that comprise the overall neuropsychological etiology of ADHD".[55]

Inhibitory deficits and delay aversion in ADHD can be dissociated by specific types of tasks; either deficit alone is only moderately associated with ADHD, whereas combined these two deficits correctly classify nearly 90% of children with children with ADHD. Thus a formulation was proposed in which executive function (EF) is divided into cognitive aspects associated with the dorsolateral prefrontal cortex ("cool" EF) and affective aspects associated with the orbital and medial prefrontal cortex ("hot" EF). Inattention symptoms were attributed to deficits in cool EF, whereas hyperactivity-impulsivity symptoms reflected hot EF deficits. The authors noted: "the neuroanatomical substrates of cortical-striato-thalamo-cortical circuitry are now revealed to include spirals of one directional information from 'hot' ventral-medial/orbital/ventral striatal regions to dorsolateral/superior medial/anterior striatal 'cool' regions to even 'cooler' premotor and motor circuits".[56]

A functional magnetic resonance imaging (fMRI) study found that adolescents with ADHD had difficulty accomplishing a task involving cognitive or cool aspects of executive functions such as working memory, planning, cognitive flexibility, and forethought, as manifest by a significantly greater number of activated brain regions and greater activation of those regions in adolescents with typical development than those with ADHD. The authors also found "an unbalance between the high activation of the basal ganglia and cerebellum and the low activation of the prefrontal cortex for the forethought condition in ADHD. A compensatory network including basal ganglia and cerebellum may have intervened in forethought processing in adolescents with ADHD off MPH".[57]

Advances in structural and functional imaging, clinical neurophysiologic techniques, and molecular genetics have been applied to the evaluation of children with ADHD and have provided important insights into this condition. However, inconsistency in the inclusion and exclusion criteria among studies, particularly related to comorbidity, limits comparisons between studies and their conclusions.

Structural Imaging

Reports of reductions in volume of prefrontal regions, more so in the right than left hemisphere, have been described in children with ADHD.[58,59] A later study further localized involvement to prefrontal and premotor areas.[60] In this study of 12 males with ADHD, children with conduct, mood, and anxiety disorders were excluded, but 3 children with coexistent ODD were included. A study involving other brain regions reported reductions in total cerebral volume, with a negative correlation between gray-matter volume and symptom severity.[61] However, the impact of coexisting conditions on anatomic findings was not considered or described (i.e., it was unclear if there was an association between severity of symptoms and coexisting conditions). Serial examinations found that most volume differences between ADHD and control subjects remained stable; however, the size of the caudate nucleus, which initially was smaller in the ADHD group, became comparable with that in the control group during adolescence. This finding reflected a greater rate of reduction in caudate size in the normal than in the ADHD group. Normalization of the caudate nucleus in adolescents with ADHD may relate to the observation that ratings for hyperactivity and impulsivity are decreased in that age group compared with those in younger children.[62]

Findings in the basal ganglia have been inconsistent, with reports of volume reductions in the right caudate nucleus and globus pallidus[58] or in the left caudate.[59] The study by Castellanos and colleagues[58] included children with "mild to moderate" conduct disorder (CD), ODD, anxiety disorder, and reading disorders. However, reanalysis of the data by excluding the children who had CD or ODD found a more robust correlation between volume reductions in the right prefrontal, caudate, and globus pallidus and ADHD. In the study by Filipek and coinvestigators,[59] children with coexistent conditions were excluded. In addition to the anatomic differences between children with ADHD and control subjects, this study revealed differences in structural abnormalities between children with ADHD who were considered responders to psychostimulants and those who were not. A study of monozygotic twins discordant for ADHD[63] revealed reduced caudate volume in the affected twin. In another report on twins discordant for ADHD,[64] fathers of twins discordant for ADHD had lower ADHD scores than fathers of ADHD singletons. The rate of breech presentation was greater in affected twins than affected singletons. The data suggest that the discordant twins represented nongenetic instances of ADHD, possibly caused by injury in utero, and that the caudate abnormalities in these individuals might not be pertinent to ADHD that is genetic in nature. No abnormalities have been reported in the putamen, and there have been few studies of the globus pallidus in children with ADHD.[65] A study utilizing large deformation diffeomorphic mapping (LDDMM) found that boys with ADHD had significant shape differences and decreases in overall volume of the basal ganglia compared with controls, whereas girls with ADHD did not have volume or shape differences. Children with comorbidities, including other neuropsychiatric disorders, conduct disorders, mood disorder, generalized anxiety disorder, obsessive compulsive disorder, learning disabilities, or speech and language disorders, were excluded from this analysis.[66]

A study comparing children with ADHD (combined type) who had been on chronic treatment with stimulants to untreated children with ADHD and a control group found that children with ADHD had significantly larger prefrontal regions

than the controls, with no effect for medication history; the caudate volumes of the children with ADHD were smaller bilaterally, also with no medication effect. The ADHD/no-Rx group showed smaller anterior cingulate cortex volume on the right compared with the ADHD/Rx and control groups; this was the only finding for a medication difference.[67]

Reductions in total cerebellar volume[58,61] and in volume reductions limited to the cerebellar vermis in ADHD compared with control subjects have been described.[68,69] These differences could have been caused by different methods for serially measuring volume, making comparisons between studies difficult. These studies included children who had a high percentage of coexistent conditions, such as ODD, CD, and learning, mood, and anxiety disorders, but the decreased volume of the cerebellar vermis in the ADHD group remained when children with disruptive behavioral disorders were removed from the analysis. However, the subgroup with ADHD and coexisting mood or anxiety disorders had the smallest vermis volumes.

A study highlighting the impact of comorbidities on imaging studies found that when the analysis of cerebral microstructure was restricted to a subgroup with no comorbidities (i.e., an pure-ADHD subgroup), there was "greater tissue microstructural complexity, compared with typically developing children, in bilateral frontal and parietal lobes, insula, corpus callosum, right external and internal capsules".[70] The authors also found that the pure-ADHD subgroup lacked the normal age-related progression in gray- and white-matter microstructural complexity from the ages of 8 to 18 years. This lack of age-related progression was limited to the pure-ADHD group; when the pure-ADHD and mixed groups were combined, this difference from the typically developing children was not apparent. The authors conclude: "our results highlight the shortcomings of including diverse psychiatric comorbidities in the investigation of tissue microstructure in ADHD. Although aberrant findings have been observed with heterogeneous ADHD cohorts, these may lack clinical specificity, as potentially reflected in conflicting results from prior microstructural studies on ADHD".[70] The authors emphasize that distinguishing pure-ADHD children from those with comorbid forms of ADHD could have an impact on the nature of the specific treatment provided.[70]

Functional Imaging

The clinical benefit from medications affecting catecholamine levels has led to a focus on frontostriatal circuitry and dopamine pathways in ADHD. fMRI studies have demonstrated abnormal activation of the frontostriatal regions in children with ADHD. In normal children, maturation is associated with an increased activation of the ventral frontostriatal regions and improved inhibitory control.[71] A comparison of ADHD with normal control subjects demonstrated greater frontal activation and lower striatal activation during response inhibition in 10 children with ADHD (8 ADHD/C, 2 ADHD/I; children with high comorbidity scores were excluded). Administration of methylphenidate also resulted in improved performance in a test of response inhibition, associated with increased frontal activation in ADHD children and control subjects and increased striatal activation in the children with ADHD.[72]

Single-photon emission computed tomography (SPECT) has been used to study children with ADHD. One study compared 8 adolescents with "pure" ADHD versus 11 with ADHD and coexistent conditions during a test of variables of attention (TOVA).[73] Children with coexistent conditions (e.g., ODD, CD, mood disorders, learning disorder; alone or in combination) had decreased temporal lobe perfusion in

response to the TOVA compared with the pure-ADHD children, who had some but not statistically significant decreases in frontal lobe perfusion. Regional differences in perfusion between the two groups may explain the better rate of response to stimulants in the pure-ADHD group and suggests that different treatments for the two groups may be warranted.

