A Clinical Perspective of Attention-Deficit/Hyperactivity Disorder Into Adulthood

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Objective: Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder that affects all age groups. Recent data on the clinical presentation, comorbidity, neurobiology, and treatment are reviewed.

Method: Using the search term *ADHD*, a selective PubMed review of the clinical literature was undertaken to evaluate recent data relevant to ADHD with attention to a life span perspective of the disorder.

Results: A growing literature indicates that ADHD is more persistent than previously thought and has a developmental variability in its presentation. The disorder impairs academic, social, and occupational functioning and is often associated with comorbidity, including cigarette smoking and substance abuse. Considerable evidence suggests that the disorder has a strong genetic component and a biological underpinning; the pathophysiology includes dysfunction in both noradrenergic and dopaminergic systems. Both psychosocial therapy and pharmacotherapy have been shown effective in the treatment of the disorder throughout the life span. The therapeutic effectiveness of pharmacologic agents in the treatment of ADHD has been attributed to noradrenergic and/or dopaminergic effects.

Conclusion: ADHD is associated with impairment and comorbidity throughout the life span. Growing evidence suggests the importance of short- and long-term management of the disorder. While the long-term treatment of ADHD is expected to lessen the individual's impairment, the outcome for adults who have received treatment since childhood requires further study.

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Attention-deficit/hyperactivity disorder (ADHD) is the most common emotional, cognitive, and behavioral disorder treated in children.[1–3] It carries a high rate of psychiatric comorbidity, notably oppositional defiant disorder (ODD), conduct disorder, mood and anxiety disorders, and cigarette and substance use disorders.[4] Across the life span, the social and societal costs of untreated ADHD are considerable, including academic underachievement, conduct problems, underemployment, motor vehicle safety, and difficulties with personal relationships.[5–8] Current and developing treatment strategies involving cognitive/behavioral and pharmacologic interventions often help patients overcome the obstacles to normal functioning.[9–16]

ADHD is more prevalent than schizophrenia, obsessive-compulsive disorder, and panic disorder,[17–19] affecting an estimated 4% to 12% of school-aged children in the United States[2] (a 2002 Mayo Clinic study found the lowest prevalence to be 7.4%[3]). A recent meta-analysis of the world's literature indicates that ADHD exists in the United States and other countries to a similar degree.[17]

In children diagnosed with ADHD, the ratio of boys to girls is approximately 3:1,[2] though figures vary based on data from clinically referred versus community-based patients. Survey studies[20,21] estimate that approximately 4% of college-aged students and adults have ADHD.[22] In recent years, the recognition, diagnosis, and treatment of ADHD in adults have been increasing, and the gender ratio is about 1:1.[4]

DIAGNOSING ADHD

Although the validity of the ADHD diagnosis continues to be debated in the media, the scientific community has accepted the existence of the disorder, even in adulthood,[23,24] for a number of years. ADHD can be reliably diagnosed in both children and adults.[11,24] Under the current guidelines,[25] the child or adult patient must meet the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV). Symptoms, one of the criteria, are categorized as follows: inattention—difficulty sustaining attention, forgetfulness, and distractibility; hyperactivity—fidgeting, excessive talking, and restlessness; and impulsivity—difficulty waiting one's turn and frequent interruption of others.[1] The DSM-IV criteria also include onset by age 7, impaired functioning in at least 2 settings (home, work, school, job), and more than 6 months of duration.

Three subtypes of the syndrome are currently recognized: predominantly inattentive, hyperactive-impulsive, and the combined type, which is the most common and most debilitating.

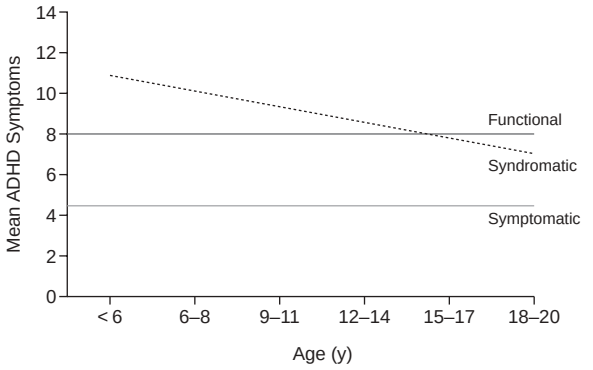
Many clinicians believe the inattentive subtype has been underdiagnosed—particularly in girls. Typically, girls with this subtype do not disrupt classes, but they have clinically meaningful levels of inattention and underachievement related, in part, to poor self-esteem.[26]

To meet the DSM-IV criteria for the inattentive or hyperactive-impulsive subtypes, an individual must have 6 or more of the 9 symptoms from either group of criteria (18 possible traits in all). For the combined subtype, an individual must have 6 or more inattentive symptoms and 6 or more hyperactive-impulsive symptoms. To warrant the ADHD diagnosis, symptoms must cause significant impairment. Adults diagnosed with the disorder must have had childhood onset and persistent and current symptoms, although allowance is made for incomplete persistence of full criteria (ADHD-in partial remission).

Clinical diagnosis is made through a combination of a careful clinical history[25] and ancillary evidence, such as teacher and/or family reports. The patient's symptoms, severity of impairment, possible comorbidity, family history, and psychosocial stressors may be determined during the parent and patient interview. In pediatric evaluations, the child's behavior and parent-child interaction are observed, and the child's educational, medical, and neurologic status are evaluated.[27,28]

Several diagnostic tools are employed with the child: the Conners Parent and Teacher Questionnaires, the ADHD Rating Scale-IV, the Achenbach Behavioral Checklist, the ADD-II Comprehensive Teacher Rating Scale, the Child Behavior Rating Scale, and the Copeland Symptom Checklist for ADD. Symptom scales used with all age groups (to assess home, school, and job performance) include the ADHD Symptom Checklist, SNAP-IV Teacher and Parent Rating Scale, Conners Rating Scales-Revised, Brown Attention-Deficit Disorder Scales, Brown Attention-Deficit Disorder Scales for Children, and the ADHD Symptoms Rating Scale.[29,30] Although these tools quantify behavior deviating from norms, they should not be used alone to make or refute the diagnosis. In some instances, the scales are employed to assess and monitor the patient's response to treatment.[11,31]

Figure 1. Age-Dependent Decline of Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms: Total DSM-III-R ADHD Symptoms[a,b]



[a]Based on Biederman et al.[5]
[b]β = –0.77 (–0.97 to –0.56).

Diagnosing adults involves careful querying for developmentally appropriate criteria from the DSM-IV concerning the childhood onset, persistence, and current presence of symptoms. The diagnostic reliability of reporting adult ADHD symptoms largely retrospectively from childhood has been validated. For example, Murphy and Schachar[32] found a high correlation (R values > 0.75) between reports of childhood ADHD made by adults with the disorder and their parents, and ratings of current symptoms made by adults with ADHD and their partners. Self-report forms such as the Wender Utah Rating Scale, ADHD rating scale, Brown Attention-Deficit Disorder Scales, and Conners rating scales have all been psychometrically evaluated and found valid and reliable as diagnostic aids for adult ADHD.[33–36]

Recent literature and follow-up studies show that prominent symptoms and impairment related to the disorder persist into adulthood in approximately one half of cases.[37–39] Beginning in adolescence, ADHD symptoms decline and change their presentation (Figure 1).[5] A majority of youth will lose full *syndromatic* criteria for ADHD as they grow up: they will no longer present with the full criteria. However, an even larger number will manifest *symptomatic* persistence (e.g., partial diagnostic criteria) of the disorder into adulthood: they will present with most of the symptoms and other criteria and with ADHD-related impairments.

