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Review Article

Attention-Deficit/Hyperactivity Disorder: Etiology and Pharmacotherapy

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Attention-deficit/hyperactivity disorder is a common neurobehavioral disorder of childhood and adolescence. The etiology of attention-deficit/hyperactivity disorder is not well understood. Neurochemical studies suggest, alterations in catecholaminergic, mainly dopaminergic and noradrenergic, transmitter functions markedly contribute to the symptoms of this disorder. The symptoms of attention-deficit/hyperactivity disorder are significantly ameliorated by the agents that specifically influence these neurotransmitters. Animal studies implicate areas of the brain in which these neurotransmitters are most dominant. Psychostimulant medications are generally the first choice in the treatment of attention-deficit/hyperactivity disorder. Approximately 70% of the children treated show improvement in the primary attention-deficit/hyperactivity disorder symptoms and in comorbidity such as conduct disorder, although the benefits may not hold beyond two years. Despite the well-established efficacy and safety of stimulants for attention-deficit/hyperactivity disorder, alternative medicines are still needed for several reasons. About 30% of children and adolescents with this disorder may not respond to stimulants or may be unable to tolerate potential adverse events such as decreased appetite, mood lability and sleep disturbances. Although stimulants do not increase the risk for later substance abuse in attention-deficit/hyperactivity disorder, concerns have been raised about special prescription rules and a potential for abuse by persons other than the attention-deficit/hyperactivity disorder subjects. This review focuses on etiology, assessment, and treatment of attention-deficit/hyperactivity disorder.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder of childhood and adolescence. It affects approximately 3 – 5% of school-age children.[1, 2]

ADHD is characterized by symptoms of inattention and/or hyperactivity/impulsivity that have persisted for at least six months, to a degree that is maladaptive and inconsistent with developmental level. Usually, some of the symptoms that cause impairment are present before the seventh year of life. Some impairment is present in two or more settings (e.g., at home and at school).

Children with ADHD may experience significant functional problems, such as school difficulties, academic underachievement, troublesome interpersonal relationships with family members and peers, and low self-esteem.

Individuals with a history of untreated childhood ADHD are more likely to experience conduct disorder, substance abuse, antisocial behavior, and injuries later in life. Early recognition, assessment, and management of this condition can redirect the educational and psychosocial development of most children with ADHD.[3 – 5]

Assessment

For assessment, presence and severity of the symptoms, and the degree of impairment should be

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evaluated. Information from the family and the educational environments should also be gathered. Physicians must evaluate the other conditions that can explain the presenting symptoms or those that commonly coexist with ADHD.

ADHD can be present with or without comorbid learning disabilities, conduct disorder, or other emotional disabilities. The questionnaires prepared based on DSM-IV criteria, can add the objective information about the child's symptoms and can be used to evaluate the symptoms in both home and educational environments.

It is important that the symptoms are present often or very often.[6] A much higher percentage of the population will be diagnosed if the symptoms are only present sometimes. The physician must consider other explanations for the child's behavior and coexisting conditions such as learning disabilities, oppositional defiant disorder, conduct disorder, and anxiety disorders.[6 – 8]

Signs and symptoms

Children with ADHD may fit into three common patterns: predominantly inattentive type (30% to 40%); hyperactive-impulsive type (10%); and combined type (50% to 60%).[3, 9, 7]

Predominantly inattentive children have difficulty in focusing on particular tasks. They may skip from one uncompleted activity to another, be easily distracted by seemingly irrelevant stimuli, and avoid tasks requiring focused attention. Inattentive type of ADHD is the most common pattern among the affected girls. Such children often have difficulty following directions and completing tasks such as homework. They fail to pay attention to details and make careless mistakes. They also seem disorganized, "spacey" or "dreamy", and commonly lose their belongings such as books and forget to do homework and assignments. Such children commonly complain of being "bored", yet may have no trouble paying attention to activities that they find exciting or really enjoy.

Children who are hyperactive may always seem to be "on the go" or in constant motion. They may appear restless or fidgety, have difficulty remaining seated, and run or climb in situations where sitting or quiet behavior is expected. Children who are impulsive have difficulty in thinking before any action. They act often without apparent regard to the consequences of their actions. They may blurt out answers or inappropriate comments at school, intrude upon or interrupt others, and have difficulty waiting in lines or taking turns.[10 – 14]

Etiology

The etiology of ADHD is unknown, and it is a heterogeneous disorder. There is little evidence to believe that the disorder can be caused by social factors or child rearing practices alone.[4, 15] Approximately one-third of affected children have a first-degree relative with a history of ADHD.

