

CLINICAL PRACTICE

Attention Deficit–Hyperactivity Disorder

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A mother brings in her eight-year-old son for evaluation after he is suspended from riding the school bus for jumping out of his seat, teasing other children, and not following directions. He spends two to three hours a night with homework that he never successfully completes. His mother wants to know whether he has attention deficit–hyperactivity disorder. How should he be evaluated and treated?

THE CLINICAL PROBLEM

Attention deficit–hyperactivity disorder (ADHD) is characterized by the inability to marshal and sustain attention, modulate activity level, and moderate impulsive actions. The result is maladaptive behaviors that are inconsistent with age and developmental level. Evidence from neuropsychological, pharmacologic, and brain-imaging studies implicates dopamine and norepinephrine neurotransmitter systems in frontostriatal circuitry in the pathophysiology of the disorder. Genetic factors appear to play an important role.^{1–3} Extremely low birth weight (less than 1000 g)⁴ and environmental conditions, such as head trauma and exposure to lead, are also associated with symptoms of ADHD.

The diagnosis of ADHD requires the identification of specific behaviors that meet the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, revised (DSM-IV-R)⁵ (Table 1). Three types of ADHD are diagnosed: combined inattentive, hyperactive, and impulsive (about 80 percent of patients); predominantly inattentive (about 10 to 15 percent); and predominantly hyperactive and impulsive (about 5 percent).

The prevalence of ADHD is estimated at 3 to 7 percent of all children. Boys are more often affected than girls (the ratio ranges, according to the population studied, from 9 to 1 to 2.5 to 1), but increasingly, cases involving girls are being identified.^{5,6} ADHD is a chronic condition with symptoms experienced over a lifetime.⁷ This review focuses on ADHD in children and adolescents.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The abilities to focus attention, regulate activity, and control impulses emerge for all children in a developmental process. Thus, the diagnosis of ADHD is based on a comprehensive history that elicits symptoms specific to the diagnosis, the context in which these symptoms occur, and the degree to which these are inconsistent with age and persist to cause impairment.⁸

Evidence of symptoms is obtained directly from the child, the parents, and the teachers. The National Initiative for Children's Healthcare Quality Vanderbilt Assessment Scale for parents and teachers consists of checklists of behaviors that can help the primary care physician assess the child with ADHD.⁹ Parents and teachers rate the child's symptoms on a scale of "never" to "very often" on items derived from the DSM-

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Table 1. Criteria for the Diagnosis of ADHD.*

The diagnosis requires evidence of inattention or hyperactivity and impulsivity or both	
Inattention	
Six or more of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:	
Often fails to give close attention to details and makes careless mistakes	
Often has difficulty sustaining attention	
Often does not seem to listen	
Often does not seem to follow through	
Often has difficulty organizing tasks	
Often avoids tasks that require sustained attention	
Often loses things necessary for activities	
Often is easily distracted	
Often is forgetful	
Hyperactivity and impulsivity	
Six or more of the following symptoms of hyperactivity and impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:	
Often fidgets	
Often leaves seat	
Often runs about or climbs excessively	
Often has difficulty with quiet leisure activities	
Often is "on the go" or "driven by a motor"	
Often talks excessively	
Often blurts out answers	
Often has difficulty awaiting turn	
Often interrupts or intrudes	
Symptoms that cause impairment:	
Are present before 7 years of age	
Are present in two or more settings (e.g., home, school, or work)	
Do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or another psychotic disorder	
Are not better accounted for by another mental disorder (e.g., a mood disorder or an anxiety disorder)	

* The criteria are adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, revised.⁵

IV-R criteria for ADHD. They also rate the child's school performance and interpersonal relationships. The scores indicate whether impairment meets the diagnostic criteria for ADHD. Although the checklists reflect subjective impressions, they allow a comparison of the patient with children of the same age and are the best available tool to discern behavior that exceeds normal variation.