Table 1. ADHD Clinical Presentation: School Age (6–12 years)[a]

Easily distracted
Homework poorly organized, contains careless errors, often not completed
Blurts out answers before question completed (often disruptive in class)
Often interrupts or intrudes on others and displays aggression (difficulties in peer relationships)
Fails to wait turn in games
Often out of seat
Perception of "immaturity" (unwilling or unable to complete chores at home)

[a]Based on Greenhill[27] and Conners and Jett.[31]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 2. ADHD Clinical Presentation: Adolescence (13–18 years)[a]

May have a sense of inner restlessness (rather than hyperactivity)
Schoolwork disorganized and shows poor follow-through; fails to work independently
Engages in "risky" behaviors (speeding and driving mishaps)
Poor self-esteem
Poor peer relationships
Difficulty with authority figures

[a]Based on Greenhill[27] and Conners and Jett.[31]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 3. ADHD Clinical Presentation: Adulthood[a]

Inattention/concentration problems
Disorganized, fails to plan ahead
Forgetful, loses things
Difficulty in initiating and finishing projects or tasks
Shifts activities prematurely
Misjudges available time
Makes impulsive decisions related to spending money, travel, jobs, or social plans
May have job instability and marital difficulties

[a]Based on Greenhill,[27] Conners and Jett,[31] and Millstein et al.[40]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

There appears to be some developmental variance in the ADHD symptom profile across the life span (Tables 1–3).[27,31,40] Longitudinally derived data in ADHD youth growing up indicate that the symptom cluster of hyperactivity and impulsivity decays over time, while the symptoms of inattention largely persist.[5,41,42] In support of this notion, data derived from a group of clinically referred adults with ADHD indicate that approximately half of adults endorse clinically significant levels of hyperactivity/impulsivity, but 90% endorse prominent attentional symptoms.[40]

Hyperactivity in children becomes a sense of inner restlessness in adolescents and adults, accompanied by poor concentration, daydreaming, and forgetfulness. Childhood impulsivity symptoms can lead to low frustration tolerance, explosive emotional episodes, and reckless driving in adulthood. Presenting adults typically have poor self-discipline, short temper, difficulty establishing and keeping a routine, and difficulty thinking clearly.[43,44]

Despite known neuropsychological differences between children and adults with ADHD and non-ADHD controls, the role of neuropsychological testing in all age groups with the disorder remains unclear. Current consensus is that neuropsychological testing is used not to *diagnose* ADHD, but to better understand the extent of learning disabilities and learning dysfunction in affected individuals.[25,45]

AREAS OF FUNCTIONAL IMPAIRMENT

Academic Impairment

School is the single most common referral source for children and adolescents with ADHD, who typically do not achieve their academic potential and may be behaviorally disruptive. Compared with non-ADHD peers, they perform more poorly on standardized tests; have higher rates of grade retention (42% vs. 13%), suspension (60% vs. 19%), and dropout (32% vs. 0%); and are less likely to graduate high school.[12] In the estimated 25% of ADHD youth with comorbid learning disabilities, academic impairment is even more profound.[12]

While treatment may help short-term academic improvement,[46–48] the longer-term effects of treatment remain unclear. For example, a systematic literature review of long-term ADHD treatment[49] found no difference among the effects of medication management, community care, and behavior treatments on academic performance. The results from several ongoing longitudinal studies of long-term treatment of ADHD on academic outcomes may help clarify this issue.

Health and Injury

The economic and medical ramifications of ADHD are substantial, and impairments have been observed across the life span. A 9-year study of medical utilization showed that people with ADHD use double the amount of health services that controls do ($4306 vs. $1944), not including the ADHD treatment.[50] Farmer and Peterson[51] have reported that boys with ADHD are likely to predict less severe consequences to hazardous situations and are less able to provide prevention strategies and safety principles. Without treatment, adolescents with ADHD have 4 times as many serious injuries and 3 times as many motor vehicle accidents as either those who do not have ADHD or those who have ADHD and consistently take medication.[8,52]

Barkley and colleagues[53] have found the motor vehicle skills of young adults with the disorder to be worse than those of their non-ADHD counterparts. Poorer outcomes in this study were attributed to poorer performance behind the wheel, not to less knowledge about driving. Individuals with ADHD were more likely to receive cita-

tions for speeding, receive license suspensions, be involved in more crashes, and even self-report using poorer driving habits.

Sexual Behavior

ADHD may also affect sexual behavior, as evidenced by a longitudinal follow-up of a cohort of children with ADHD (and a sizable number with comorbid conduct disorder) now in their mid-to-late 20s. Of the 43 children born to study participants in both the ADHD and control groups, 42 were born to those in the ADHD group, limiting their academic and occupational attainment, and 54% of the ADHD parents had already lost custody of their children.[54] Similarly, the Milwaukee Young Adult Outcome Study[12] (MKE) found those with ADHD to be at greater sexual and reproductive risk than their non-ADHD peers. Sexually transmitted disease was 4 times more prevalent among them; they also had far more children by age 20, but only 50% of the ADHD parents had custody of their children.[12]

Executive Functioning

Executive functioning (EF) has become an area of intense research in the study of ADHD.[55,56] Many children and adults with the disorder have additional and severe dysfunction in this domain.[57] Problems in EF clinically present as deficits in time management, organization, and sequential and hierarchical thinking. Executive functioning is a self-regulatory and goal-oriented activity.[58]

Executive functioning is also thought to encompass important aspects of working memory. Barkley observed that EF highlights "the delay between stimulus and response or maintenance of internal representations to guide actions."[58(pp67–69)] Welsh and Pennington have defined EF clinically as "the ability to maintain an appropriate problem solving set for attainment of a future goal."[59(pp201–202)] Executive functioning may include aspects of the following: (a) an intention to inhibit a response or to defer it to a later, more appropriate time; (b) a strategic plan of action sequences; and (c) a mental representation of the task, including the relevant stimulant information encoded in memory and the desired future goal-state.[59,60]

Biederman et al.[61] recently found that ADHD youth who exhibited impairments on 2 of 6 EF neuropsychological measures were more likely to repeat a grade and have lower academic achievement than ADHD youth with 2 or fewer measures impaired, even after controlling for social class, IQ, and learning disabilities. Other studies have also found an association with EF measures and adaptive functioning in the domains of socialization and communication.[62]

Like some youth with ADHD, adults with the disorder are thought to have EF deficits, such as less ability to attend, encode, and manipulate information; to organize; and to manage time.[55,56] They may appear normal in conversation, but their symptomatology becomes evident when they are faced with getting organized or completing a task. Exceptionally intelligent adults are often able to compensate for the disorder's manifestations through childhood, adolescence, and even young adulthood, but the cumulative challenges eventually overwhelm their compensatory mechanisms.

NEUROBIOLOGY

There is strong evidence that ADHD has a neurobiological underpinning, with important environmental influences also involved. It is not yet clear whether the dysfunction is intrinsic to the frontal lobes, where lesions in the frontal cortex may be responsible for behavioral or cognitive abnormalities, or whether it is influenced by brain areas with subcortical projections.[63] Structural and functional magnetic resonance imaging (fMRI) studies have shown neurologic differences between those with ADHD and those without.[64] The fMRI data show that the circuits controlling attention—including parts of the prefrontal cortex that affect working memory, alerting, and response inhibition—are less active and smaller in individuals with the disorder than in non-ADHD controls.[65]

Results from studies of positron emission tomography (PET) complement the MRI findings. Data from Ernst and colleagues' PET study[66] of dopaminergic presynaptic function in ADHD revealed abnormally low DOPA decarboxylase activity, primarily in the medial and left lateral areas of the prefrontal cortex. Zametkin and colleagues' PET studies[67] found abnormal regional and global glucose metabolism in the brains of adults with childhood-onset ADHD. More-recent PET studies[68,69] have identified differences in the binding potential of the dopamine transporter, the protein responsible for inactivation and recycling of intrasynaptic dopamine.