Central catecholaminergic neurotransmission system is involved in the pathophysiology of ADHD. Effective treatments for ADHD modulate dopaminergic and noradrenergic neurotransmission in the prefrontal cortex.

Brain imaging studies show differences between children with ADHD and unaffected children (i.e., frontal lobes, temporal gray matter, caudate nucleus, and cerebellum). The cause of such differences is unknown but brain imaging cannot be used as a diagnostic tool to differentiate children with ADHD from those without AHDH. Traumatic brain injury has been associated with ADHD, in a small percentage of affected children.

Environmental factors, exposure to tobacco or alcohol during the fetal period, and exposure to lead in the early years of life have also been associated with ADHD.

Though up to 5% of children with ADHD may respond to dietary manipulations for food allergies, there is little evidence that exposure to refined sugar or food additives are responsible for ADHD in most affected children.[16 – 19]

Prevalence and course of ADHD

The prevalence of ADHD is estimated to be from 3% to 7% of the school-age children in the United States.[2, 20] The data about the prevalence are not conclusive because they can be affected by the diagnostic criteria and the measures used to determine the disorder.

Although boys with ADHD outnumber girls, estimates of the ratio of boys to girls vary significantly. Ranges of 2:1 to 9:1 have been reported. Gender difference is less obvious in inattentive type. Boys are more likely to be aggressive and to have other behavioral problems.[21] Girls can be overly talkative and social but demonstrate the same core symptoms and high levels of comorbid disorders, as do boys. In community-based samples, the ratio of boys to

girls is closer to 1:1; however, in clinic-based samples, it is about 6:1 because of the disruptive and noncompliant aspects of the boys' behavior.

ADHD children make up 30% to 40% of referrals to child mental health practitioners. Determining the prevalence of ADHD in other countries and cultures has been difficult. Although there is a general agreement that ADHD is a worldwide phenomenon, it has been difficult to obtain and compare the prevalence data. Prevalence rates in some countries have been reported to be between 3% and 9.5%, roughly analogous to the data reported from the United States. It has been difficult to make comparisons of prevalence measures because of differing criteria and methodology used in different cultures and ethnic groups in the United States.[22 – 24]

Medication

Stimulant medications

Stimulant medications help most children with ADHD.[25] The short-term efficacy of stimulants for the treatment of core ADHD symptoms has been well established by numerous placebo-controlled randomized trials. Interestingly, placebo response rates for children with ADHD are quite low.

Stimulants have been shown to decrease interrupting, fidgetiness, and finger tapping in the classroom. They can also improve attention and increase on-task behavior.

At home, stimulants can improve interactions between the parents and children, and improve listening and on-task behavior. Stimulants can decrease aggressive behaviors with peers, increase attention during sports, and improve the social ranking by their peers. Extended trials of 12 months and longer suggest that response to stimulants tends to be enduring as long as the medication is taken.[26, 27]

Methylphenidate is the most widely used and best-studied stimulant medication. Dextro-amphetamine (d-amphetamine) and mixed amphetamine salts (d,l-amphetamine) are also commonly used and have been well studied.[28]

Amphetamine preparations are approximately twice as potent as methylphenidate. Recent reports of sudden death in a handful of youth treated with amphetamine salts have generated understandable concern. Although most of those dead youth had preexisting structural cardiac abnormalities, a few of them had not such findings.

At the present time, existing knowledge about the possible side effects of amphetamine salts should be shared with the patients and their families, and a careful history of preexisting cardiac problems, "drop attacks", or family history of sudden death should be taken prior to initiating treatment with amphetamine salts.

Pemoline is another stimulant that has been used to treat children, adolescents, and adults with ADHD who did not respond to or could not take methylphenidate. The reports of rare but potentially fatal hepatotoxicity in association with the use of pemoline have discouraged its use.

Approximately 70% of youth with ADHD will respond to the first stimulant taken, and at least 80% will respond to one stimulant if the medications are tried systematically.[25, 27] Consequently, given the current state of knowledge, it has been recommended that children who fail to respond to one stimulant should try another. Approximately 40% of youth with ADHD will respond equally well to methylphenidate or amphetamine preparations, but about one-third will respond to one of these drugs better than the other one.[29]

Standard preparations of methylphenidate or amphetamine are relatively short acting. Their range of action is from 3 to 6 hours. So, they should be administered two or three times per day.

The development of new stimulant formulations with rapid onset of action and a longer duration of effect has been important in the treatment of ADHD, because their use can eliminate the need for multiple doses across the day and during the school time. These preparations can be prescribed as the initial stimulant treatment.

