

ADHD and Its Treatment in Children and Adolescents

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Goal. The goal of this lesson is to explain attention-deficit/hyperactivity disorder (ADHD) in children and adolescents with focus on its pathogenesis, clinical characteristics and confirmation, and its treatment.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. recognize historical events and epidemiologic information relevant to ADHD;
2. identify symptomatology that characterizes ADHD and the principles that govern its clinical confirmation and management; and
3. select from a list specific nonpharmacologic and pharmacologic measures that are reported to modify signs and symptoms of ADHD.

Attention-deficit/hyperactivity disorder (ADHD) affects approximately 4 to 12 percent of children and adolescents, and persists throughout adulthood. It is the most commonly diagnosed psychiatric condition of childhood and adolescence. ADHD persists into adulthood in up to 60 percent of diagnosed cases, with 4 to 5 percent of adults worldwide affected. It is, thus, a major public health problem because of associated morbidity and disability across the lifespan of affected persons.

Annual medical costs of affected individuals are 50 to 75



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percent higher than expenses for non-affected persons. Overall costs of illness are estimated to be upwards of \$40 billion annually in the United States alone.

Background

Although ADHD was first described in 1845, it was not until 1902 that a description was published.

ADHD can lead to serious long-term effects including impairment of major life activities and premature morbidity. Persons with ADHD may exhibit underachievement and disruptive behavior in school, as well as antisocial and criminal behavior. They typically have unsafe driving habits, and are twice as likely to use tobacco.

Males are reportedly affected more often than females (2:1 to 3:1 ratio). These numbers can be deceptive because females with ADHD may be diagnosed less frequently since many of them have the inattentive (i.e., less disruptive) form. Many girls are not diagnosed until middle school or later.

Pathogenesis

Although the precise cause of ADHD is unknown, a deficiency in central stores of the neurotransmitters dopamine and norepinephrine has been implicated. These deficits are associated with both genetics and environmental influences. Recent imaging studies have failed to find evidence of gross brain damage in children with ADHD.

In the 1970s, it was hypothesized that the core problem in hyperkinetic children was one of inattention. This led in 1980 to adoption of the new diagnostic label *attention-deficit disorder*.

Since the symptoms of ADHD respond well to treatment with central stimulants, and because these drugs enhance the availability of dopamine, the *dopamine hypothesis* has captured the attention of many researchers. The dopamine hypothesis proposes that ADHD is caused by an inadequate supply of dopamine in the CNS. Dopamine plays a major role in initiating purposeful movement and increasing motivation and alertness, behaviors that are often noted when a child with ADHD responds positively to stimulant therapy. The dopamine hypothesis has thus influenced much of the recent research into the cause(s) of ADHD.

Genetic Influence. The fact that ADHD runs in families lends strong support to the theory that heredity is an important risk factor. Ten to 35 percent of children with ADHD have a first-degree rel-

ative with a past or present history of ADHD. Approximately one-half of parents with ADHD have a child with the disorder. Studies suggest that ADHD is among the most familial (affecting other members of the family) of psychiatric disorders.

Research to identify specific abnormal genes has concentrated on two: a dopamine-receptor gene on chromosome 11 and the dopamine-transporter gene on chromosome 5. Evidence is mounting that children with ADHD have genetic variations in one of the dopamine-receptor genes. Several studies have found evidence for abnormalities of the dopamine-transporter gene in children with very severe forms of ADHD.

While the high heritability of ADHD suggests that it is a “genetic” disorder, it is inaccurate to assert that any single gene is at fault. Rather, some gene variants boost an individual’s susceptibility to environmental triggers.

Even though many imaging studies have failed to identify evidence of gross brain damage in ADHD, some have noted that exposure to toxins such as lead, or episodes of fetal oxygen deprivation, may adversely affect dopamine-rich areas of the brain. These findings support the many observations that hyperactivity and inattention of ADHD are more common in children whose mothers smoked or used alcohol during pregnancy (especially during the first trimester), in children with impaired oxygenation leading to fetal distress and low birth weight, in children who have been exposed to high quantities of lead or carbon monoxide, and in children with infections of the CNS and those with serious head injury. Recently published data have shown that children born to nonsmoking mothers who were exposed to chronic secondhand smoke during pregnancy face serious problems of ADHD and conduct disorder.