Untreated adults with ADHD (with no psychiatric comorbidity) have increased striatal dopamine transporter (DAT) levels compared with normal control subjects (as measured by binding to technetium 99m TRODAT-1, the first 99mTc-labeled ligand identified by SPECT that specifically binds DAT), which decreased after 4 weeks of methylphenidate treatment.[74] This finding, along with increased striatal activity on positron emission tomographic (PET) scanning in adolescents with ADHD compared with normal control subjects,[75] suggests a role for excess dopaminergic activity in the striatum or nucleus accumbens in persons with ADHD.[76]

Proton magnetic resonance spectroscopy has also been used to study children with ADHD.[77] N-acetyl-aspartate (NAA), glutamate/glutamine/γ-aminobutyric acid (Glx), choline, and creatine (Cr) levels in the right prefrontal cortex and left striatum during a test of response inhibition were compared between ADHD children and a control group. A negative correlation between the NAA/Cr ratio and reaction time in the ADHD group was found, compared with a positive correlation in the control group. Children with ADHD with NAA/Cr levels more comparable with those in controls also had much longer reaction times. These findings were thought to reflect the preferential use of the prefrontal cortex by children with ADHD during tasks of response inhibition. Of the eight children with ADHD in this study, five had ODD, and one had a generalized anxiety disorder; thus the interpretation of these results as they apply to ADHD compared with other disorders is unclear.

A review and critique of functional imaging studies of ADHD[72] notes that functional imaging studies have found multiple loci of abnormalities that are not limited to frontal-striatal circuitry, the regions thought to be most important for executive and motivational function, but also in the parietal, temporal, and motor cortices and the cerebellum. However, it is pointed out that: "activation patterns are influenced by task-specific factors that may induce variable performance levels and strategies across development".[72] In the absence of cross-sectional or longitudinal studies "the developmental origin of differences in activation cannot be inferred".[72] The authors concluded that "current, task-evoked functional imaging provides information about dynamic or state-dependent differences rather than fixed or trait-related differences".[72]

Clinical Neurophysiology

Event-related potential (ERP) studies in ADHD children suggest a lack of frontal lobe inhibitory processes, particularly in pathways involving the anterior cingulate cortex. In one study using a Go/No-Go task designed to assess inhibition, no significant performance differences were found between children with ADHD and normal control subjects.[78] However, children with ADHD had larger ERPs than the control group to a warning stimulus that provided no information helpful for task performance, suggesting a lack of inhibition to an irrelevant stimulus in the ADHD group. A second study found shorter-latency and higher-amplitude ERPs that were thought to reflect an inhibitory process in the ADHD group.[79] These findings suggested that children with ADHD need to trigger inhibition processes earlier and more strongly to achieve the same behavioral performance as control subjects. Individuals in this study likely did not represent a pure-ADHD group

because they had higher scores in oppositional, delinquent, and aggressive behaviors and social problems. A third study found that the children with ADHD and without coexisting conditions had significantly longer reaction times to target stimuli and made significantly more omission errors than the control group but did not differ in the number of commission errors.[80] The ERP data indicated diminished activation of the anterior cingulate cortex in the Go/No-Go trials in the ADHD group, suggesting deficits in prefrontal response control. This deficit in prefrontal response control was distinguished from deficits in response inhibition. Because the latter study excluded ADHD children with comorbidity, it more strongly suggests that abnormalities in activation of the anterior cingulate cortex may be specific to the ADHD phenotype.

Genetic Studies

Concise reviews of advances in the genetics of ADHD, including findings that may account for the ADHD subtypes, comorbidities, and responses to specific medications, are provided in a commentary and editorial in journal issues devoted to this topic. As summarized by D. V. Pauls: "there is overwhelming evidence that ADHD is inherited and that genetic factors play a significant role in its manifestation".[81,82] The fact that ADHD is an inherited condition[83] coupled with evidence of dopaminergic involvement led to molecular genetic studies of dopamine transporter and receptor genes.[84] Pursuit of the *DAT* gene (*SLC6A3*, formerly designated *DAT1*) was in part caused by the finding that psychostimulant medications inhibit the activity of DAT. An association between ADHD and the 480 base-pair (bp) alleles at a variable-number tandem repeat (VNTR) in *SLC6A3* has been reported.[85] A subsequent study confirmed these findings and demonstrated a significant relation between *SLC6A3* high-risk alleles and the number of hyperactive-impulsive symptoms but not inattentive symptoms.[86] The study involved 117 probands, all but one of whom met criteria for ADHD; the remaining child had ODD. Most children with ADHD frequently had symptoms of or were also diagnosed with ODD, CD, and depression or dysthymia. Two subsequent studies, one with a similar rate of coexisting conditions[87] and one with a much lower rate,[88] failed to replicate the association between *SLC6A3* and ADHD.

The dopamine D4 receptor gene (*DRD4*) has also been associated with ADHD. A 48-bp VNTR in the third exon of *DRD4*, also referred to as the DRD4 7-repeat allele, was suggested based on a review of previous studies.[82] Children with ADHD who had the 7-repeat allele had a greater degree of impulsivity (i.e., faster and less accurate responses), were significantly more active (based on Actigraph measures), and had greater total ADHD symptoms scores than those without the allele. However, no differences were seen using measures of attention or response inhibition. The ADHD children with the 7-repeat allele also had higher rates of ODD and CD.

A third dopamine receptor gene, *DRD5*, has been linked to ADHD. One study that examined a number of candidate genes, including *DRD3*, *DRD4*, *DRD5*, and genes for four enzymes involved in dopamine metabolism, found no significant association between the children with ADHD and genetic polymorphisms.[89] However, the 138 children with ADHD in this study frequently had coexisting conditions, including ODD (57.5%), CD (11.6%), and tic (12.3%), anxiety (2.7%), and depressive (1.4%) disorders. Another study also included children with coexistent conditions (Tourette syndrome or tics in 34%, CD or ODD in 25%, anxiety or depression in 8%), and linkage to *DRD5* only reached significance when restricted to the children who had a documented positive response to methylphenidate treatment.[90] Information was not provided about whether the methylphenidate responders had fewer coexisting conditions. Linkage of the *DRD4* gene to methylphenidate responders was also observed. However, this study found an inverse relationship between *DRD4* and DSM scores and comorbidity ratings.