The most critical neurotransmitters in ADHD are the catecholamines dopamine and norepinephrine, which appear to regulate the inhibitory influences in the frontal-cortical processing of information—accentuating some aspects, dampening others, and enhancing signals. The specific neurobehavioral roles of dopamine and norepinephrine remain unclear. It may be that the dopamine enhances signals and improves attention, focus, vigilance, acquisition, on-task behavior and cognition, and perception. Norepinephrine may dampen "noise"; decrease distractibility and shifting; improve executive operations; and increase behavioral, cognitive, and motoric inhibition.[70,71]

Both dopamine and norepinephrine have relatively specific pathways that modulate attention, concentration, and other cognitive functions.[72] The frontal areas of the brain not only receive signals, but also mold information that connects with the striatum and areas deeper in the mesocephalic brain stem.

In terms of the pathophysiology of ADHD, Zametkin and colleagues[72,73] have postulated that catecholamine dysfunction causes dysregulation of the inhibitory influences of frontal-cortical activity, which is predominantly noradrenergic, and of lower striatal structures, which are predominantly dopaminergic. Striatal structures are driven by dopaminergic agonists controlled or modulated by higher inhibitory structures sensitive to adrenergic agents.[72,73]

A considerable body of evidence shows that ADHD is highly familial (25%–50% of cases), and transmission in families is mediated by genetic factors.[65] While from 15% to 25% of first-degree relatives of children with ADHD have the disorder, 1 study[65] suggests that 50% of children whose parents have ADHD also have the disorder. Molecular genetics studies[74,75] have implicated the dopamine transporter (DAT1) and D_2 and D_4 postsynaptic receptors as candidate genes.

COMORBIDITY

ADHD is highly comorbid with other psychiatric and learning disorders (Figures 2–3).[76–85] Similarly, ADHD is overrepresented in children and adults with other psychiatric disorders. The most common comorbid diagnoses in children with ADHD are oppositional defiant, anxiety, mood, conduct and learning disorders. Adults with ADHD most commonly manifest comorbidity with depression, anxiety, and substance use disorders.[79]

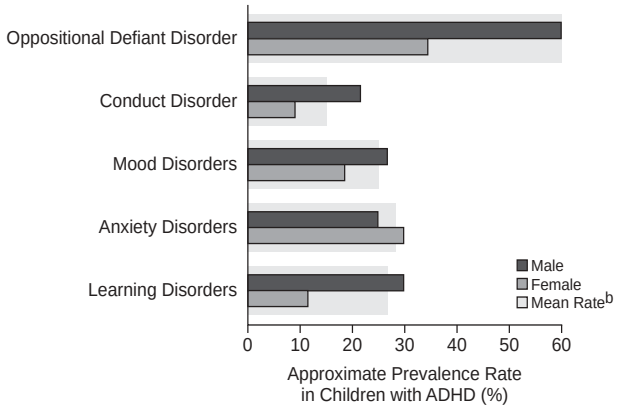
There has been increasing interest in the co-occurrence of substance use disorders. Over one half of individuals with untreated ADHD into adulthood will develop a substance use disorder in their lifetime.[83] Although parents worry that treating ADHD aggressively with psychostimulants will predispose their children to substance abuse, recent studies indicate that the opposite is true. If ADHD is consistently treated, the risk of substance abuse is the same as in the general population.[37,84] Psychostimulant treatment appears to protect against the development of substance abuse.[37,84]

Approximately 10% of ADHD patients develop bipolar disorder (BPD), and 15% of BPD adults may have ADHD.[85] There is considerable symptom overlap, creating the potential for diagnostic confusion.[86] Yet the key distinguishing features of ADHD are inattention and hyperactivity-impulsivity; BPD is characterized by severe mood instability, psychosis, and grandiosity.[85] The earlier the onset of BPD, the more likely the individual will have comorbid ADHD and BPD.[87]

In a 4-year follow-up of psychiatric diagnoses in boys with ADHD, Biederman and colleagues[88] reported an increase—from 11% to 23%—in the rate of comorbid BPD. Pediatric studies report that many children diagnosed with BPD often have symptoms suggestive of ADHD. Whether or not these are truly ADHD symptoms is currently under investigation, but children with symptoms of both disorders have been found to be more impaired and less responsive to mood stabilizers.[89] Children and adolescents with BPD do not mood-cycle and are consistently irritable.[85]

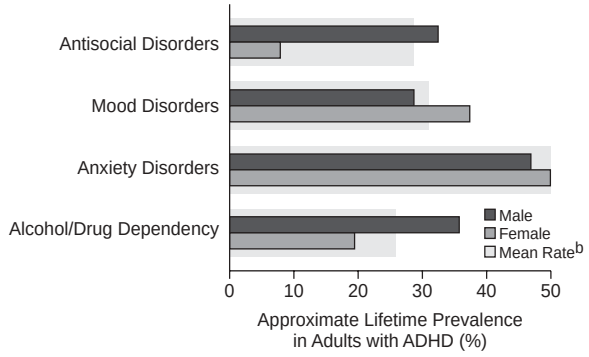
To obtain an optimal outcome in these patients, both past and current comorbidities should be identified, and the sequence of treating the ADHD and the comorbidity should be carefully considered.

Figure 2. Common Comorbid Diagnoses in Children With ADHD[a]



[a]Based on Biederman et al.,[76] Pliszka,[77] Biederman et al.,[78] and Spencer et al.[79]
[b]Mean rate at which children with ADHD will also have this disorder.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 3. Common Comorbid Diagnoses in Adults With ADHD[a]



[a]Based on Biederman et al.,[80] Biederman et al.,[81] and Shekim et al.[82]
[b]Mean rate at which adults with ADHD will also have this disorder.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

NONPHARMACOLOGIC THERAPY

The management of ADHD includes nonpharmacologic and pharmacologic intervention. Support groups help youth, parents, and adults with ADHD learn

Table 4. Medications Used in Juvenile Attention-Deficit/Hyperactivity Disorder

Medication (generic)	Medication (brand)	Daily Dose (mg/kg)	Daily Dosage Schedule	Common Adverse Effects
Stimulants		0.3–2.0		Common to all stimulants:
Methylphenidate	Ritalin		2–4 times	Insomnia, decreased appetite/weight loss, possible reduction in growth velocity with chronic use, stomachaches, headaches, dysphoria, rebound phenomena (short-acting preparations)
	Metadate CD, Concerta, Ritalin LA		1 time	
	Focalin	0.6–1.0	2–4 times	
Amphetamine		0.3–1.5		
Dextroamphetamine	Dexedrine		2–3 times	
Mixed amphetamine salts	Adderall		2–3 times	
	Adderall XR		1 time	
Magnesium pemoline	Cylert	1.0–3.0	1–2 times	Drug specific: abnormal liver-function tests
Nonstimulants				
Noradrenergic agent				
Atomoxetine	Strattera	0.5–1.8	1–2 times	Somnolence or insomnia, stomachaches/gastrointestinal distress, appetite suppression, headaches, manic activation (with bipolar disorder)
Antidepressants				
Tricyclics				
Imipramine	Tofranil	2.0–5.0	1–2 times	Dry mouth, constipation, weight fluctuation, vital sign and electrocardiogram changes
Desipramine	Norpramin	2.0–5.0		
Nortriptyline	Pamelor	1.0–3.0		
Bupropion	Wellbutrin	3–6	3 times	Irritability, insomnia, risk of seizures (in doses > 6 mg/kg); contraindicated in bulimics
	Wellbutrin SR	3–6	2 times	
	Wellbutrin XL	3–6	1 time	
Venlafaxine	Effexor	0.5–3	2 times	Nausea, sedation, gastrointestinal distress
Antihypertensives				
Clonidine	Catapres	3–10 µg/kg	2–3 times	Sedation, dry mouth, depression, confusion (with high dose), rebound hypertension, localized irritation with patch
Guanfacine	Tenex	30–100 µg/kg	2 times	Similar to clonidine but less sedation; insomnia and irritability reported

about the disorder and available resources. Support groups can be accessed by calling an ADHD hotline (1-800-233-4050), or by contacting Children and Adults With Attention-Deficit/Hyperactivity Disorder (CHADD) on the Internet (www.chadd.org).