Some studies have reported that parents of hyperactive children are often overintrusive and overcontrolling, which suggests

that parental behavior is another possible risk factor for ADHD.

To date, no single mechanism has been identified as the definitive cause of ADHD. It is believed that its development most likely results from combined action of multiple genetic and environmental risk factors.

Clinical Confirmation

There is no laboratory or imaging test, or battery of psychological tests, that reliably confirm the presence of ADHD. Rather, confirmation is based mainly on the patient’s behavior history (Table 1) and elimination of other sources for the troublesome behaviors.

ADHD diagnosis is subject to a variety of influences, particularly because it is often first suggested by school teachers (52 percent) and parents (30 percent) rather than health professionals. A diagnosis is first suggested by a primary care physician, child psychiatrist or psychologist in only 14 percent of cases. Regardless of who first suggests that a child may have ADHD, physicians and mental health professionals typically depend on suggestions by parents, teachers and other school personnel in confirming a diagnosis. The DSM IV criteria for ADHD are summarized in Table 2. Most clinicians report they are hesitant to confirm a diagnosis prior to six years of age because of the wide variability in levels of activity that overlap with symptoms of ADHD, and therefore are considered normal in early childhood.

Treatment

Goals of therapy include controlling symptoms, improving classroom attention and learning ability, enhancing interpersonal relationships and enriching transition to adult life. Pharmacotherapy has been the mainstay of treatment for decades, with hundreds of well-controlled clinical trials documenting its usefulness in children, adolescents and adults. The most widely available option for treatment of ADHD, an option supported by a vast litera-

ture, are the central stimulants.

Pharmacotherapy

Stimulants. First shown to be beneficial for treatment of abnormal behavior more than seven decades ago, central stimulants have become the first-line treatment option for ADHD with benefit attained in 75 to 90 percent of recipients. Their precise mechanism of action in ADHD is not fully understood, although they are believed to increase release of dopamine and/or norepinephrine from pre-synaptic neurons or inhibit their reuptake. These actions result in increased adrenergic activity. The stimulant drugs exert these actions to various degrees, thus working by slightly different mechanisms of action. Therefore, failure of therapy with one agent does not translate to a class failure and alternate agents within this class often may be administered to the patient’s benefit.

The drugs are rapidly absorbed and typically result in an onset of action within 30 minutes. Their action extends over three to six hours. Administration is timed to meet the individual’s school or work schedule, to enhance the person’s ability to pay attention and meet his or her academic or work demands, and to mitigate side effects. Their greatest effects are on symptoms of hyperactivity, impulsivity, and inattention and the associated features of defiance, aggression, and oppositionality. They also improve classroom performance and behavior and promote increased interaction with teachers, parents and peers.

Stimulant drugs include mixed amphetamine salts (Adderall, etc.), dextroamphetamine (Dexedrine, etc.), methylphenidate (Ritalin, etc.) and dexmethylphenidate (Focalin). Lisdexamfetamine (Vyvanse) is a prodrug of dextroamphetamine with a longer duration of action. The American Academy of Pediatrics (AAP), working through its Committee on Quality Improvement – Subcommittee on Attention-Deficit/Hyperactivity Disorder, published its Clinical Practice

Guidelines for treatment of school-aged children with ADHD in 2001. AAP determined that there were no clear differences among dextroamphetamine, lisdexamfetamine and methylphenidate. Newer products were not available at the time of guideline development. Subsequent reports suggest that the use of methylphenidate and mixed amphetamine salts are first-line therapy because of ample evidence of their safety and efficacy.

Clinical trials consistently document that stimulants reduce the core symptoms of ADHD. Recent trials tend to focus on use of the newer agents to assist with dosing convenience and overall ease of patient care. Advances in dosage formulations such as long-acting agents aid treatment adherence, decrease embarrassment for children in school who must take multiple daily doses, lessen burdens for school staff to administer these doses and decrease the potential for drug diversion and abuse. Long-acting formulations extend the action of these drugs over eight to 12 hours to allow once-daily dosing.

Advances in methylphenidate formulations include chewable tablets, oral solution and a patch formulation. The patch (Daytrana) has demonstrated statistically significant reductions in ADHD symptoms for children ages six through 12 years. The patch is worn for nine hours daily. In clinical trials, application site reactions, insomnia, anorexia and nervousness were the adverse effects most commonly reported leading to discontinuation of therapy.