Studies of DNA from ADHD probands, parents, and healthy controls found a significant association of ADHD with two *NET1* single-nucleotide polymorphisms and two *DRD1* single-nucleotide polymorphisms. There was no association with polymorphisms in 10 other genes previously reported as candidate genes. There were no significant differences in anatomic brain MRI measurements between the children with *NET1* or *DRD1* gene types, nor was there a relationship between the genetic findings and cognitive or behavioral measures. This study represented the first replication of a previously described association between ADHD and polymorphisms in *NET1* and *DRD1* genes.[91]

In a study of a group of children from families of European descent with an ADHD proband, the ADHD probands were assessed by a child psychiatrist; parental ADHD was assessed through the use of an ADHD self-report scale. The ADHD cohort consisted of 335 parent–child trios of European descent and a set of 2026 ethnically matched, disease-free children as a control group. There were no significant differences in copy-number variants (CNVs; deletions, duplications, or size) between the patient and control groups. A search for CNVs spanning more than 10 consecutive single-nucleotide polymorphisms (SNPs) for deletions or greater than 20 SNPs for duplications present in at least one parent along with one or more related probands but not in the controls yielded 158 deletions and 64 duplications from 154 probands. These CNVs encompassed or overlapped 229 distinct genes, with the largest family of genes affected being the olfactory receptor superfamily. Twenty-two of these genes had previously been implicated in various neurologic and neuropsychiatric disorders, including Tourette syndrome (2 genes), autism (4 genes), schizophrenia (15 genes). An additional eight genes had been recently identified as having structural variants in autism and schizophrenia. Reviewing the gene set for genes associated with nervous system development, function, and behavior, the authors found genes associated with learning, cognition, and hindbrain development. Two genes, the *PTPRD* and *GRM5* genes, were thought to be particularly interesting putative candidate genes for ADHD; one, involving the protein tyrosine phosphatase gene, was detected in four unrelated ADHD probands. Two of the four ADHD probands with the *PTPRD* deletion reported symptoms consistent with RLS. All three children in a family found to have the *GRM5* variant met the criteria for ADHD; the *GRM5* gene, a glutamatergic receptor gene, has been postulated to play a role in ADHD. Thus the CNVs found in this ADHD cohort were significantly enriched for genes reported as candidate genes in other various neuropsychiatric disorders and in neurodevelopmental pathways.[92]

The Psychiatric Genetics Consortium has published two papers reviewing the findings on genetic relationships between five psychiatric disorders, including ADHD, based on an analysis of genome-wide SNPs.[93,94] The studies found high genetic correlation for common SNPs between schizophrenia and bipolar disorder; moderate correlation between schizophrenia and major depressive disorder, bipolar disorder, and major depressive disorder and ADHD and major depressive disorder; low correlation between schizophrenia and autism spectrum disorder (ASD); and no significant correlation for other pairs of disorders or between psychiatric disorders and the control group with Crohn's disease. In particular, two of the four genome-wide significant signals in SNP analysis localized to brain-expressed genes encoding L-type voltage-gated calcium-channel subunits (*CACNA1C* and *CACNB2*), leading the authors to suggest: "voltage-gated calcium signaling, and,

more broadly, calcium-channel activity, could be an important biological process in psychiatric disorders".[93]

Other Potential Causes of Attention Deficit–Hyperactivity Disorder

Data reported from the National Longitudinal Survey of Youth[95] associated hours of television watched per day at ages 1 and 3 years with parental reports of attentional problems at age 7.[96] The children did not necessarily have clinically diagnosed ADHD; rather, they were scored as having attentional problems by the parents. Although the interaction between environmental influences and genetic endowment is well accepted, such preliminary data suggest the need for further investigation because of issues of cause and effect, limitations in adjusting for confounders, potential for biased reporting, and selective recall.

A review of the literature on the role of nutritional factors in ADHD, including food additives, sugars, food allergies or sensitivities, and essential fatty acids, identified methodological problems with negative studies without similar discussion of problems with positive studies, possibly revealing bias of the authors.[97] Nevertheless, the summary statement is reasonably cautious: "There is increasing evidence that there is a subset of children with behavioral problems who are sensitive to one or more food components that may precipitate or contribute to their hyperactive behavior. Research indicates that it is futile to try to identify a specific food or substance that will precipitate negative behavior in all hyperactive children".[97] There have been many reviews of the literature of food additives, noting major flaws in the methodology of those studies.[98] However, randomized controlled trials have shown that sodium benzoate intake, a common preservative used in soft drinks and fruit juices, contributed to ADHD-like symptoms in young children.[99,100]

A study looking at the effect of gestational diabetes mellitus (GDM) and socioeconomic status (SES) on ADHD found that "the risk for ADHD increased over 14-fold ($P = .006$) when children were exposed to both GDM and low SES. Neither children exposed to maternal GDM alone nor those exposed to low SES alone had a notable increased risk for ADHD".[101] A study of a sample of 7- to 9-year-old children born extremely prematurely and/or with extremely low birth weight (ELBW) who were making normal progress at school found "reliable relations between biomedical variables (birth weight and neurobiological risk) and aspects of EF, such that the higher birth weights and lower levels of risk were associated with better performance".[102] The finding that "the negative impact of neurobiological risk was attenuated for participants from higher SES backgrounds is suggestive of a contribution of nurture to the development of EF".[102] Along those lines, a review of the causes of ADHD concluded that the dichotomy between genetic/biological and environmental factors in ADHD "is incorrect and unhelpful. Indeed, they are complementary rather than competing explanations".[103]

COEXISTING CONDITIONS

Many children who present with symptoms suggestive of ADHD have neurologic or psychiatric conditions that are the cause of those symptoms (e.g., depression, sleep disorders, epilepsy). There are other instances when multiple conditions coexist. The implications for management are significant. Just as correction of a sleep disorder may resolve the symptoms of inattention, hyperactivity, or impulsivity, addressing a child's previously undiagnosed learning disability may resolve these symptoms. Alternatively, a child may have both problems, and

remediation of the learning disability may still leave him or her with inattention, hyperactivity, or impulsivity that must be independently addressed. It has been proposed that ADHD be divided into subgroups based on the patterns of comorbidity.[43] ADHD and CD have been posited to be distinct disorders.[104] From a practical standpoint, most studies of children with ADHD and coexisting CD treated with psychostimulants demonstrated a reduction in physical and nonphysical aggression and had improvement of ADHD symptoms.[105] Antidepressants also reduced symptoms of aggression and ADHD in these children. Anxiety disorder has been shown to be transmitted independently from ADHD in families,[106] suggesting that these two conditions are distinct disorders. Most studies of children with ADHD and coexisting anxiety or depression found a reduced response in ADHD symptoms when treated with psychostimulants compared with children only with ADHD.[105]

It has been proposed, inasmuch as ADHD and mood instability include impulsivity and behavioral problems in their definitions, that both ADHD and mood instability involve an impairment in executive function, and that given findings of overlapping neuroanatomical abnormalities and treatments, mood instability should be considered a core feature of ADHD rather than a comorbidity.[107] A twin study[108] found a strong genetic association between ADHD symptoms and emotional lability, supporting the idea that emotional lability may be a component of ADHD; this association was stronger in older than younger children. The authors proposed that "emotional lability in childhood may be qualitatively different from emotional lability in adolescence. For example, emotional lability in childhood could arise for a number of reasons besides ADHD; however as these heterogeneous symptoms taper off during development, what is left might be a chronic state of emotional lability that is more strongly related to hyperactive-impulsive and inattentive symptoms at an etiologic level".[108]

A review of the overlapping symptoms associated with ADHD and sleep disorders noted that many children with primary sleep disorders have symptoms highly suggestive of ADHD. Conversely, many children with ADHD are reported to have sleep disturbances, which may be primary, attributable to the side effects of medication, or a result of comorbid conditions such as ODD, depression, and/or anxiety disorders. A comorbid sleep disorder may significantly increase the daytime impairment in a child with ADHD. It was recommended that all children presenting with ADHD symptoms be clinically assessed for the presence of sleep problems.[109]