Behaviors of ADHD may overlap or coexist with other mental health conditions (Table 2). The most common conditions are learning and language disorders, oppositional defiant disorder, conduct disorder, anxiety, and depression, as well as bipolar, post-traumatic stress, tic, and adjustment disorders.¹⁰

A careful history is warranted of the development of motor, social, and language skills, as well as of temperament, sleep habits, school achieve-

ment, moods, worries, and relationships. Furthermore, the primary care physician should be informed about prenatal and birth events, including prematurity and prenatal exposure to substances associated with behavioral and learning problems, such as tobacco and cocaine.¹¹ The assessment should include circumstances that might influence behavior and school performance, such as frequent moves or bitter custody disputes.¹² It is also important to determine whether there is a family history of ADHD, depression, bipolar disorder, anxiety disorders, or tic disorders. Genetic disorders that may have symptoms similar to those of ADHD (such as the fragile X syndrome) should be considered.

No physical findings are diagnostic of ADHD. Laboratory studies are not routinely obtained. Testing for achievement, intelligence, and specific learning disabilities may aid the differential diagnosis and help with planning for school services; such testing may be obtained through school-based assessment or by referral to a psychologist. Computerized or manual performance tests of attention and impulsivity are not diagnostic of ADHD.¹³

TREATMENT OF THE PATIENT

Treatment of the patient with ADHD focuses on control of the symptoms (which vary with the patient's development), classroom education, interpersonal relationships, and the transition to adult life.¹⁴ Therapy is guided by measurable target outcomes, such as the number of calls in a week from the teacher to report disciplinary action, the amount of time spent on homework assignments, or participation in other activities without disruption (Table 3).⁷

THERAPY

PHARMACOLOGIC INTERVENTIONS

Methylphenidate and Dextroamphetamine

There is strong evidence to support the use of stimulant medication for the management of inattention, impulsivity, and hyperactivity in school-age children.²¹ Methylphenidate and dextroamphetamine have consistently shown efficacy and safety when compared with placebo in randomized, controlled trials.²² Two studies are particularly informative. The Multimodal Treatment Study of ADHD involved 597 children at six centers who were followed for 24 months, including a 14-month treatment phase.²³ The study by Abikoff et al. involved 103 children at two centers who were randomly as-

Table 2. Mental Health Conditions That Mimic or Coexist with ADHD.

Disorder	Symptoms Overlapping with ADHD	Features Not Characteristic of ADHD	Diagnostic Problem
Learning disorders	Underachievement in school Disruptive behavior during academic activity Refusal to engage in academic tasks and use academic materials	Underachievement and disruptive behavior in academic work, rather than in multiple settings and activities	It can be difficult to determine which to evaluate first — a learning disorder or ADHD (follow the preponderance of symptoms)
Oppositional defiant disorder	Disruptive behavior, especially regarding rules Failure to follow directions	Defiance, rather than unsuccessful attempts to cooperate	Defiant behavior is often associated with a high level of activity It is difficult to determine the child's effort to comply in instances of a negative parent-child or teacher-child relationship
Conduct disorder	Disruptive behavior Encounters with law-enforcement and legal systems	Lack of remorse Intent to harm or do wrong Aggression and hostility Antisocial behavior	Fighting or running away may be reasonable reactions to adverse social circumstances
Anxiety, obsessive-compulsive disorder, or post-traumatic stress disorder	Poor attention Fidgetiness Difficulty with transitions Physical reactivity to stimuli	Excessive worries Fearfulness Obsessions or compulsions Nightmares Reexperiences of trauma	Anxiety may be a source of high activity and inattention
Depression	Irritability Reactive impulsivity Demoralization	Pervasive and persistent feelings of irritability or sadness	It may be difficult to distinguish depression from a reaction to repeated failure, which is associated with ADHD
Bipolar disorder	Poor attention Hyperactivity Impulsivity Irritability	Expansive mood Grandiosity Manic quality	It is difficult to distinguish severe ADHD from early-onset bipolar disorder
Tic disorder	Poor attention Impulsive verbal or motor actions Disruptive activity	Repetitive vocal or motor movements	Tics may not be apparent to the patient, the family, or a casual observer
Adjustment disorder	Poor attention Hyperactivity Disruptive behavior Impulsivity Poor academic performance	Recent onset Precipitating event	Chronic stressors, such as having a sibling with mental illness, or attachment-and-loss issues may produce symptoms of anxiety and depression