Specialized educational planning with frequent reevaluations of the child's progress in school should be undertaken. Parents should be encouraged to work closely with the child's teacher, guidance counselor, and school psychologist, who can provide direct contact with the child and valuable liaison with various school operations. Increased structure, predictable routines, learning aids, resource room time, and checked homework are typical educational arrangements to help these youth.[12] Similar modifications at home may optimize the child's ability to complete homework. Identification of comorbid learning disorders, found in approximately one third of individuals with ADHD, should lead to the development of specific remediation plans. Adults with ADHD may also require modifications in their academic and/or work settings. Those attending college should be encouraged to participate in their school's study center.

Focused therapies incorporating cognitive-behavioral features have reportedly been effective in children, adolescents, and adults with ADHD; however, the benefit of these treatments independent of pharmacotherapy has yet to be determined.[28,90] Behavioral therapy with the child and parents is used in cases of co-occurring disruptive behaviors, inflexibility, anxiety, or outbursts.

Although the efficacy of various psychotherapeutic interventions remains to be established, a retrospective assessment of adults with ADHD indicated that traditional insight-oriented psychotherapies were not helpful.[91]In contrast, a cognitive therapy protocol adapted for adults with ADHD has been developed, and open data suggest that it may be effective when used with pharmacotherapy.[86] Two National Institutes of Health (NIH)–funded prospective studies are currently under way to evaluate the efficacy of cognitive-based therapies for adults with ADHD.

PHARMACOTHERAPY

Medications remain a mainstay of ADHD treatment.[11] In fact, longer-term multisite studies support medication management as the most important outcome variable of multimodal treatment.[92] The stimulants, antihypertensives, and antidepressants comprise the current ADHD armamentarium (Tables 4 and 5). In children, multiple stimulants and atomoxetine are U.S. Food and Drug Administration (FDA)–approved for ADHD; in adults, only amphetamine compounds and atomoxetine are approved to date. Respon-

Table 5. Medications Used in Adult ADHD

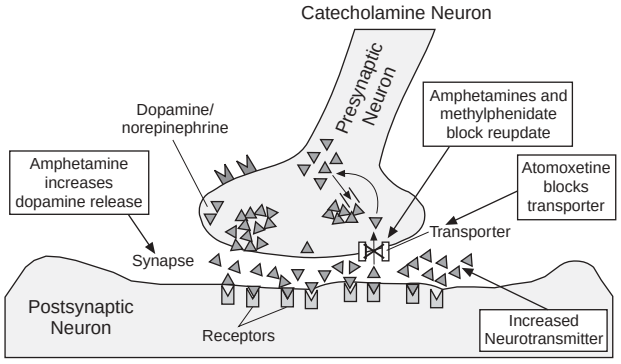
Medication (generic)	Medication (brand)	Typical Daily Dose (mg)	Daily Dosage Schedule	Common Adverse Effects
Stimulants				Common to all stimulants:
Methylphenidate	Ritalin, Focalin	20–100	2–4 times	Insomnia, decreased appetite/weight loss, headaches,
	Metadate CD, Concerta, Ritalin LA	20–100	1 time	dysphoria, mild increases in pulse/blood pressure, rebound phenomena (short-acting preparations)
Amphetamine				
Dextroamphetamine	Dexedrine	10–60	2–3 times	
Mixed amphetamine salts	Adderall	10–60	2–3 times	
	Adderall XR[a]	10–60	1 time	
Magnesium pemoline	Cylert	75–150	1–2 times	Drug specific: abnormal liver-function tests
Nonstimulants				
Noradrenergic agent				
Atomoxetine	Strattera[a]	40–120	1–2 times	Sleep disturbance, gastrointestinal distress, nausea, headaches, mild increase in pulse/blood pressure
Antidepressants				
Tricyclics			1–2 times	Dry mouth, constipation, weight fluctuation, vital sign and electrocardiogram changes
Desipramine	Norpramin	100–300		
Imipramine	Tofranil	100–300		
Nortriptyline	Pamelor	50–200		
Bupropion	Wellbutrin	150–450	3 times	Irritability, insomnia, risk of seizures
	Wellbutrin SR/XL	150–450	2 times/1 time	(in doses > 6 mg/kg); contraindicated in bulimics
Venlafaxine	Effexor	75–225	2 times	Nausea, sedation, gastrointestinal distress

[a]Approved for ADHD in adults by the U.S. Food and Drug Administration.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

siveness to pharmacotherapy has been observed similarly in children, adolescents, and adults with ADHD.

The most efficacious agents for ADHD appear to be those that elevate the transmission of synaptic dopamine or norepinephrine. Psychostimulants, among first-line agents for children and adults, work primarily in the mesocortical and frontostriatal pathways on both dopaminergic and noradrenergic neurons.[93,94] Methylphenidate and amphetamines affect the noradrenergic and/or dopaminergic systems; the extent to which each works in these areas is under investigation. Atomoxetine, tricyclic antidepressants (TCAs), and antihypertensives appear to work predominantly through the noradrenergic system. Bupropion has mixed noradrenergic and dopaminergic effects.[73,95]

Figure 4. Probable Mechanisms of Action of Pharmacotherapies for ADHD[a]



[a]Reprinted with permission from Wilens and Spencer.[98]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Psychostimulants

Methylphenidate and amphetamine compounds appear to have a similar clinical effect but differ somewhat in their presynaptic mechanisms of action (Figure 4).[96] Amphetamines increase synaptic catecholamines by enhancing the release of presynaptic catecholamines and blocking their presynaptic reuptake and storage. Methylphenidate blocks reuptake only of the dopamine transporter protein.[96] Hence, because of subtle differences between methylphenidate and amphetamine at the presynaptic level, the clinical efficacy and tolerability of the stimulant classes may differ among ADHD patient groups. Individuals without a satisfactory response to one stimulant may respond well to another.[97]

Psychostimulants are the most studied ADHD treatments: in more than 250 controlled trials with more than 6000 subjects, a 75% to 80% favorable response rate has been documented.[74] The most commonly used are methylphenidate, mixed amphetamine salts, dextroamphetamine, and magnesium pemoline. Methylphenidate and dextroamphetamine are both short-acting compounds: onset of action is within 30 to 60 minutes of ingestion, peak clinical effect is usually between 1 and 2 hours after administration, and duration is 2 to 5 hours (Table 6).

The amphetamine compounds and sustained-release preparations of methylphenidate and dextroamphetamine are intermediate-acting compounds, with onset of action within 60 minutes and duration of 6 to 8 hours. Extended-release preparations last 8 to 12 hours, thereby

Table 6. ADHD Stimulant Dosing[a]

Medication	Starting Dosage	Maximum Dosage	Usual Dosage (h)
Ritalin	5 mg qd/bid	2 mg/kg/d	tid (4)
Focalin	2.5 mg	1 mg/kg/d	bid (5–6?)
Concerta	18 mg qd	2 mg/kg/d	Once (12)
Metadate CD	20 mg qd		Once (8–10)
Ritalin LA	10 mg qd		Once
Adderall	2.5–5 mg qd	1.5 mg/kg/d	bid (6)
Adderall XR	10 mg		qd (12)
Dexedrine	2.5–5 mg qd	1.5 mg/kg/d	bid/tid (4)
Dex Spansule	5 mg		bid (6)
Cylert	37.5 mg qam	3 mg/kg/d	qd

[a]Based on Wilens et al.[74]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

eliminating the need for dosing during the school day. Because children receiving long-acting stimulants do not need to visit the school nurse for their medication and cannot give their midday medication to a friend, these agents reduce stigma and the likelihood of drug diversion and improve compliance.

For children, adolescents, and adults with ADHD, long-acting formulations eliminate the possibility that the patient will forget to take the midday dose. They also greatly reduce peak and trough adverse effects of stimulants, such as headaches and moodiness, and eliminate afternoon wear-off and rebound.