Reading disability and ADHD are two distinct disorders that may occur together.[110] There is evidence of genetic linkage for ADHD and reading disability to the same region on the short arm of chromosome 6. This connection may represent a pleiotropic effect (i.e., the same gene increasing susceptibility to more than one disorder).[55] A survey of audiologists and pediatricians found that although auditory processing disorder and ADHD/I have symptoms in common, there were features that allowed them to be distinguished from each other.[111]

A meta-analysis of the literature reporting on tests of overall cognitive ability in ADHD analyzed data from 137 studies in which full-scale IQ (FSIQ) scores for children with ADHD were compared with a healthy control group. The ADHD groups had significantly lower FSIQ scores relative to the control groups, with an average decrement of 9 points in the FSIQ; the verbal and performance IQs were lower in the ADHD group. There was no difference in ADHD subtypes, although the number of children with inattentive-type ADHD was small. The authors concluded that these findings "may indicate that the disorder is characterized by mild global cognitive inefficiencies or by multiple specific deficits affecting

several cognitive abilities".[112] They raised the possibility that the decrement could also be attributable to test-taking differences between the groups. In support of this latter possibility, the authors found that the effect size of the FSIQ was largest when ability was based on the complete test as opposed to estimates from subtests; the larger effect on the complete test may possibly be a result of longer testing times in studies using a full intellectual assessment battery, with decreasing performance over time caused by deficient sustained attention in the ADHD group. The authors expressed surprise at the finding that for only a few of the measures was the effect size for executive functioning tasks significantly larger than effect sizes for the FSIQ. Only the academic achievement tests and Continuous Performance Test (CPT) measures displayed substantially larger effects than the FSIQ; the Wisconsin Card Sorting Test (WCST)-variables, Stop Signal Task (SST)-probability of inhibition, and Matching Familiar Figures Test-time tests had smaller effect sizes than the FSIQ. In a comparison of the mean effect size of tests of executive versus nonexecutive functions, there was greater impairment in the tests of executive function. The authors allowed for the possibility that an impairment of executive function accounted for differences in overall ability, inasmuch as measures of overall ability are heavily influenced by executive function. Academic measures of spelling and arithmetic were significantly more sensitive to ADHD than overall cognitive abilities measured by FSIQ; the authors commented that achievement measures "may be useful not only for screening comorbid learning disabilities but also for characterizing behavioral and motivation deficits resulting from executive dysfunction".[112]

DIAGNOSTIC EVALUATION

ADHD is a clinical diagnosis; there are no diagnostic laboratory or cognitive tests.[113] A child presenting with symptoms suggestive of ADHD should undergo screening for hearing and vision problems, potentially treatable issues that may be mistaken for ADHD. If the child's difficulties are predominantly in the school setting, an evaluation for learning disabilities should be pursued, with educational remediation if problems are identified. Social stressors may also be a significant factor,[114] which may justify intervention by social services agencies. In general, routine diagnostic testing is not needed in the evaluation of a child for ADHD.[115] However, specific testing may be indicated in some circumstances.

Laboratory Studies

Features in the history or on examination may lead to specific tests for disorders manifesting as or coexisting with ADHD, such as hypothyroidism,[116] hyperthyroidism,[117] or phenylketonuria.[118] Reports of an association between lead exposure and ADHD have been inconsistent.[119,120] Depending on the results of such laboratory studies, therapy targeting the specific condition may be initiated. An uncontrolled study reported improvement in the parents' but not the teachers' Connors Rating Scales scores in children with ADHD treated with iron supplementation, even though they were not iron deficient.[121] Better studies are needed before concluding that routine testing of or supplementation with iron or screening for iron deficiency is advisable.

Electroencephalography

Studies reporting an increased frequency of epileptiform discharges in children with ADHD[39,122,123] and reports of ADHD-type symptoms resolving when spike activity was suppressed with antiepileptic drugs[39,40] have led to proposed guidelines for obtaining an electroencephalogram (EEG). These include a history of clinical events suggesting a seizure (even if only nocturnal or febrile), perinatal stress, head trauma, fluctuating behavioral manifestations, or a family history of epilepsy.[124]

Sleep Studies

A sleep history should be obtained. If the results suggest a diagnosis of a sleep disorder or if there is a strong family history of sleep disorders, an overnight sleep study should be considered.[34,36,125]

Imaging Studies

There are few clinical indications for imaging studies in children with ADHD. ADHD has been reported in association with head trauma,[126,127] prematurity,[128] perinatal injury,[129] and neurofibromatosis.[130] However, if the child is clinically stable, the presence of ADHD symptoms does not call for imaging studies beyond those indicated for the primary condition.

TREATMENT
Nonpharmacologic Therapies

Children with ADHD need a classroom environment with minimal distractions and with seating that is somewhat isolated and close to the front of the room in front of the teacher.[131] The setting should be fairly structured with organizational techniques such as checklists and homework assignment pads, and an uncluttered desk at home should be devoted exclusively to schoolwork.

A multicenter clinical trial of various treatment strategies for ADHD[132] concluded that stimulants were more effective than behavioral therapies for ADHD symptoms. The combination of stimulants and behavioral therapy resulted in improved social skills but did not significantly improve ADHD symptoms over stimulants alone. A review of treatment modalities of children diagnosed with ADHD in the period from 1995 to 1999 found that among children diagnosed with ADHD, 24% also had mental illness. The most frequent treatments were stimulant medication alone (42%), stimulant medication combined with psychotherapy or mental health counseling (32%), and psychotherapy or mental health counseling alone (10.8%). Fifteen percent of children received no treatment other than office visits for initial and follow-up medical care. The percentage of children receiving psychotherapy or mental health counseling alone or in combination with stimulant medication increased with age, and males were more likely than females to receive treatment.[133]

Sleep

A recent study found a positive association between spindle-frequency EEG activity and motor skill learning improvement in children with ADHD.[134] This may account, at least in part, for the overlap in symptoms of ADHD and sleep disorders in children. This may also offer an opportunity for nonpharmacologic intervention in children with ADHD. Inasmuch as there is enriched sleep spindle activity in the latter part of sleep, having children with ADHD go to sleep early enough that they wake up spontaneously, rather than have the latter part of their sleep disrupted, might be beneficial to their function.[134]

Biofeedback Programs

Various forms of computerized training programs have been studied in treating children with ADHD. Computerized

working memory training improved working memory capacity in children with ADHD and adults without ADHD. Improvement generalized to nonpracticed tasks involving the prefrontal cortex, and associated with improvement in working memory was a decrease in head movements in children with ADHD.[135] Children with ADHD trained to modify their slow cortical potentials also showed an increase in contingent negative variation (CNV) during a continuous performance task compared with those who did not receive training. Associated with this electrophysiologic phenomenon were fewer impulsivity errors on the continuous performance task, suggesting that the CNV increase represented a neurophysiologic correlate of improved self-regulatory capabilities.[136] A meta-analysis of studies of nonpharmacologic treatments of ADHD, which was limited to studies of treatment and control groups and excluded studies using within-subjects in an effort to minimize placebo effects, found that "behavior modification is efficacious in the treatment of ADHD in children, improving functioning across a number of domains—including symptoms, behaviors, and neuropsychological test performance." In addition: "Neurofeedback treatment resulted in statistically significant improvement in DSM-IV symptoms, neuro-psychological test performance, and behavior." The authors found: "No statistically significant benefit was established for the school based, parent training, working memory training, self-monitoring, or multimodal psychosocial treatment interventions across any of the measured ADHD functional domains."[197] Psychological treatments for ADHD were more effective among girls than boys and were least effective for children with combined-type ADHD.