signed to 24 months of treatment.²⁴ The two studies included children seven to nine years of age and involved randomized pharmacologic and psychological interventions. Both studies assessed behavioral outcomes in the settings of the home and the school. Consistent with previous smaller studies, these trials showed that 68 to 80 percent of children treated with stimulants had improvements in behavior such that at the end of the treatment phase the children no longer met the criteria for a diagnosis of ADHD. The benefit of treatment was reduced in the Multimodal Treatment Study of ADHD after the children completed the active-study phase, whereas the benefit was sustained in the study by Abikoff et al. during the 24 months of treatment.

Randomized trials directly comparing methylphenidate and dextroamphetamine have shown

similar benefits from the two medications but more frequent mild side effects with dextroamphetamine.^{25,26} Evidence supports either medication as a first choice; 70 to 80 percent of children show improved attention with the use of one or the other.²² Preparations are available as short-, intermediate-, and long-acting, with a duration of 3 to 10 hours and similar efficacy (Table 4). The administration of short-acting medications can be timed to correspond to certain of the child's activities. Long-acting medications obviate the need for doses during the school day.

Dosages of methylphenidate and dextroamphetamine are not weight-based. Guidelines consistently recommend starting with lower doses and titrating to an effective dose that does not cause side effects (Table 4).^{7,15} Side effects are generally

Table 3. Guidelines for the Diagnosis and Treatment of Patients with ADHD.*

<p>Diagnosis</p> <ul style="list-style-type: none"> Comprehensive developmental, social, and family history Standardized checklists to assess behaviors^{9,19} Consideration of coexisting mental health disorders Physical examination, not to diagnose ADHD but to assess genetic and other conditions <p>Treatment</p> <ul style="list-style-type: none"> Management of ADHD as a chronic health condition Establishment of treatment goals agreed on by the child, the family, and school personnel Medication with stimulants to manage symptoms (monotherapy)[†] Behavioral therapy for parent-child discord and persistent oppositional behavior <p>Desired outcomes of treatment</p> <ul style="list-style-type: none"> Improved relationships with family, teachers, and peers Decreased frequency of disruptive behavior Improved quality of and efficiency in completing academic work, and increased quantity of work completed Increased independence in caring for self and carrying out age-appropriate activities Improved self-esteem Enhanced safety (e.g., care in crossing streets, staying with an adult in public places, and reduced risk-taking behavior)

* This information has been compiled from the guidelines of the American Academy of Pediatrics,^{7,13} the American Academy of Child and Adolescent Psychiatry,^{15,16} the European Society for Child and Adolescent Psychiatry,¹⁷ and the Scottish Intercollegiate Guidelines Network.¹⁸

[†] Atomoxetine is recommended by the American Academy of Child and Adolescent Psychiatry as a possible alternative to stimulant medication.²⁰

mild and managed by attention to dose and timing. The most common side effects are appetite suppression, stomachache, and headache, leading to discontinuation of the medication in approximately 1 percent to 4 percent of children.^{25,29} Delayed onset of sleep, previously thought to be associated with treatment, may be associated with the underlying disorder.³⁰ In a 24-month follow-up, the Multimodal Treatment Study of ADHD showed a deceleration in growth of approximately 1 cm per year with the use of stimulant medication.³¹ However, growth remained within the normal curve for most children, except those at the lowest percentiles of height for age. It is not known whether this effect is cumulative or can be ameliorated by summers off medication, allowing time for growth to catch up.

Follow-up visits in the Multimodal Treatment Study of ADHD²³ and the study by Abikoff et al.²⁴ were monthly. In general practice, however, once a stable dose of medication has been established, visits every three to four months are reasonable to monitor the effectiveness and potential side effects of the medication. Blood pressure, pulse, height,

and weight are followed, given the potential for the medication to affect these measures (Table 4).