The side effects of stimulants are generally mild and can be managed by adjusting the medications' timing and dosage. The most common short-term side effects are diminished appetite, insomnia, mood disturbance, headache, and gastrointestinal distress.[98]

Methylphenidate. Extended-release Concerta releases methylphenidate for up to 12 hours. An OROS extended osmotic release system (part osmotic pump, part medication chamber) is used for controlled release of the medication. A 2-year, open-label, multicenter study of 407 children treated with Concerta showed sustained efficacy, with no clinically significant adverse effect on blood pressure, pulse, height or weight growth, sleep quality, or alterations in blood chemistries, white blood cell counts, platelet counts, hemoglobin levels, or hematocrit.[99] Ritalin LA, a beaded technology with a mean half-life of about 3 hours, delivers an immediate release and then another release approximately 4 hours after administration, resulting in 8 hours of coverage.[100] Focalin (dexmethylphenidate) is the *d-threo* enantiomer of racemic methylphenidate hydrochloride, which is a 50/50 mixture of *d-threo* and *l-threo* enantiomers. Dosing is half that of regular methylphenidate.

Amphetamine and amphetamine compounds are about twice as potent as methylphenidate. Adderall is a constellation of dextro- and levoamphetamine salts that has a variable onset and release resulting in a 6-hour behavioral effect. Adderall XR, a 12-hour preparation, uses a beaded, pulsed medication-release system. A large, prospective, community-use study in over 2600 youth with ADHD indicated efficacy exceeding that of previous medications. Recent data[101] showed continued maintenance of significant improvement in ADHD symptoms over 1.5 years in doses of 10 mg to 30 mg daily. In addition, measures of quality of life were significantly better, and the treatment was reported to be well tolerated.[101] Adderall XR is the only stimulant approved specifically for use in adults. Preliminary results from a large multisite study of Adderall XR in adults with ADHD demonstrated dose-dependent efficacy up to 60 mg daily with excellent tolerability.[102]

Dextroamphetamine is approximately twice as potent as methylphenidate. The side effect profile of dextroamphetamine is about the same as that of methylphenidate and amphetamine compounds.

Magnesium pemoline, a long-acting stimulant with a long half-life, functions mainly in the dopaminergic system and may take 4 to 6 weeks to titrate. The side effect profile of this stimulant is about the same as that of methylphenidate, although concerns of hepatotoxicity with pemoline require frequent testing of liver function. In fact, several studies have shown pemoline's association with adverse liver function.[103,104]

Nonstimulants

Atomoxetine is a potent norepinephrine reuptake inhibitor with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Like the stimulants, it is considered a first-line therapy for ADHD, especially in adults. More than 8 controlled trials of atomoxetine in youth and 2 in adults have demonstrated efficacy in all subtypes of ADHD. Onset of action is not totally clear. Some investigators report as little as 1 week,[105] but in slower titration studies and clinical experience, the full therapeutic benefit of atomoxetine appears to be between 4 and 6 weeks. Atomoxetine may be used for the common ADHD comorbidities, including tics, anxiety, and depressive disorders. Apparent side effects are hypersomnia or insomnia, nausea, dizziness, and stomachache. Atomoxetine is the first nonstimulant medication approved by the U.S. FDA for ADHD.[106]

Bupropion, an aminoketone antidepressant, decreases noradrenergic and dopaminergic tone and may very likely be a norepinephrine and dopamine reuptake inhibitor. Bupropion can be metabolized to an active metabolite that has more powerful norepinephrine reuptake blocking effects than bupropion itself.[107] Onset of action is 4 to 6 weeks. Bupropion may be helpful in treating complex cases of ADHD accompanied by mood instability, substance abuse, or bipolar disorder.[98] A multisite study of recently available bupropion XL, a once-daily preparation, reported efficacy and tolerability (no significant adverse effects vs. placebo) in adults with ADHD.[108] Side

effects include agitation, tic exacerbation, irritability, and seizures caused by overdose.[109]

Tricyclic antidepressants block the reuptake of dopamine and/or norepinephrine; some may also affect serotonin reuptake inhibition. In more than 1000 subjects in 13 controlled studies, all TCAs appear effective.[110] Desipramine and imipramine are more selective for the norepinephrine reuptake blockade. Studies show that TCAs are effective for all age groups and for ADHD with tic disorders, although adverse effects limit their use. The adverse effects, mediated by histamine, muscarinic cholinergic, and α-adrenergic receptor actions, include dry mouth, constipation, tachycardia, headache, nightmares, and weight fluctuation.[107] Clinical data also suggest an incidence of cardiotoxicity in children taking TCAs.[111]

Selective serotonin reuptake inhibitors (SSRIs)—fluoxetine, paroxetine, and sertraline—have not shown efficacy for ADHD but are used with comorbid disorders.

Venlafaxine is a selective norepinephrine and serotonin reuptake inhibitor that 4 open studies have found to be minimally to moderately effective for ADHD in adults.[112]

Antipsychotics, such as risperidone, are reserved for refractory ADHD or temporary measures; recent reviews have shown no efficacy for ADHD.[113]

The ***antihypertensives*** guanfacine and clonidine are α-adrenergic agonists that are approved for the treatment of hypertension. The α-agonists are typically used to treat the hyperactive-impulsive or aggressive symptoms of ADHD. Two recent multisite studies have shown the efficacy of clonidine alone, or in combination with methylphenidate, for the treatment of children with ADHD plus tic disorders.[114,115] Clonidine has been associated with sedation, and both agents may cause depression and rebound hypertension.[73]

Combined pharmacotherapy is increasingly utilized to treat patients with refractory ADHD or ADHD and a comorbidity, and to manage treatment-emergent adverse effects. Such combinations may involve an antidepressant plus a stimulant for ADHD and comorbid depression, bupropion plus a stimulant for ADHD and comorbid mood disorder, a stimulant plus clonidine, a TCA plus a mood stabilizer, or a stimulant plus a TCA.

Treatment of Frequent Comorbidity

Tourette's syndrome and tic disorders. When children start taking stimulants, about 9% develop observable tics, but only about 1% of these are impairing or embarrassing.[116,117] Research indicates that stimulant medications do not cause tics but may uncover the potential for them in genetically predisposed individuals.[118] Equally as many patients lose tics as gain them when they start stimulants. Some clinicians avoid using first-line stimulants if there is a family history of tics; others who use these stimulants cite research showing that tics commonly improve with stimulants.

The recommended treatment for tics involves advising the patient to avoid caffeine (the most potent trigger), reducing the stimulant dose or switching to another stimulant, and adding an adrenergic agonist (clonidine/guanfacine), metoclopramide, or a neuroleptic.[119,120] Recently, Wilens and colleagues[121] reported minimal tic activation in a group of ADHD youths (10% with a past history of mild or moderate tics) treated with an OROS formulation of methylphenidate for 1 year.

Two recently published multisite studies[114,115] indicate the safety and efficacy of methylphenidate plus clonidine for treating ADHD plus tics. Other studies have demonstrated the usefulness of other nonstimulants for ADHD youth with tics. Singer and colleagues[122] showed that desipramine was useful in children with tics plus ADHD. Atomoxetine is currently being used in treating children with ADHD with comorbid tic disorder and appears efficacious; further study is warranted.

Oppositional defiant disorder is often comorbid with ADHD. ODD symptoms improve with stimulant treatment independent of ADHD treatment.[123] A number of studies, including Klorman and colleagues' investigation,[124] have also demonstrated the efficacy of stimulants in aggressive conduct disordered children with ADHD. Other agents used to treat oppositional youth with ADHD include atomoxetine and tricyclic antidepressants.

In conjunction with medications, behavioral programs teach children self-control and discipline. Two programs have shown consistent effectiveness: family group training and the Real Economy System for Teens.[125–130]

Anxiety disorders. Mild cases of ADHD and anxiety are treated with psychosocial/behavioral treatment and a single agent, such as atomoxetine, nortriptyline, or venlafaxine.[131] Stimulants may exacerbate anxiety symptoms, necessitating careful observations of anxious adults and children receiving these agents. Alternatively, combination pharmacotherapy to treat anxious patients with ADHD may employ one of the usual therapeutic options for anxiety and then sequence the treatment for ADHD.