Concerta® was designed to replace a thrice daily regimen of immediate release methylphenidate, with approximately a 10- to 12-hour duration of action, whereas Metadate® and Ritalin LA® replaced the twice daily methylphenidate via a long-acting preparation with duration of 16 to 18 hours.[30, 31]

Non-stimulant medications

Between 10% to 30% of those who are affected with ADHD may not respond to stimulants or may not be able to tolerate associated side effects such as appetite suppression, sleep disturbance, mood difficulties, or exacerbation of comorbid tic disorders. In such instances or when families are unwilling to consider a stimulant, non-stimulant medications can be appealing.

Several nonstimulant medications that affect noradrenergic and/or dopaminergic pathways are effective in the treatment of ADHD; although, their effects are somewhat less than those of stimulants in short-term treatment, and less data exist about the safety profile of nonstimulants in general.

This group includes drugs with noradrenergic, dopaminergic, and serotonergic properties such as venlafaxine; monoamine oxidase inhibitors (MAOIs) (selegiline and moclobemide); buspirone; cholinergic drugs such as donepezil; carbamazepine; neuroleptics; and theophylline.[32 – 34] Atomoxetine is a highly selective norepinephrine reuptake inhibitor that is the best-studied, and the first and only nonstimulant medication approved by the FDA for the treatment of ADHD in both youth and adults.[26 35, 36] Unlike the stimulant medications, atomoxetine does not have the potential for abuse and is not a controlled substance.

Atomoxetine increases the concentrations of norepinephrine and dopamine in the prefrontal cortex, where dopamine is primarily inactivated by the presynaptic norepinephrine transporter. It does not affect the other brain regions such as the striatum and nucleus accumbens. This criterion explains why the drug does not have the potential for abuse.

Several studies have demonstrated the efficacy of atomoxetine for ADHD in both short-term and long-term trials (even lasting for 24 months). Total daily doses range from 1 to 1.8 mg/kg/day, and the drug improves the ADHD symptoms, as well as in family and social functioning.

Atomoxetine is generally started at 0.5 mg/kg/day and will be increased to approximately 1.2 mg/kg/day after three or four days, if tolerated. The maximum recommended dosage in youth is 1.4 mg/kg/day or 100 mg, whichever is less.

Unlike stimulants, which show effects on core ADHD symptoms virtually immediately, symptoms improvements are usually shown after one to two months of prescribing the recommended dosage of atomoxetine.[26 35, 36] In addition, atomoxetine can generally be given once daily with resultant “around the clock” coverage.

The drug is reasonably well tolerated, with few serious safety concerns. Only two cases of atomoxetine-associated hepatotoxicity have been reported recently.[26 35, 36] Other than slight increases in the pulse and blood pressure, the effects on cardiovascular system are not clinically significant. Other common side effects include weight loss, poor appetite, nausea, insomnia, fatigue, dizziness, and irritability. Urinary retention and sexual dysfunction have been reported in adults. [26 35, 36]

Atomoxetine is metabolized primarily by cytochrome P450-2D6 (CYP2D6). Roughly, 7% of the Caucasian population are poor metabolizers and are potentially more vulnerable to experiencing the side effects of the drug on typical dosages. So, it is necessary to adjust the dosage when prescribing atomoxetine in combination with CYP2D6 inhibitors such as fluoxetine.[26 35, 36]

Venlafaxine, an antidepressant with both serotonergic and noradrenergic properties, has been investigated as a possible alternative treatment in ADHD. It has no significant affinity for muscarinic, cholinergic, histaminic, or alpha-1-adrenergic receptors. It has a short half-life and is given in divided doses.[34]

Some small open-label studies suggest that venlafaxine may be an effective medication (50 –75% response rate in completers; 25% drop-out due to side effects) in the treatment of the core symptoms of ADHD in children, adolescents, and adults.[34] Its side effects include irritability, insomnia, and gastrointestinal disturbance.

Two open-label studies of fluoxetine in a total of 51 children and adolescents with ADHD suggested that fluoxetine may be beneficial in the treatment of ADHD, but the effectiveness of serotonin reuptake inhibitors (SRIs) in the treatment of core ADHD symptoms is not supported by clinical experience. Considering the lack of comparison trials, the role of the SRIs in the treatment of ADHD remains unclear.[26]

A small number of studies with MAOIs suggested that both irreversible and reversible MAOIs may improve ADHD symptoms.[32, 36] The mechanism of MAOIs in reducing ADHD symptoms is probably related to their ability to block the metabolism of noradrenaline and dopamine. However, the use of irreversible MAOIs (e.g., phenelzine, tranylcypromine) is strongly limited because of their potential for hypertensive crises, the problems with dietary violations (tyramine-containing foods), and the drug interactions. Reversible MAOIs (e.g., moclobemide, selegiline) need to be further evaluated.