Other Medications

Two other medications are effective with core symptoms of ADHD. Atomoxetine, a norepinephrine-reuptake inhibitor, is not classified as a stimulant. Randomized trials including more than 1000 children and adults showed that 58 to 64 percent of children treated during a 6-to-12-week period achieved 25 to 30 percent or greater improvement in symptoms.^{32,33} Two recent reports of severe liver injury (which apparently reversed after drug cessation) have led to the addition of a bolded warning to the label indicating that atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury.³⁴ Side effects such as appetite suppression and weight loss are reported at a frequency similar to that for side effects seen with methylphenidate.^{32,35} A study conducted in several countries showed a treatment benefit that was sustained over nine months.³⁶ Seizures and prolonged QT intervals corrected for heart rate are reported with overdoses of atomoxetine, but not with therapeutic doses.³⁷ Cases of tics developing during treatment with atomoxetine were recently reported³⁸ but were not described in randomized trials.

Bupropion, an aminoketone antidepressant, is also effective for inattention and impulsivity, but has not been approved by the Food and Drug Administration for use in children. Two randomized trials comparing bupropion with methylphenidate reported a smaller treatment effect and more side effects with bupropion among a total of 124 children and adolescents (Table 4).^{39,40} Atomoxetine and bupropion might be effective for children who require control of symptoms 24 hours a day and for those who do not respond to methylphenidate or dextroamphetamine.³²

The tricyclic antidepressants imipramine and desipramine, and the alpha-adrenergic agonist clonidine, are not often used in the treatment of ADHD because of concerns about cardiac effects and the availability of safe, effective medications described above. The stimulant pemoline remains available but is no longer recommended owing to reports of fatal hepatotoxicity.

A single medication is generally all that is needed to treat uncomplicated ADHD. Combinations of psychotropic medications have not been well studied and are reserved for very severe ADHD and coexisting mental health disorders.

Table 4. Recommended Medications for ADHD.

Medication*	Initial Dose	Usual Dose	Doses per Day	Side Effects	Contraindications
<i>mg</i>					
Methylphenidate†					
Ritalin, Methylin	5–10	10–20	2–3	Appetite suppression, stomach-aches, headaches, irritability, weight loss, deceleration in rate of growth, exacerbation of psychosis, exacerbation of tics, mild increase in blood pressure and pulse	Marked anxiety, tension, agitation, glaucoma, use of monoamine oxidase inhibitors, seizures, tics
Concerta	18–27	27–54	1		
Metadate ER, Metadate CD, Methylin ER	10	10–20	1		
Ritalin LA	20	20–40	1		
Focalin‡	2.5–5	2.5–10	2–3		
MethyPatch§					
Dextroamphetamine (sulfate alone and in combination with amphetamine salts)†					
Dexedrine	5	5–20	2–3	Appetite suppression, weight loss, stomachaches, headaches, irritability, possible growth inhibition, exacerbation of psychosis, exacerbation of tics, mild increase in blood pressure and pulse	Cardiovascular disease, hypertension, hyperthyroidism, glaucoma, drug dependence, use of monoamine oxidase inhibitors
Dexedrine Spansule	5–10	5–15	1–2		
Adderall	5–10	5–30	1–2		
Adderall XR	5–10	10–30	1		
Atomoxetine¶					
Strattera	10–25	18–60	1	Appetite suppression, nausea, vomiting, fatigue, weight loss, deceleration in rate of growth, mild increase in blood pressure and pulse	Jaundice or other clinical or laboratory evidence of liver injury, use of monoamine oxidase inhibitors, narrow-angle glaucoma
Bupropion					
Wellbutrin SR	100–150	150	1–2	Weight loss, insomnia, agitation, anxiety, dry mouth, seizures, others	Seizures, bulimia, anorexia nervosa, abrupt discontinuation of alcohol or benzodiazepines, use of monoamine oxidase inhibitors or other bupropion products (e.g., Zyban)
Wellbutrin XL	150	150–300	1		

* For each category the generic drug is given and dosing information for each named marketed drug.