Adverse effects associated with stimulants used in ADHD include appetite suppression with initial weight loss, insomnia, headache, jitteriness and stomach pain. If insomnia is a problem, giving the stimulant earlier in the day, discontinuing the afternoon or evening dosage, or giving an adjunct medication such as a low-dosage antidepressant may help. Other concerns include tic development, growth delay and potential for

substance abuse. Mild adverse effects may be partially controlled by reducing the dose or altering the timing of administration. Most adverse effects are mild, recede over time and respond to dose changes. Appetite may fluctuate, usually being low during the middle of the day and more normal by suppertime. Parents may choose to have their child take a “drug holiday” on weekends and vacations to reduce overall exposure, but the utility of this strategy has not been demonstrated. Concerns remain about inhibition of long-term growth; however, most studies conclude that such effects are minimal and of small clinical importance. As with all medication use, risks versus benefits must be weighed.

Recent concerns have highlighted the possibility of cardiovascular events with stimulants. In April 2008, the American Heart Association (AHA) released a statement calling for a thorough examination including family history and an electrocardiogram, and routine cardiac monitoring for children and adolescents prescribed stimulant medication for ADHD. The call for closer cardiac monitoring was given to identify the very small number of children and adolescents who may have an undiagnosed cardiac problem.

Non-stimulants. Atomoxetine (Strattera) is the newest non-stimulant treatment option for ADHD. It is a selective norepinephrine reuptake inhibitor in presynaptic neurons with less action to reduce dopamine reuptake in the prefrontal lobes. The drug has a slower onset of action than stimulants; thus, effects may not be seen until the end of the first week of treatment. Atomoxetine seems to have a longer duration of action after once-a-day dosing with suggestions of symptom relief during the evening and early-morning hours.

A meta-analysis evaluated atomoxetine for safety and tolerability. Following 601 subjects for up to two years of study, only 5.2 percent discontinued medication use because of adverse effects.

Table 1
Presentation of ADHD

Reported by child or adolescent

- Does not like school or particular subjects or teachers
- No close or long-term friends
- Conflict with parents
- Low self-esteem
- Always getting in trouble

Reported by parents

- Aggression and problems with anger
- Difficulty completing tasks
- Disorganized, messy
- Does not follow directions
- Impulsive
- Difficulties with school
- “Always on the go”
- Does not make or keep friends
- Socially or emotionally immature
- Engages in dangerous activities
- “Spaced out” or absentminded
- Loses possessions

Reported by teachers

- Hyperactive
- Inattentive, easily distracted
- Interferes with others, disrupts class
- Underachiever, school failure
- Does not listen
- Fidgets, will not stay in seat
- Blurts out answers, does not consider others
- Frequent behavior problems

Adapted in part from Culpepper L. J Clin Psychiatry. 2006;67[suppl 8]:32-37.

There were no discontinuations due to tics, seizures, hepatic toxicity or growth concerns. The most common treatment-emergent adverse effects occurring at 10 percent incidence included cough, decreased appetite, dizziness, fatigue, irritability, upper respiratory tract infection and vomiting. Most effects occurred within three months and tapered off thereafter. Weight and height increased as expected, even though there was an initial weight decrease over the first three months of treatment. Statistically significant changes were noted in pulse rate and both diastolic and systolic blood pressures, but these were consistent with age-expected increases.

Table 2
Summary of DSM-IV* diagnostic criteria for ADHD

Criterion	Description
A	Patients must exhibit 6 to 9 symptoms of inattention or 6 to 9 symptoms of hyperactivity-impulsivity that have persisted for at least 6 months.
B	Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C	Some impairment from the symptoms is present in 2 or more settings (e.g., at school [or work] and at home).
D	There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E	The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

**Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington DC, American Psychiatric Association, 1994.*

Adapted in part from Findling RL, Arnold LE, Greenhill LL, et al. J Clin Psychiatry. 2007;68:1963-1970.

Atomoxetine labeling contains a warning about the potential for severe liver injury in rare cases. It should be discontinued when there is evidence of jaundice or hepatic injury. The drug also has a black box warning concerning the potential for increased risk of suicidal ideation in children and adolescents being treated for ADHD. Patients starting atomoxetine should be monitored closely for changes in behavior. Compared with stimulants, atomoxetine has relatively low potential for abuse. Recommendations are as a second-line option following unsuccessful trials with stimulant therapy.