Depression. As with anxiety disorders, effective treatment of ADHD and comorbid depression is most often combined pharmacotherapy, such as a stimulant or atomoxetine plus an antidepressant. Certain classes of antidepressants, including tricyclic antidepressants or bupropion, may treat both conditions effectively, especially in adults. The presence of mania in these patients often requires more aggressive therapy, with initial stabilization of the mania followed by treatment of the ADHD.[86]

Substance abuse. The first phase of treatment is stabilization of the substance abuse, followed by reassessment for ADHD and comorbid conditions. Clinicians should use caution when prescribing short-acting stimulants for patients with a history of chemical dependency. Many

clinicians consider bupropion, atomoxetine, and pemoline the first-line agents for these patients.[132–134] Other clinicians still use first-line stimulant medications if the patient has been in stable recovery for more than 6 months.

CONCLUSION

ADHD is a highly prevalent, complex cognitive disorder affecting all age groups and both genders. The disorder is far more common than originally thought and is increasingly recognized in girls and in adults. Similarities between children and adults in the disorder's presentation, characteristics, neurobiology, and response to pharmacotherapy support the belief that ADHD persists across the life span.

There is strong evidence supporting a neurobiological and genetic basis for ADHD. Abnormalities in the frontostriatal network, primarily in the noradrenergic and dopaminergic systems, appear to be central to the disorder's pathophysiology. Pharmacologic agents used to treat ADHD appear to affect norepinephrine and dopamine, which modulate cognitive function.

Multimodal treatment that includes behavioral therapy and medication has been found most effective in treating children with ADHD. Extensive studies have shown that pharmacotherapy is highly effective in treating both the behavioral symptoms of ADHD and its related impairments, including academic, social, and family functioning. Methylphenidate, amphetamine, and atomoxetine are the most commonly used agents for ADHD.

While it is has increasingly become evident that ADHD is a chronic disorder amenable to treatment, further study is needed to determine the long-term outcome of patients who have received treatment over a number of years.

Drug names: amphetamine (Adderall and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), clonidine (Catapres, Duraclon, and others), desipramine (Norpramin and others), dexmethylphenidate (Focalin), dextroamphetamine (Dexedrine, Dextrostat, and others), fluoxetine (Prozac and others), guanfacine (Tenex and others), imipramine (Tofranil and others), methylphenidate (Ritalin, Metadate, and others), metoclopramide (Reglan and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil and others), pemoline (Cylert and others), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
2. American Academy of Pediatrics. Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. Pediatrics 2000;105:1158–1170
3. Barbaresi WJ, Katusic SK, Colligan RC, et al. How common is attention-deficit/hyperactivity disorder? incidence in a population-based birth cohort in Rochester, Minn. Arch Pediatr Adolesc Med 2002;156:217–224
4. Faraone SV, Biederman J, Mick E, et al. Family study of girls with attention deficit hyperactivity disorder. Am J Psychiatry 2000;157:1077–1083
5. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry 2000;157:816–818
6. Weiss G, Hechtman LT. Hyperactive Children Grown Up. 2nd ed. New York, NY: Guilford Press; 1993
7. Mannuzza S, Klein RG. Diagnosis and longitudinal course of attention-deficit/hyperactivity disorder. Econ Neurosci 2001;3:47–53
8. Barkley RA, Guevremont DC, Anastopoulos AD, et al. Driving-related risks and outcomes of attention-deficit/hyperactivity disorder in adolescents and young adults: a 3- to 5-year follow-up survey. Pediatrics 1993;92:212–218
9. Bauermeister J, Canino G, Bird H. Epidemiology of disruptive behavior disorders. Child Adolesc Psychiatr Clin N Am Disruptive Disord 1994;3: 177–194
10. Jensen P, Kettle L, Roper M, et al. Are stimulants overprescribed? treatment of ADHD in four US communities. J Am Acad Child Adolesc Psychiatry 1999;38:797–804
11. Goldman L, Genel M, Bezman R, et al. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Council on Scientific Affairs, American Medical Association. JAMA 1998;279: 1100–1107
12. Barkley R. Attention-Deficit/Hyperactivity Disorder: A Clinical Workbook. New York, NY: Guilford Press; 1998
13. Mannuzza S, Klein RG, Bessler A, et al. Adult outcome of hyperactive boys: educational achievement, occupational rank and psychiatric status. Arch Gen Psychiatry 1993;50:565–576
14. Barkley RA, Fischer M, Edelbrock CS, et al. The adolescent outcome of hyperactive children diagnosed by research criteria, 1: an 8-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 1990;29: 546–557
15. Barkley R. Attention deficit hyperactivity disorder: long-term course, adult outcome, and comorbid disorders. In: NIH Consensus Development Conference; Nov. 16–18, 1998; Bethesda, Md
16. Mannuzza S, Gittelman-Klein R, Horowitz-Konig P, et al. Hyperactive boys almost grown up, IV: criminality and its relationship to psychiatric status. Arch Gen Psychiatry 1989;46:1073–1079
17. Faraone SV, Sergeant J, Gillberg C, et al. The worldwide prevalence of ADHD: is it an American condition? World Psychiatry 2003;2:104–113
18. Kessler RC. Epidemiology of psychiatric comorbidity. In: Tsuang MT, Tohen M, Zahner GEP, eds. Textbook in Psychiatric Epidemiology. New York, NY: John Wiley & Sons, Inc.; 1995:179–197
19. Kessler RC, Nelson CB, McGonagle KA, et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 1996;168(suppl):17–30
20. Murphy K, Barkley RA. Preliminary normative data on DSM-IV criteria for adults. The ADHD Report 1995;3:6–7
21. Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr Psychiatry 1996;37: 393–401
22. Heiligenstein E, Conyers LM, Berns AR, et al. Preliminary normative data on DSM-IV attention deficit hyperactivity disorder in college students. J Am Coll Health 1998;46:185–188
23. Spencer T, Biederman J, Wilens TE, et al. Adults with attention-deficit/hyperactivity disorder: a controversial diagnosis. J Clin Psychiatry 1998; 59(suppl 7):59–68
24. Faraone SV, Biederman J, Spencer T, et al. Attention-deficit/hyperactivity disorder in adults: an overview. Biol Psychiatry 2000;48:9–20
25. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 1997;36:85S–121S
26. Thurber JR, Heller TL, Hinshaw SP. The social behaviors and peer expectations of girls with attention deficit hyperactivity disorder and comparison girls. J Clin Child Adolesc Psychol 2002;31:443–452
27. Greenhill LL. Diagnosing attention-deficit/hyperactivity disorder in children. J Clin Psychiatry 1998;59(suppl 7):31–41
28. Baumgaertel A, Wolraich ML. Practice guideline for the diagnosis and management of attention-deficit/hyperactivity disorder. Ambulat Child Health 1998;4:24–58
29. Conners CK, ed. Conners Rating Scales Revised. North Tonawanda, NY: Multi-Health Systems; 1997
30. Conners CK, Barkley RA. Rating scales and checklists for child psychopharmacology. Psychopharmacol Bull 1985;21:809–843
31. Conners CK, Jett JL. Attention Deficit Hyperactivity Disorders (in Adults