† The manufacturer states that seizures and tic disorder are contraindications; research supports the use of stimulants in children with seizures that have stabilized with the use of anticonvulsants and in children with tic disorder or Tourette’s disorder.^{27,28} With use of a long-acting methylphenidate or dextroamphetamine product, a short-acting product may be added at 4 p.m. to 6 p.m. for homework or special activities; appetite and sleep onset are then carefully monitored.

‡ Focalin is a dextro isomer of methylphenidate that is given at a lower dose.

§ The MethyPatch is a sustained-action transdermal patch that is not yet available.

¶ Younger children may need two doses a day.

|| Bupropion has not been approved by the Food and Drug Administration for pediatric use. Only sustained release (twice daily) or extended release (once daily) are recommended for adolescents. There is a higher incidence of side effects with the immediate-release preparation.

NONPHARMACOLOGIC INTERVENTIONS

Behavioral Therapy

Behavioral therapy is not routinely recommended as first-line treatment for uncomplicated ADHD in school-age children. Large randomized trials directly compared behavioral therapy with pharmacologic therapy. The trials showed that behavioral therapy alone was less effective than pharmacolog-

ic therapy alone, and they showed mixed results for behavioral therapy in combination with medication.

The behavioral-treatment group of the Multimodal Treatment Study of ADHD involved 35 individual and group sessions over 14 months and focused on behavior-management techniques, a summer treatment program, consultation with each child’s teacher, and the presence of a behavioral

aide in the child's classroom for 12 weeks.⁴¹ This intensive behavioral therapy alone was not as effective as medication alone for improving attention. However, the combination was more effective for oppositional behavior and parent-child discord, among other outcomes, than either of the treatments alone.

The study by Abikoff et al.²⁴ examined psychosocial treatment, not as the sole treatment, but in addition to medication. The sessions were weekly in the first year and monthly in the second year and included parent training, family therapy, organizational-skills training, individual tutoring, social-skills training, and individual psychotherapy. No benefit was found for adding psychosocial treatment to treatment with medication.

Behavioral treatment that is generally available in communities and schools usually involves 8-to-12-week group sessions with children and parents, provided by psychologists or social workers. Sessions focus on improving the understanding of ADHD, teaching parents skills such as effective use of rewards and disincentives, and modifying the physical and social environment to change the child's behavior, such as structuring daily routines.⁷ Behavioral therapy is added to medication for specific indications, such as persistent oppositional behavior and parent-child discord. Psychological treatment is indicated for coexisting mental health conditions, such as depression and anxiety.

Other Interventions

Physicians cannot prescribe an educational assessment, but they can support a parent's request for an assessment when it is indicated by persistent academic problems. In the United States, children with ADHD are entitled to interventions within the school setting if the parents and school officials determine that the child's behavior or condition interferes with his or her ability to participate in the educational process. The interventions might be simple, such as seating the child near the teacher to minimize classroom distractions, or they might involve assigning specific staff members to review daily assignments with the child.⁴² Collaboration among the doctor, the parents, and the teacher can be facilitated with very brief lists of target behaviors, rated by the teacher, and taken by parents to appointments; these can be useful in gauging the effectiveness of treatment (Table 3).^{7,9}

Other treatment interventions, such as physical exercises, neurofeedback, chelation therapy, sys-

temic antifungal treatment, and vitamins, are often promoted at substantial expense to families. Little evidence supports a role for these interventions in the treatment of ADHD. Diets, including those involving the reduced consumption of sugar, were studied and found to affect behavior in no more than 1 percent of children.⁴³⁻⁴⁵

Reasons to refer to a specialist such as a developmental or behavioral pediatrician or a child psychiatrist include coexisting mental health conditions, adverse social circumstances that warrant team management, and treatment failure.⁷