Use of an EEG biofeedback program has been compared with the effectiveness of methylphenidate.[137] Children were trained to increase the power of the sensory motor rhythm (12–15 Hz) and low beta activity (15–18 Hz). Assignment to the biofeedback versus methylphenidate group was based on parental preference. Two-thirds of parents chose the biofeedback training program, raising issues of selection bias, and there was no placebo arm in this study. After 3 months of the program, both groups had significant improvements in all four subscales on the TOVA and improvement on a behavior rating scale. Changes in the EEG as a result of biofeedback were not monitored in this study. A previous study using biofeedback reported greater improvement on the TOVA in participants with significant EEG changes than in those without changes (although there were improvements in both groups).[138] There was no correlation between behavioral changes reported by the parents and changes in the EEG. This study did not include a control group. A study of EEG biofeedback that used a control group (i.e., association between EEG patterns and feedback to the participants was random) found no benefit from EEG biofeedback.[139] The investigators observed that an analysis of the data that failed to control for overall behavioral trends unrelated to training and that also excluded dropouts would have led to the spurious conclusion that the treatment was effective.

A study looking at the effect of aerobic exercise on executive function in children with ADHD found that aerobic exercise facilitated inhibition and set-shifting, impairments in which are thought to account for executive dysfunctions in ADHD.[140] Another study found that aerobic exercise resulted in smaller theta/alpha ratios in the frontal and central brain regions compared with a control group.[141]

Pharmacologic Therapy

In the 1930s, Charles Bradley administered benzedrine (an amphetamine) to children with a history of neurologic and behavioral problems in whom he had done a lumbar puncture, in an attempt to stimulate secretion of cerebrospinal fluid by the choroid plexus and diminish headaches after lumbar puncture. Although not affecting the incidence of headaches, the children's teachers reported major improvement in learning and behavior in a number of children that lasted the entire time they were treated.[142] A subsequent open trial of benzedrine in children with neurologic and behavioral problems who had normal intelligence resulted in improvement in learning, a greater interest in and higher quality of their schoolwork, behavioral and social improvements, and increased voluntary control.[143] However, the use of medication in children was viewed unfavorably in the medical and educational community, and it was not until the 1960s, when methylphenidate was found to be effective in treatment of attention disorders, that stimulant use was accepted by physicians and parents.[4] Between 1990 and 1998, there was a 3.7-fold increase in the diagnosis of ADHD, and prescription of stimulants for children 5 to 18 years old increased from 11.5 to 42 per 1000.[144] Recently and controversially, the American Heart Association recommended that all children placed on stimulant medications for ADHD should have a screening electrocardiogram (ECG)[145]; the American Academy of Pediatrics concluded that this is neither necessary nor recommended and, instead, recommended selected cardiovascular screening based on personal, past, and family histories and the cardiovascular examination.[146]

Stimulant Medications

Stimulant drugs, sympathomimetic agents structurally similar to endogenous catecholamines, act centrally and peripherally by enhancing dopaminergic and noradrenergic transmission. Stimulants have been demonstrated to improve cognitive ability, school performance, and behavior.[147-149] A study of children with ADHD with a high degree of comorbidity (ODD, 10%; CD, 30%; anxiety disorder, 17%; dyslexia, 32%) found differential effects of methylphenidate on various attentional functions at different doses.[150] Specifically, alertness and focused and sustained attention improved in a linear fashion with increasing dose, inhibition and set-shifting were enhanced at a low dose but worsened at a moderate dose, and divided attention did not change at all. The different dose–response relationships for various cognitive and behavioral functions were explained by the differential effects of these agents in different brain regions.[76]

The positive effects of methylphenidate on cognitive functions were caused by facilitation of dopaminergic activity in some brain regions, whereas improvement in hyperactivity and impulsivity was mediated by reduction in dopaminergic stimulation in other brain regions. This study did not uncover any differences in the response to methylphenidate between children with ADHD/C versus ADHD/I, nor was there any effect of comorbidity. Such data suggest that a single measure of response to stimulant treatment may be insufficient because different doses may be necessary to improve particular functions.

The response to methylphenidate in a group of 28 preschoolers (3–5 years old), as measured by behavioral ratings by teachers and parents, documented improvement, with 82% rated as having normal behavior after treatment, higher than the rate generally achieved in older children.[151] With the exception of decreased appetite, there were no adverse side effects. The investigators speculate that the higher normalization rate for preschoolers than elementary-age schoolchildren may be a function of fewer demands placed on the preschooler (e.g., shorter school day, no homework).

The most commonly reported side effects of stimulants include appetite suppression and sleep disturbance. Absorption

of stimulant medications is not notably affected when taken with or after meals, which may ameliorate appetite suppression.[152] Insomnia can be a side effect from the medication but may also be caused by a rebound effect as the medication effect subsides. This distinction is important because in the latter situation, a late afternoon or evening dose of stimulant medication may ease falling asleep.[153] Uncommonly, there have been reports of mood disturbances and lethargy after stimulant use.[154] Stimulants may also affect heart rate and blood pressure, but in healthy children, this change is unlikely to have clinical significance.[151,155] There have been reports of psychostimulants inducing or exacerbating tic disorders, but subsequent studies have not found this to be a universal problem.[156] Although this possibility should be discussed with children and their families, the presence of tics in a child with ADHD or a family history of tics is not an absolute contraindication to the use of psychostimulants. Concerns are often expressed regarding an increased risk of substance abuse in children treated with psychostimulants,[157] but there is no supporting evidence. One study found that pharmacologic treatment for ADHD actually decreased the risk of subsequent substance abuse.[158] However, although the risk of substance abuse in individuals with ADHD appears to be reduced by treatment, it is still higher than in the general population. Inasmuch as illicit substance abuse can manifest with attention difficulties, hyperactivity, and/or impulsivity, the possibility that substance abuse is accounting for symptoms is to be considered; reevaluation after a period of abstinence may be warranted.[159] There have also been reports of a decrease in the height of children taking stimulant medications,[160] but other studies indicated no effect.[161] The reported decrease in height may reflect a transient maturational delay associated with ADHD, rather than a growth-stunting effect of medication.[162]

Koneski et al.[163] evaluated the use of methylphenidate in 24 children with at least two epileptic seizures in the previous 6 months and a diagnosis of ADHD and found an improvement in ADHD symptoms for 70.8% of the children, no change in ADHD symptoms for 20.8%, and a worsening of symptoms in 8.3%. Of these 24 children, 22 (71%) showed no increase in seizure frequency; however, there was worsening in two. Santos et al.[164] found that of 22 children with active epilepsy and ADHD treated for 3 months with methylphenidate, 4 patients reported some increase in seizure frequency and one patient withdrew as a result of increased seizure frequency. There was substantial improvement in ADHD symptoms, such that 16 (73%) of the patients no longer had clinically significant ADHD symptoms. Other studies of children with ADHD and epilepsy or interictal discharges treated with methylphenidate did not find any increase in seizure frequency.[165,166] Thus, although there is evidence of some risk of seizure exacerbation with stimulant use in children with ADHD and epilepsy, this does not occur in the majority of cases, and there is clear evidence of benefit; the decision to use stimulants in such cases requires an individualized consideration of the risk versus benefit.