Tricyclic antidepressants, once commonly used, have lost favor over the years because of their adverse effect profile; several deaths in the early 1990s were associated with desipramine use. Tricyclics are typically recommended following a poor response with one or more stimulants or atomoxetine. Baseline and periodic electrocardiogram monitoring are needed to assess safety of therapy.

Bupropion (Wellbutrin, etc.) has shown modest efficacy in

ADHD. Its use may be considered as an option for adjunct therapy in persons who also smoke tobacco or possess underlying depression or bipolar disorder, or those with a history of substance abuse. Because bupropion may induce seizures, the drug should not be used in persons with a seizure history.

Non-pharmacologic Therapies

Behavioral Intervention.

Behavioral intervention in combination with medication use is the optimal approach to treatment of ADHD. The MTA Study has shown that patients with combined medication and behavioral intervention improved in the core areas of ADHD; moreover, family members consistently benefited from this approach. The combined approach to treatment also resulted in less challenging behaviors and permitted reduced doses of medication to be used.

Dietary Intervention. Some medical researchers and clinicians have proposed that dietary intervention has potential benefit in treatment of ADHD. Parents may therefore choose to supplement or,

in some cases, replace medication with dietary intervention. One commonly promoted intervention is the Feingold diet, in which dietary salicylates, artificial colors, flavors and preservatives are removed from the diet. Other proposed dietary interventions include removing all sugars, adding high-dose vitamin/mineral supplementation, and supplying essential fatty acids to help alleviate ADHD symptoms. At this point, none of these approaches have been supported by well-designed clinical trials.

Summary and Conclusions

ADHD is a chronic condition with unknown etiology and potentially harmful sequelae if not treated. Central stimulants remain the most widely used therapy. Innovative dosage forms and longer acting agents assist with ease of dosing and improvement of drug adherence, and as a means to discourage abuse and diversion. Stimulant use is not without safety concerns, including the recent call from the AHA to monitor patients for cardiovascular events. Non-stimulant therapies, including atomoxetine and antidepressants, may be of benefit in persons who do not respond adequately to stimulant therapy.

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continuing education quiz

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1. While the precise cause of ADHD is unknown, a deficiency in central stores of which of the following sets of neurotransmitters has been implicated?
 - a. Norepinephrine and serotonin
 - b. Acetylcholine and serotonin
 - c. Dopamine and norepinephrine
 - d. Acetylcholine and dopamine
2. Which of the following plays a major role in initiating purposeful movement and increasing motivation and alertness when a child with ADHD responds positively to stimulant therapy?
 - a. Acetylcholine
 - b. Dopamine
 - c. Norepinephrine
 - d. Serotonin
3. There have been findings that support the many observations that hyperactivity and inattention of ADHD are more common in children in all of the following instances except those:
 - a. whose mothers have diabetes or hypertension.
 - b. with impaired oxygenation leading to fetal distress.
 - c. whose mothers smoked during pregnancy.
 - d. with infections of the CNS.
4. Confirmation of the presence of ADHD is based mainly on:
 - a. laboratory tests.
 - b. imaging tests.
 - c. psychological tests.
 - d. patient behavior history.
5. Which of the following is a prodrug of dextroamphetamine?
 - a. Focalin
 - b. Ritalin
 - c. Strattera
 - d. Vyvanse
6. Advances in long-acting oral dosage forms of drugs used to treat ADHD have shown all of the following benefits EXCEPT:
 - a. significantly increased effectiveness.
 - b. fewer burdens on school staff.
 - c. decreased embarrassment for children in school.
 - d. aiding treatment adherence.
7. Which of the following is a non-stimulant treatment option for ADHD?
 - a. Focalin
 - b. Ritalin
 - c. Strattera
 - d. Vyvanse
8. All of the following are common treatment-emergent adverse effects that occur in patients receiving the drug referred to in question # 7 with the exception of:
 - a. fatigue.
 - b. seizures.
 - c. irritability.
 - d. dizziness.
9. The drug referred to in question # 7 has a black box warning for increased potential risk of:
 - a. bulimia.
 - b. growth concerns.
 - c. jaundice.
 - d. suicidal ideation.
10. Which of the following is the optimal approach in combination with medication for the treatment of ADHD?
 - a. Behavioral intervention
 - b. Dietary intervention

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