SPECIAL POPULATIONS

Children less than five years of age may demonstrate severely disruptive behaviors; these are probably associated with other chronic physical and mental health conditions.^{46,47} Randomized trials show that training parents improves symptoms in preschoolers. In one trial, parents of 87 three-year-olds were randomly assigned to a control group or to 10 to 12 sessions in which they were taught to set consistent limits and positively interact with their preschooler. Children of parents in the intervention group were significantly more likely to achieve at least a 30 percent reduction in negative behaviors than were children of parents in the control group (62 percent vs. 28 percent), and 80 percent of the children in the intervention group showed improvement at one year of follow-up (there was no comparison group at that time).⁴⁸ An 8-week randomized trial involving parents of three-year-olds showed that training the parents had a significant benefit on the children, and improvement was sustained 15 weeks after the intervention.⁴⁹

A short-term study (three to four weeks) involving 28 children with ADHD, who were 4 to 5.9 years of age, showed normalization of behavior for 25 children who received stimulant medication as compared with 3 who received a placebo. Irritability and decreased appetite were frequent side effects.⁵⁰ Although approximately 1 percent of children two to four years of age may be treated with psychotropic medications, there is little evidence to support or guide this treatment,^{51,52} and the overuse of medication is a particular concern in this group.

Children with mental retardation may have symptoms that meet the criteria for a separate diagnosis of ADHD. However, according to DSM-IV-R criteria, symptomatic behaviors should not be diagnosed as ADHD if they can be better explained by another diagnosis.⁵ Randomized, controlled trials

support the use of stimulant medication to treat children and adults who have symptoms of ADHD and mental retardation.^{53,54}

ADHD affects 4 percent of adults; as many as 60 to 80 percent of children continue to have problems in adulthood with inattention and impulsivity, which adversely affect achievement and interpersonal relationships. The diagnosis of ADHD in adults, as in children and adolescents, is established through DSM-IV-R criteria, and coexisting mental health disorders must be considered in the diagnosis and treatment. Short-term studies have indicated improvement in attention and impulsivity with the use of stimulants and atomoxetine, but long-term data are lacking.⁵⁵ A detailed discussion of adult ADHD is beyond the scope of this article.

AREAS OF UNCERTAINTY

The subjective nature of judging behavior contributes to concern that ADHD is overdiagnosed and overtreated. Epidemiologic studies consistently show either underdiagnosis or overdiagnosis, with wide geographic and demographic variation.^{56,57} Data are not yet available to assess the long-term benefits and risks of medication. Although a concern has been raised regarding a risk of substance abuse in patients treated with stimulant medication, studies indicate that children with ADHD who are treated have a lower risk of substance abuse later in life than children with ADHD who are not treated.^{58,59}

GUIDELINES

Guidelines for diagnosing and treating ADHD have been issued by several organizations representing pediatrics and child psychiatry (Table 3). These are consistent, and taken together, establish the standard of care for ADHD.

CONCLUSIONS AND RECOMMENDATIONS

The evaluation of a child for ADHD involves taking a careful history, including the use of a standardized checklist to assess behaviors, and paying attention to the possibility of other mental health conditions or adverse social circumstances causing or exacerbating symptoms (Table 2). If the evaluation reveals behaviors meeting DSM-IV-R criteria for the diagnosis of ADHD (Table 1), a plan for care should take into consideration that ADHD is a chronic health condition and should involve the parents, the child, and the teacher in identifying behaviors to which therapy is targeted (Table 3).

In school-age children such as the one described in the vignette, I begin treatment with methylphenidate, because it is the treatment best supported by research. I prescribe a long-acting preparation, typically a low dose (10 to 18 mg) for a child less than 10 years of age and a midrange dose (20 to 36 mg) for older children or teenagers. A higher starting dose (30 to 54 mg) is reasonable for patients with severe symptoms. If medication is ineffective at the maximal dose or causes intolerable side effects, I try prescribing two to four daily doses of short-acting medication or switching to a long-acting preparation of dextroamphetamine; an alternative is atomoxetine. I see the child and his or her parents every month initially and every three months once a stable dose has been reached, to assess effectiveness and side effects. I recommend behavioral therapy for children and families experiencing conflict with one another and for children with a coexisting mental health condition.

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