A longitudinal study[167] revealed that children treated with medication had a reduced height gain compared with those who were not treated. Growth suppression was still evident during the second year of treatment in the group treated continuously, indicating that this was a persistent effect. The observation that there was less growth suppression in the children who were not treated continuously suggests that interrupting treatment with stimulant medication may limit growth suppression, supporting the concept of drug holidays to address this side effect. However, there have been reports of behavioral deterioration when stimulant medications are abruptly discontinued.[168]

The most commonly used drugs in the stimulant class include methylphenidate, dextroamphetamine, and mixed salts of L-and D-amphetamine. Although in the same class, these drugs have slightly different mechanisms of action, and patients may respond differently to each of them.[169] Failure of one drug does not preclude success with another drug in the same class. A number of these agents are available in short-and long-acting formulations. The results of studies comparing short-and long-acting preparations have been inconsistent,[170-172] making the choice of formulation an empirical one.

Methylphenidate

Methylphenidate has fewer side effects than amphetamine.[173] In the standard formulation, methylphenidate reaches peak concentrations between 1 and 3 hours after oral intake. It is rapidly and extensively metabolized by nonmicrosomal hydrolytic esterases in liver and other tissues, with an average half-life of 3 hours. In children, the starting dose is 0.3 mg/kg in the morning, rounded to the nearest 5-mg tablet.[174] It can be useful to have teachers complete a behavior checklist before and after initiation of treatment (preferably without being aware of exactly when the medication is started) to assess efficacy. If, after 1 to 2 weeks, there is inadequate benefit, the dose can be increased to 0.6 mg/kg. With an average half-life of 3 hours, a morning dose does not persist through the afternoon. Increasing the morning dose may increase the duration of the effect. Alternatively, a second dose 3 to 4 hours after the initial dose may be necessary. A dose in the middle to late afternoon to facilitate completion of homework may also be warranted. Alternatives to multiple daily doses are the long-acting formulations of methylphenidate. These formulations reach peak concentration 6 to 8 hours after oral intake, obviating the need for a midday dose. When using the longer-acting formulations, the entire daily dose is given in the morning. If there is no significant improvement in symptoms at a total daily dose of 1 to 2 mg/kg, alternate medication should be considered.

The regular formulation of methylphenidate is available in 5-, 10-, and 20-mg tablets (Ritalin). There are multiple extended-release formulations that use different mechanisms to achieve their sustained-release effect; they are available in 10- and 20-mg tablets (Metadate ER); 10-, 20-, and 30-mg capsules (Metadate CD); 20-, 30-, and 40-mg capsules (Ritalin LA); and 18-, 27-, 36-, and 54-mg tablets (Concerta).

Another sustained-release form of methylphenidate is available as a skin patch that is placed on the skin daily for 9 hours. It is available in 12.5-, 18.75-, 25-, and 37.5-cm² sizes (Daytrana).

Dexmethylphenidate

Dexmethylphenidate is the D-threo-enantiomer of methylphenidate. A positron emission tomography (PET) study found specific binding of the D-enantiomer to a dopamine transporter in the basal ganglia, whereas the L-enantiomer had widespread, nonspecific binding.[175] Studies comparing dexmethylphenidate and methylphenidate have concluded both to be effective in ADHD, but dexmethylphenidate has a longer duration.[176] The time to peak concentrations after oral intake is similar to methylphenidate, between 1 and 3 hours, and like methylphenidate, it is rapidly and extensively metabolized by nonmicrosomal hydrolytic esterases in liver and other tissues, with an average half-life of about 2 hours. In children the starting dose of dexmethylphenidate is one-half of the methylphenidate dose (0.15 mg/kg in the morning, rounded to the nearest 2.5-mg tablet).[174] If after 1 to 2 weeks there is inadequate benefit, the dose can be increased in 2.5-mg increments,

to a maximum of 20 mg/day. The report of longer clinical efficacy than methylphenidate (despite the similar half-life) may eliminate the need for a midday dose, depending on the clinical response. There is no evidence that giving the D-isomer (dexmethylphenidate) at one-half of the dose of the D,L-enantiomer (methylphenidate) confers any clinical advantage. Dexmethylphenidate is available in 2.5-, 5-, and 10-mg tablets (Focalin).

Dextroamphetamine

Dextroamphetamine has a time to peak concentration of 60 to 160 minutes and is metabolized in the liver. The average half-life of dextroamphetamine is 10 to 12 hours, but this varies considerably with urinary pH; at a urine pH less than 6.6, more than two-thirds of unmetabolized drug is excreted in the urine, whereas at a urine pH greater than 6.7, it is less than one-half. The initial dose of dextroamphetamine is 0.15 to 0.3 mg/kg (rounded to the nearest 5 mg).[174] This dose can be gradually increased for the desired effect up to a peak dose of approximately 1 mg/kg per day. Dextroamphetamine's longer half-life compared with methylphenidate may obviate the need for a midday dose. An extended-release preparation of dextroamphetamine eliminates the need for midday dosing. The regular formulation of dextroamphetamine is available in 5-mg tablets (Dexedrine); the extended-release formulation is available in 5-, 10-, and 15-mg capsules (Dexedrine Spansules).

Adderall is a combination of four amphetamine salts (D-amphetamine saccharate, D-amphetamine sulfate, D,L-amphetamine sulfate, and D,L-amphetamine aspartate), with a 3 : 1 ratio of D-isomer to L-isomer. The time to peak concentration and half-life are similar to those for dextroamphetamine. The initial dose of Adderall is 2.5 or 5 mg, with weekly increments based on the response to a maximum dose of 1.5 mg/kg per day, up to about 40 mg. The half-life of Adderall is such that a midday dose may or may not be necessary. Adderall is available in 5-, 7.5-, 10-, 12.5-, 15-, 20-, and 30-mg tablets. Adderall XR capsules, with one-half of the contents in a delayed-release formulation, eliminate the need for midday dosing; the entire daily dose is given in the morning. Adderall XR is available in 5-, 10-, 15-, 20-, 25-, and 30-mg capsules.

Noradrenergic Potentiation

Atomoxetine

Atomoxetine (Strattera) is a norepinephrine-specific reuptake inhibitor that is effective in the treatment of children with ADHD. In a study comparing atomoxetine to methylphenidate and placebo, the response rate to atomoxetine and methylphenidate was essentially identical, and both were better than placebo. Appetite suppression was somewhat lower in atomoxetine compared with methylphenidate (22% versus 32%), and there was significantly less insomnia on atomoxetine (7% versus 27%).[177] Atomoxetine is metabolized by the cytochrome P-450 (CYP) 2D6 pathway. Peak plasma concentrations of atomoxetine occur 1 to 2 hours after oral administration. In extensive metabolizers (most patients), atomoxetine half-life is 4 to 5 hours. Substantial decreases in clearance and prolongation of the half-life are seen in poor metabolizers. The starting dose is 0.5 mg/kg per day, with gradual increase to a target dose of 1.2 mg/kg per day. In poor metabolizers (about 7% of the population), the half-life is substantially longer, and the dose requirement may be much lower. Depending on the response, midday dosing may be required for extensive metabolizers. Food does not affect absorption.[174] Because atomoxetine is not a controlled substance in the United States,

prescriptions with multiple refills can be provided, and renewals can be done over the phone, in contrast to the procedures for stimulant medications. Atomoxetine is available in 10-, 18-, 25-, 40-, and 60-mg capsules. In December 2004 the U.S. Food and Drug Administration (FDA) asked the manufacturer to add a bolded warning about severe liver injury to the labeling, indicating that the medication should be discontinued in patients who develop jaundice or laboratory evidence of liver injury. In September 2005 the FDA directed the manufacturer to further revise the labeling to include a boxed warning regarding an increased risk of suicidal thinking in children and adolescents being treated with this drug.