and Children): The Latest Assessment and Treatment Strategies. Kansas City, Mo: Compact Clinicals; 1999
32. Murphy K, Schachar R. Use of self-ratings in the assessment of symptoms of attention deficit hyperactivity disorder in adults. Am J Psychiatry 2000;157:1156–1159
33. Ward MF, Wender PH, Reimherr FW. The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry 1993;150:885–890
34. DuPaul GJ, Ervin RA, Hook CL, et al. Peer tutoring for children with attention deficit hyperactivity disorder: effects on classroom behavior and academic performance. J Appl Behav Anal 1998;31:579–592
35. Brown TE. Brown Attention-Deficit Disorder Scales. Toronto, Ontario: The Psychological Corporation; 1996
36. Conners CK. Clinical use of rating scales in diagnosis and treatment of attention-deficit/hyperactivity disorder. Pediatr Clin North Am 1999;46: 857–870
37. Barkley RA, Fischer M, Smallish L, et al. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? a 13-year prospective study. Pediatrics 2003;111:97–109
38. Weiss G, Hechtman L, Milroy T, et al. Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. J Am Acad Child Psychiatry 1985;24:211–220
39. Biederman J. Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: findings from a longitudinal follow-up of youths with and without ADHD. J Clin Psychiatry 2003;64(suppl 11):3–8
40. Millstein RB, Wilens TE, Biederman J, et al. Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. J Atten Disord 1997;2:159–166
41. Achenbach TM, Howell CT, McConaughy SH, et al. Six-year predictors of problems in a national sample, 4: young adult signs of disturbance. J Am Acad Child Adolesc Psychiatry 1998;37:718–727
42. Hart EL, Lahey BB, Loeber R, et al. Developmental change in attention-deficit hyperactivity disorder in boys: a four-year longitudinal study. J Abnorm Child Psychol 1995;23:729–749
43. Wolf LE, Wasserstein J. Adult ADHD: concluding thoughts. Ann N Y Acad Sci 2001;931:396–408
44. Wender PH. Attention Deficit Hyperactivity Disorder in Adults. New York, NY: Oxford University Press; 1995
45. American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics 2001;108:1033–1044
46. Yang P, Chung LC, Chen CS, et al. Rapid improvement in academic grades following methylphenidate treatment in attention-deficit hyperactivity disorder. Psychiatry Clin Neurosci 2004;58:37–41
47. Schmidt K, Solanto MV, Sanchez-Kappraff M, et al. The effect of stimulant medication on academic performance, in the context of multimodal treatment, in attention deficit disorders with hyperactivity: two case reports. J Clin Psychopharmacol 1984;4:100–103
48. Pelham WE Jr, Carlson C, Sams SE, et al. Separate and combined effects of methylphenidate and behavior modification on boys with attention deficit-hyperactivity disorder in the classroom. J Consult Clin Psychol 1993;61:506–515
49. Schachar R, Jadad AR, Gauld M, et al. Attention-deficit/hyperactivity disorder: critical appraisal of extended treatment studies. Can J Psychiatry 2002;47:337–348
50. Leibson CL, Katusic SK, Barbaresi WJ, et al. Use and costs of medical care for children and adolescents with and without attention-deficit/hyperactivity disorder. JAMA 2001;285:60–66
51. Farmer JE, Peterson L. Injury risk factors in children with attention deficit hyperactivity disorder. Health Psychol 1995;14:325–332
52. Swensen AR, Birnbaum HG, Secnik K, et al. Attention-deficit/hyperactivity disorder: increased costs for patients and their families. J Am Acad Child Adolesc Psychiatry 2003;42:1415–1423
53. Barkley RA, Murphy KR, Kwasnik D. Motor vehicle driving competencies and risks in teens and young adults with attention deficit hyperactivity disorder. Pediatrics 1996;98(6 pt 1):1089–1095
54. Barkley RA. ADD research: a look at today and tomorrow. Attention 1996:8–11
55. Oosterlaan J, Sergeant JA. Response inhibition and response re-engagement in attention-deficit/hyperactivity disorder, disruptive, anxious and normal children. Behav Brain Res 1998;94:33–43
56. Barkley RA. Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatr 1997; 18:271–279
57. Weiss MA, Hechtman LT, Weiss G. ADHD in Adulthood: A Guide to Current Theory, Diagnosis, and Treatment. Baltimore, Md: Johns Hopkins University Press; 1999
58. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121:65–94
59. Bianchi L. The Mechanism of Brain Function of Prefrontal Lobes. Edinburgh, Scotland: Livingstone; 1922. Luria AR. Higher Cortical Functions in Man. New York, NY: Basic Books; 1966. Cited by: Welsh MC, Pennington BF. Assessing frontal lobe functioning in children:views from developmental psychology. Dev Neuropsychol 1988;4:199–230
60. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J Child Psychol Psychiatry 1996;37:51–87
61. Biederman J, Monuteaux M, Seidman L, et al. Impact of executive function deficits, ADHD on academic outcomes in children. J Consult Clin Psychol. In press
62. Clark C, Prior M, Kinsella G. The relationship between executive function abilities, adaptive behaviour, and academic achievement in children with externalising behaviour problems. J Child Psychol Psychiatry 2002; 43:785–796
63. Satterfield JH, Dawson ME. Electrodermal correlates of hyperactivity in children. Psychophysiology 1971;8:191–197
64. Spencer TJ, Biederman J, Wilens TE, et al. Overview and neurobiology of attention-deficit/hyperactivity disorder. J Clin Psychiatry 2002;63 (suppl 12):3–9
65. Faraone SV, Biederman J. The neurobiology of attention deficit hyperactivity disorder. In: Charney DS, Nestler EJ, Bunney BS, eds. Neurobiology of Mental Illness. New York, NY: Oxford University Press; 1999:788–801
66. Ernst M, Zametkin AJ, Matochik PH, et al. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults: a [fluorine-18] fluorodopa positron emission tomographic study. J Neurosci 1998;18: 5901–5907
67. Zametkin AJ, Nordahl TE, Gross M, et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. N Engl J Med 1990;323: 1361–1366
68. Dougherty D, Bonab A, Spencer T, et al. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 1999;354: 2132–2133
69. Krause K, Dresel SH, Krause J, et al. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett 2000;285:107–110
70. Solanto MV, Arnsten AFT, Castellanos FX, eds. Stimulant Drugs and ADHD: Basic and Clinical Neuroscience. New York, NY: Oxford University Press; 2001
71. Arnsten AF. Catecholamine regulation of the prefrontal cortex. J Psychopharmacol (Oxf) 1997;11:151–162
72. Zametkin AJ, Rapoport JL. Neurobiology of attention deficit disorder with hyperactivity: where have we come in 50 years? J Am Acad Child Adolesc Psychiatry 1987;26:676–686
73. Zametkin AJ, Liotta W. The neurobiology of attention-deficit/hyperactivity disorder. J Clin Psychiatry 1998;59(suppl 7):17–23
74. Wilens TE, Biederman J, Spencer TJ. Attention-deficit/hyperactivity disorder across the lifespan. Annu Rev Med 2002;53:113–131
75. LaHoste GJ, Swanson JM, Wigal SB, et al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry 1996;1:121–124
76. Biederman J, Faraone S, Milberger S, et al. Predictors of persistence and remission of ADHD into adolescence: results from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 1996;35: 343–351
77. Pliszka SR. Comorbidity of attention-deficit/hyperactivity disorder with psychiatric disorder: an overview. J Clin Psychiatry 1998;59(suppl 7): 50–58
78. Biederman J, Faraone SV, Mick E, et al. Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and psychiatric referral sources. J Am Acad Child Adolesc Psychiatry 1999;38:966–975
79. Spencer TJ, Biederman J, Wilens T. Attention-deficit/hyperactivity