Buspirone has a high affinity to pre- and post-synaptic 5-hydroxytryptamine 1_A (5-HT 1_A) receptors as well as a modest effect on the

dopaminergic system plus alpha-adrenergic activity.[32 – 34] An open clinical trial on 12 children with ADHD who were treated with 0.5 mg/kg/day (range: 15 to 30 mg/day) in two divided doses suggested that buspirone helped to improve hyperactivity, impulsivity, and oppositionality. However, results from a recent multicenter controlled clinical trial of transdermal buspirone failed to distinct it from placebo in a large sample of children with ADHD.[34]

A recent multicenter, open-label, and short-term dose titration study suggested that GW320659, a chemically novel inhibitor of noradrenaline and dopamine reuptake, may have clinically relevant efficacy in treating symptoms of ADHD.[37]

In recent years, evidence has emerged that nicotinic dysregulation may contribute to the pathophysiology of ADHD. Central nicotinic activation stimulates the release of several neurotransmitters such as dopamine, noradrenaline, acetylcholine, 5-hydroxytryptamine, gamma-aminobutyric acid (GABA), and endorphins. It can also improve vigilance, attention, and executive function, probably by its noradrenergic or dopaminergic effects.[32] But the therapeutic uses of nicotine are limited due to its side effects. Nausea, gastric pain, itching under the patch, and dizziness are the most frequently reported adverse effects associated with transdermal nicotine.[34]

Other cholinergic drugs such as acetylcholinesterase inhibitors (donepezil) as well as novel nicotinic analogues (ABT-418), have also been used in treating ADHD. In a double-blind, placebo-controlled, randomized, and crossover study, ABT-418, a novel cholinergic-activating agent with structural similarities to nicotine, has been a potentially useful agent for the treatment of adults with ADHD. At a dose of 75 mg daily, the response rate was significantly higher than placebo (40% versus 13%). Treatment with ABT-418 was relatively well tolerated; dizziness and nausea were the most frequently reported adverse effects.[32]

Alternative medicine

Approximately 70% of the children treated show improvement in the primary ADHD symptoms and in comorbidity such as conduct disorder, although the benefits may not hold beyond two years.[37]

Despite the well-established efficacy and safety of stimulants for ADHD, alternative medicines are still needed for several reasons.[38] About 30% of children and adolescents with ADHD may not respond to stimulants or may be unable to tolerate potential adverse events such as decreased appetite, mood lability, and sleep disturbances. Although stimulants do not increase the risk for later substance abuse in ADHD, concerns have been raised about special prescription rules, and a potential for abuse by persons other than the ADHD subjects.[38, 39]

Herbal medications have been shown to ameliorate ADHD-related behaviors in individuals without this disorder.[39] For example, *Ginkgo biloba* is somewhat effective for dementia and memory impairment. A review of 40 controlled trials found at least a partial positive outcome in nearly all subjects who had cerebral insufficiency and treated with *Ginkgo* (e.g., difficulties of concentration and memory). This finding may help to provide support for using *Ginkgo* in children with ADHD, especially those who are primarily inattentive. Moreover, *Ginkgo* improves cerebrovascular blood flow and attention may help to reduce hyperactivity due to boredom and lack of focus.[38,39]

A recent study showed that *Passiflora* might be a novel therapeutic agent for the treatment of ADHD. One of its advantages is the tolerable side effect profile.[40]

Behavioral treatment

Behavioral interventions encompass specific techniques such as providing rewards for desired behaviors (e.g., positive reinforcement) or exacting consequences for failure to meet expected goals (e.g., punishment, response cost).[41 – 43] Teaching the behavioral techniques to the parents and the use of behavioral interventions in the classroom can improve the behavior of youth with ADHD. Classroom management generally includes increasing the structure of activities and the application of rewards and consequences using point systems or token economies. A common technique involves working to establish a school-home daily report card that can be used to reward the child for meeting specific target outcomes at home or in the classroom. When ADHD impacts a child's educational performance, schools have the obligation to make classroom adaptations. Classroom accommodations may include preferential seating, a decreased burden of assignments and homework, and increased time for test taking.[41 – 43]

Conclusion

Stimulant medication continues to be an

effective treatment for the core symptoms of ADHD. Treatment must be individualized and the other supports such as parent information and training, behavioral treatment, and intervention for comorbid conditions are essential components in managing a child with this disorder.

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