Nonstimulant Medications

It is estimated that at least 30% of children diagnosed with ADHD do not respond to or tolerate stimulant medications.[105] Most studies have reported a reduced rate of response to psychostimulants in children with ADHD and anxiety or depression.[105] The failure to respond to psychostimulants suggests the possibility of an incorrect diagnosis. However, genetic studies have suggested that children with ADHD respond differently to methylphenidate, depending on whether they are homozygous or heterozygous for the 10-repeat allele at dopamine transporter gene *SLC6A3*.[178-180]

Tricyclic Antidepressants

Other agents found to be effective in the treatment of ADHD include tricyclic antidepressants (TCAs). In one study, comorbidity with conduct disorder, depression, or anxiety or a family history of ADHD did not result in a differential response to desipramine.[181] In studies comparing TCAs with stimulants, TCAs appear to more consistently improve behavioral symptoms rather than cognitive function.[182]

Desipramine

Desipramine, a TCA, is metabolized in the liver by the CYP-2D6 pathway, with an average half-life of 17.1 hours. For the 7% of the population with decreased activity of this enzyme, the half-life may be as long as 77 hours.[174] The effective dose of desipramine is lower and onset of action sooner for ADHD than for depression.[183] The starting dose of desipramine is 1 mg/kg per day, with gradual increments to a maximum of 5 mg/kg per day. This medication may be given once daily or in divided doses, depending on the response. For slow metabolizers, the dose requirement is much lower, and once-daily dosing should be sufficient.

There have been case reports of sudden death in children treated with desipramine.[184] Although a subsequent epidemiologic study did not find greater risk of sudden death with desipramine,[185] it has been suggested that a baseline ECG be obtained before initiating treatment and that serial ECGs be obtained after significant dose increments and periodically during treatment.[168]

Alpha-Adrenergic Agonists

The alpha-adrenergic agents clonidine and guanfacine have been widely used for treatment of ADHD, despite few clinical studies. The success of these agents for Tourette syndrome and other tic disorders[186] has made them especially useful in children with ADHD and tic disorders, particularly if a trial of stimulant medication resulted in exacerbation of tics. Reports of three deaths of children taking a combination of methylphenidate and clonidine prompted reviews that found no evidence of an adverse methylphenidate–clonidine interaction.[187,188] Nevertheless, if planning to prescribe this combination, a review of this literature and discussion of risks and

benefits with the parents is advisable. Guanfacine appears to have an advantage over clonidine because it has a longer half-life and is less sedating.[189] Guanfacine reaches a peak concentration after oral intake in 1 to 4 hours and is metabolized in the liver, with an average half-life of 17 hours.[174] The starting dose is 0.015 mg/kg per day (to the nearest 0.5 mg), with a gradual increase to a maximum of 0.05 mg/kg or 4 mg/day, based on the clinical response.[168,190] The half-life of guanfacine should allow for once-daily dosing, although in clinical studies it was administered in two to four divided doses.[189,191] Guanfacine is available in 1- and 2-mg tablets (Tenex). A sustained-release form of guanfacine (Intuniv) is also available; the half-life is 16 hours, and the time to peak serum level is approximately 5 hours. This is effective as a once-a-day dosing schedule in doses of 1 to 4 mg/day. It comes in 1-, 2-, 3-, and 4-mg tablets.[192] Other agents reported to be effective in ADHD are reviewed in Table 56-1.

A review of prospective trials of medicines used for ADHD in children noted a wide heterogeneity between studies in terms of follow-up duration and the reporting criteria for adverse effects (AEs), thus limiting the information available on the long-term effects of ADHD treatment. The authors concluded that "drugs for ADHD are generally safe and well tolerated, with decreased appetite, insomnia, headache and abdominal pain being the most common adverse effects (AEs) observed in long-term prospective trials. Tics were reported in all long-term studies of methylphenidate. Emotional lability was reported only with mixed amphetamine salts".[193] It was noted that although AEs were described as mild or moderate,

lack of tolerability resulted in the discontinuation of treatment in 10% to 25% of children "with most of the AEs and discontinuation cases occurred in the first few months of drug treatment".[193] The authors added that there was little data available regarding events that occur with a frequency of less than 1%. As a result, "many psychiatric AEs may be missed or underestimated, in particular the more severe ones (eg, suicide attempts)".[193] The studies available "provided scant information concerning the effect of treatments on growth and on the cardiovascular system".[193]

Complementary and Alternative Medications

A survey of parents of children referred for evaluation of ADHD reported that 54% of the parents used complementary and alternative medicine (e.g., acupuncture, nutritional supplements) for the child's ADHD symptoms in the prior year.[194] Only 11% of the parents discussed using such interventions with their child's physician.

OUTCOME

ADHD persists into adulthood. The symptoms of ADHD may be less obvious after the individual is older.[62] The incidence of ADHD in adults depends on diagnostic criteria and whether historical data are obtained from the patients or their parents.[53] As noted in the introduction, the revised criteria in the DSM-5 reduce the number of symptoms required to make a diagnosis in adults and adolescents 17 and older from six to five, which

TABLE 56-1 Major Drug Classes Used in the Pharmacotherapy of Attention Deficit–Hyperactivity Disorder*

Drug	Total Daily Dose	Daily Dosage Schedule	Main Indications	Common Adverse Effects/Comments
Stimulants				
Dextroamphetamine	0.3–1.0 mg/kg	2 or 3 times	ADHD	Insomnia, decreased appetite Depression, psychosis (rare, with very high doses) Increased heart rate and blood pressure (mild) Possible growth reduction with long-term use Withdrawal effects and rebound phenomena
Mixed salts of l- and d-amphetamine	0.5–1.5 mg/kg	1 or 2 times	ADHD	Regular form: 6-hour duration of action Extended-release form: 10- to 12-hour duration of action
Lisdexamfetamine	30–70 mg (total)	Daily	ADHD	Less abuse potential than dextroamphetamine
Methylphenidate	1–2 mg/kg	1–3 times	ADHD	Regular forms: 3- to 4-hour duration of action Extended-release forms: 8- to 12-hour duration of action
Methylphenidate patch	10–30 mg/9 hours (total)	Daily	ADHD	
Dexmethylphenidate	0.5–1.0 mg/kg	2 or 3 times	ADHD	
Magnesium pemoline	1.0–2.5 mg/kg	1 or 2 times	ADHD	Associated with rare, serious hepatotoxicity; requires monitoring of liver function tests
Modafinil	200–400 mg (total)	Daily	Narcolepsy	Fewer peripheral sympathomimetic effects than amphetamines
NSRIs				
Atomoxetine	0.5–1.4 mg/kg	1 or 2 times	ADHD ± comorbidity Enuresis (?) Tic disorder (?) Depression/anxiety disorders (?)	Mechanism of action: noradrenergic-specific reuptake inhibitor Mild or moderate appetite depression Gastrointestinal symptoms Mild initial weight loss Mild increase in blood pressure, pulse No ECG conduction or repolarization delays Not abusable