disorder and comorbidity. Pediatr Clin North Am 1999;46:915–927
80. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1993;150: 1792–1798
81. Biederman J, Faraone SV, Spencer T, et al. Gender differences in a sample of adults with attention deficit hyperactivity disorder. Psychiatry Res 1994;53:13–29
82. Shekim WO, Asarnow RF, Hess E, et al. A clinical and demographic profile of a sample of adults with attention deficit hyperactivity disorder, residual state. Compr Psychiatry 1990;31:416–425
83. Biederman J, Wilens T, Mick E, et al. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. Pediatrics 1999;104:e20
84. Wilens TE, Faraone SV, Biederman J, et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? a meta-analytic review of the literature. Pediatrics 2003;111:179–185
85. Wilens T, Biederman J, Wozniak J, et al. Can adults with attention-deficit hyperactivity disorder be distinguished from those with comorbid bipolar disorder? findings from a sample of clinically referred adults. Biol Psychiatry 2003;54:1–8
86. Wilens TE, Biederman J, Spencer TJ. Attention-deficit/hyperactivity disorder in youth. In: Hendren RL, ed. Disruptive Behavior Disorders in Children and Adolescents. Washington, DC: American Psychiatric Press; 1999
87. Faraone SV, Glatt SJ, Tsuang MT. The genetics of bipolar disorder. Biol Psychiatry 2003;53:970–977
88. Biederman J, Faraone SV, Millberger S, et al. Is childhood oppositional defiant disorder a precursor to adolescent conduct disorder? findings from a four-year follow-up study of children with ADHD. J Am Acad Child Adolesc Psychiatry 1996;35:1193–1204
89. Strober M, DeAntonio M, Schmidt-Lackner S, et al. Early childhood attention deficit hyperactivity disorder predicts poorer response to acute lithium therapy in adolescent mania. J Affect Disord 1998;51:145–151
90. Abikoff H. Cognitive training in ADHD children: less to it than meets the eye. J Learn Disabil 1991;24:205–209
91. Ratey JJ, Greenberg MS, Lindem KJ. Combination of treatments for attention deficit hyperactivity disorder in adults. J Nerv Ment Dis 1991; 179:699–701
92. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry 1999;56:1073–1086
93. Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 1997;68:2032–2037
94. Volkow ND, Wang G, Fowler JS, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci 2001;21:RC121
95. Biederman J, Spencer T. Nonstimulant treatments for ADHD. Eur Child Adolesc Psychiatry 2000;9(suppl 1):I51–I59
96. Wilens TE, Spencer TJ. Pharmacology of amphetamines. In: Tarter RE, Ammerman RT, Ott PJ, eds. Handbook of Substance Abuse: Neurobehavioral Pharmacology. New York, NY: Plenum Publishing; 1998:501–513
97. Elia J, Ambrosini PJ, Rapoport JL. Treatment of attention-deficit-hyperactivity disorder. N Engl J Med 1999;340:780–788
98. Wilens TE, Spencer TJ. The stimulants revisited. Child Adolesc Psychiatr Clin N Am 2000;9:573–603
99. Wilens TE, Pelham WE, Stein M, et al. ADHD treatment with a once-daily formulation of methylphenidate hydrochloride. a two-year study. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
100. Spencer T, Swanson J, Weidenman M, et al. Pharmacodynamic profile Ritalin LA, a new extended-release dosage from Ritalin in children with ADHD. Presented at the 47th annual meeting of the American Academy of Child and Adolescent Psychiatry; October 24–29, 2000; New York, NY
101. Chandler MC, Lopez FA, Biederman J. Long-term safety and efficacy of Adderall extended release in children with ADHD. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
102. Weisler RH, Biederman J, Chrisman AK, et al. Long-term safety and efficacy of once-daily Adderall-XR in adults with ADHD. In: New Research Program and Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif. Abstract NR647:242
103. Adcock KG, MacElroy DE, Wolford ET, et al. Pemoline therapy resulting in liver transplantation. Ann Pharmacother 1998;32:422–425
104. Marotta PJ, Roberts EA. Pemoline hepatotoxicity in children. J Pediatr 1998;132:894–897
105. Witcher JW, Long A, Smith B, et al. Atomoxetine pharmacokinetics in children and adolescents with attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2003;13:53–63
106. Michelson D, Faries D, Wernicke J, et al, for the Atomoxetine ADHD Study Group. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Pediatrics 2001;108:e83
107. Biederman J, Spencer TJ. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. Biol Psychiatry 1999;46: 1234–1242
108. Wilens T, Horrigan J, Haight B, et al. The safety and tolerability of extended-release bupropion in adult ADHD. Presented at the 20th annual meeting of the American Academy of Child and Adolescent Psychiatry; October 14–19, 2003; Miami, Fla
109. Belson MG, Kelley TR. Bupropion exposures: clinical manifestations and medical outcome. J Emerg Med 2002;23:223–230
110. Horschitz S, Hummerich R, Schloss P. Functional coupling of serotonin and noradrenaline transporters. J Neurochem 2003;86:958–965
111. Srinivasan K, Ashtok MV, Vaz M, et al. Effect of imipramine on linear and nonlinear measures of heart rate variability in children. Pediatr Cardiol 2004;25:20–25
112. Maidment ID. The use of antidepressants to treat attention deficit hyperactivity disorder in adults. J Psychopharmacol (Oxf) 2003;17: 332–336
113. Frazier JA, Meyer MC, Biederman J, et al. Risperidone treatment for juvenile bipolar disorder: a retrospective chart review. J Am Acad Child Adolesc Psychiatry 1999;38:960–965
114. Kurlan R, Como PG, Miller B, et al. The behavioral spectrum of tic disorders: a community-based study. Neurology 2002;59:414–420
115. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. J Am Acad Child Adolesc Psychiatry 2003;42:886–894
116. Leckman JF, Walkup JT, Riddle MA, et al. Tic disorders. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York: Raven Press; 1987:1239–1246
117. Leckman JF, Hardin MT, Riddle MA, et al. Clonidine treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry 1991;48: 324–328
118. Sverd J, Gadow KD, Paolicelli LM. Methylphenidate treatment of attention-deficit/hyperactivity disorder in boys with Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 1989;28:574–579
119. Gadow KD, Sverd J, Sprafkin J, et al. Long-term methylphenidate therapy in children with comorbid attention-deficit/hyperactivity disorder and chronic multiple tic disorder. Arch Gen Psychiatry 1999;56:330–336
120. Law SF, Schachar RJ. Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit/hyperactivity disorder? J Am Acad Child Adolesc Psychiatry 1999;38:944–951
121. Wilens T, Pelham W, Wolraich M, et al. A prospective study of once-a-day methylphenidate in the treatment of ADHD: one year follow-up data. J Am Acad Child Adolesc Psychiatry 2003;42:424–433
122. Singer HS, Brown J, Quaskey S, et al. The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. Pediatrics 1995;95:74–81
123. Klein RG, Abikoff H, Klass E, et al. Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. Arch Gen Psychiatry 1997;54:1073–1080
124. Klorman R, Brumaghim JT, Salzman LF, et al. Effects of methylphenidate on processing negativities in patients with attention-deficit/hyperactivity disorder. Psychophysiology 1990;27:328–337
125. Barkley RA. Defiant Children: A Clinician's Manual for Assessment and Parent Training. 2nd ed. New York, NY: Guilford Press; 1997
126. Comings DE, Gade-Andavolu R, Gonzalez N, et al. Comparison of the role of dopamine, serotonin, and noradrenaline genes in ADHD, ODD

and conduct disorder: multivariate regression analysis of 20 genes. Clin Genetics 2000;57:178–196
127. Donovan SJ, Stewart JW, Nunes EV, et al. Divalproex treatment for youth with explosive temper and mood liability: a double-blind, placebo-controlled crossover design. Am J Psychiatry 2000;157: 818–820
128. Hussain MZ. Novel antipsychotic in ADHD with conduct disorder. Presented at the 153rd annual meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill
129. Stein DB, Smith ED. The "REST" program: a new treatment system for the oppositional defiant adolescent. Adolescence 1990;25:891–904
130. van Goozen SH, Matthys W, Cohen-Kettenis PT, et al. Plasma monoamine metabolites and aggression: two studies of normal and oppositional defiant children. Eur Neuropsychopharmacol 1999;9: 141–147
131. Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 2002;41(suppl 2): 26S–49S
132. Riggs PD, Leon SL, Mikulich SK, et al. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry 1998;37:1271–1278
133. Riggs PD, Thompson LL, Mikulich SK, et al. An open trial of pemoline in drug-dependent delinquents with attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1996;35:1018–1024
134. Riggs PD. Clinical approach to treatment of ADHD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry 1998;37:331–332