TABLE 56-1 Major Drug Classes Used in the Pharmacotherapy of Attention Deficit–Hyperactivity Disorder* *(Continued)*

Drug	Total Daily Dose	Daily Dosage Schedule	Main Indications	Common Adverse Effects/Comments
Tricyclic Antidepressants				
Tertiary amines	2.0–5.0† mg/kg	1 or 2 times	ADHD	Mixed mechanism of action (noradrenergic/ serotonergic)
Imipramine	2.0–5.0† mg/kg	1 or 2 times	Enuresis	
Amitriptyline	2.0–5.0† mg/kg	1 or 2 times	Tic disorder	Secondary amines more noradrenergic
Clomipramine			Anxiety disorders (?)	Clomipramine primarily serotonergic
			OCD (clomipramine)	Narrow therapeutic index
				Overdoses can be fatal
				Anticholinergic effects: dry mouth, constipation, blurred vision
				Weight loss
				Mild increase in diastolic blood pressure and ECG conduction parameters with daily doses > 3.5 mg/kg
Secondary amines				
Desipramine	2.0–5.0† mg/kg	1 or 2 times		
Nortriptyline	1.0–3.0† mg/kg	1 or 2 times		
MAOIs	0.5–1.0 mg/kg	2 or 3 times	Atypical depression	Difficult medicines to use in juveniles
Phenelzine	0.5–1.0 mg/kg	2 or 3 times	Treatment-refractory depression	Reserved for refractory cases
Tranylcypromine	0.5–1.0 mg/kg	2 or 3 times		Severe dietary restrictions (i.e., high-tyramine foods)
Selegiline				Drug–drug interactions
				Hypertensive crisis with dietetic transgression or with certain drugs
				Weight gain
				Drowsiness
				Changes in blood pressure
				Insomnia
				Liver toxicity (remote)
Other Antidepressants				
SSRIs	0.3–0.9 mg/kg	1 time, in afternoon	MD, dysthymia	Serotonergic mechanism of action
Fluoxetine	0.3–0.9 mg/kg	1 time, in afternoon	OCD	Large margin of safety
Paroxetine	0.3–0.9 mg/kg	1 time, in afternoon	Anxiety disorders	No cardiovascular effects Irritability
Citalopram	1.5–3.0 mg/kg	1 time, in afternoon	Eating disorders	Insomnia
Sertraline	1.5–4.5 mg/kg	1 time, in afternoon	PTSD (?)	Gastrointestinal symptoms
Fluvoxamine				Headaches
				Sexual dysfunction Withdrawal symptoms more common with short-acting drugs
				Potential drug–drug interactions (cytochrome P-450)
Bupropion (SR)	3–6 mg/kg	2 times	ADHD	Mixed mechanism of action (dopaminergic/ noradrenergic)
			MD	
			Smoking cessation	Irritability
			Anticraving effects (?)	Insomnia
				Drug-induced seizures at doses > 6 mg/kg
Venlafaxine (XR)	1–3 mg/kg	1 time	Bipolar depression (?)	Contraindicated in bulimics
			MD	Mixed mechanism of action (serotonergic/ noradrenergic)
			Anxiety disorders	Similar to SSRIs
			ADHD (?)	Irritability
			OCD (?)	Insomnia
				Gastrointestinal symptoms Headaches
				Potential withdrawal symptoms
				Blood pressure symptoms
Nefazodone	4–8 mg/kg	1 time	MD	Mixed mechanism of action (serotonergic/ noradrenergic)
			Anxiety disorders	Dizziness
			OCD (?)	Nausea
			Bipolar depression (?)	Potential interactions with nonsedating antihistamines, cisapride (cytochrome P-450)
				Rare, serious hepatotoxicity Less manicogenic (?)
Mirtazapine	0.2–0.9 mg/kg	1 time, in the afternoon	MD	Mixed mechanism of action (serotonergic/ noradrenergic)
			Anxiety disorders	Sedation
			Stimulant-induced insomnia (?)	Weight gain
			Bipolar depression (?)	Dizziness
				Less manicogenic (?)

TABLE 56-1 Major Drug Classes Used in the Pharmacotherapy of Attention Deficit–Hyperactivity Disorder* *(Continued)*

Drug	Total Daily Dose	Daily Dosage Schedule	Main Indications	Common Adverse Effects/Comments
Noradrenergic Modulators				
α2-Agonists Clonidine	0.003–0.010 mg/kg	2 or 3 times	Tourette disorder ADHD Aggression/self-abuse Severe agitation Withdrawal symptoms	Sedation (frequent) Hypotension (rare) Dry mouth Confusion (with high dose) Depression Rebound hypertension Localized irritation with transdermal preparation
Guanfacine (see text for information on long-acting form of Guanfacine)	0.015–0.05 mg/kg	1 or 2 times		Same as clonidine Less sedation, hypotension
Guanfacine, extended-release form		1–4 mg/day given once a day		
β-Blockers Propranolol	1–7 mg/kg	2 times	Aggression/self-abuse Severe agitation Akathisia	Risk for bradycardia and hypotension (dose-dependent) and rebound hypertension Bronchospasm (contraindicated in asthmatics) Rebound hypertension on abrupt withdrawal

*Doses are general guidelines and must be individualized with appropriate monitoring. Weight-corrected doses are less appropriate for obese children, and adult doses should not be exceeded in older or larger children. When high doses are used, serum levels may be obtained to avoid toxicity.

†Dose adjusted according to serum levels (therapeutic window for nortriptyline).

ADHD, attention deficit–hyperactivity disorder; DR, delayed release; ECG, electrocardiographic; IR, immediate release; MAOIs, monoamine oxidase inhibitors; MD, mood disorder; MR, mental retardation; NSRIs, norepinephrine-specific reuptake inhibitors; OCD, obsessive-compulsive disorder; OROS, oral osmotic; PTSD, posttraumatic stress disorder; SR, sustained release; SSRIs, selective serotonin reuptake inhibitors; XR, extended release.

(Adapted from Biederman J et al. Int J Neuropsychopharmacol *2004;7:77.)*

will inevitably result in an increased incidence of ADHD in those age groups. The finding that adolescents and young adults with ADHD had more car accidents with bodily injuries indicates that this is a serious problem even in older children and adults.[195] A pilot study of 11 adults 55 years or older diagnosed with ADHD found that these patients had the same psychiatric comorbidities as younger adults with ADHD and at similar rates. Psychiatric comorbidities were pervasive in this group and tended to weaken the effect of stimulant medications on overall functioning while enhancing the effect of medication on impulsivity.[196]

CONCLUSIONS

Study of higher cortical function is inherently complex. Advances in neuroscience have brought new methods to this endeavor. There is still much research required for achieving an understanding of ADHD, not least of which is agreeing on a precise definition so that studies can be compared. Available evidence suggests that there may be value in distinguishing ADHD/I from ADHD/HI and ADHD/C and in separating cases with comorbidity because these groups have different characteristics and different responses to treatment. A crucial role for the physician assessing a child for the possibility of ADHD is recognizing features in the presentation that suggest alternative diagnoses. Although much remains to be done, substantial advances in the neurobiology, diagnosis, and management of this condition have been made, and the prospect for significant enhancement of the lives of children with ADHD continues to improve.

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