Advances and Considerations in Attention-Deficit/Hyperactivity Disorder Pharmacotherapy

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Received: 7 Jul. 2011 , Accepted: 17 Sep. 2011

Abstract- Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neuropsychiatric disorder associated with significant impairments in occupational, academic, neuropsychological, and social functioning. Central nervous system (CNS) stimulants are recommended as first-line medication therapy for children. CNS stimulants include formulations of methylphenidate and amphetamine derivatives and are available in a large variety of immediate- and extended-release preparations. Extended-release preparations are often preferred to limit drug administration during school or work and may help to limit side effects associated with rapid fluctuations in serum concentration. Stimulant medication is by far the most commonly used treatment in managing children with ADHD, 10-20% of those who take such medication do now show clinically significant improvements in their primary ADHD symptom. Even when a favorable response is obtained, some children experience side effects that are of sufficient occurrence and severity to prevent continued use of stimulant medication. In such instances or when families are unwilling to consider a stimulant, non-stimulant medications may be appealing. This review focuses on etiology, assessment and treatment of ADHD with various stimulant and non-stimulant agents.

Acta Medica Iranica, 2011; 49 (8): 487-498

Keywords: ADHD; Non-stimulants; Psychopharmacology; Stimulants

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most publicized and controversial psychiatric disorders in the United States and one of the most studied of all psychological disorders in children (1,2). It is one of the most common psychiatric conditions estimated to affect 5-10% of all children and predisposes them to impaired academic, familial, social, vocational, and emotional functioning if untreated (1,2). Once considered a childhood disease, it is now known that approximately 40% to 70% of children with ADHD will have symptoms persist into adolescence and adulthood.

ADHD is characterized along two symptom domains, inattention-disorganization and hyperactivity-impulsivity. Individuals with ADHD have significant difficulty in the areas of attention, response inhibition, and self-regulation. The effects of ADHD are life encompassing and are not limited to the 8-hour school day. Usually, some symptoms that cause impairment are present before age seven. Classification of what constitutes ADHD has changed dramatically over the last two decade, with successive revisions of the Diagnostic and Statistical Manual four (DSM) (3). Current DSM IV classification for combined type ADHD requires a minimum of six out of nine symptoms of inattention and a minimum of six out of nine symptoms of hyperactivity/impulsivity. In addition some impairment from the symptoms is present in two or more settings (e.g., at home and at school) and clear evidence of significant impairment in social, school, or work functioning. The DSM IV also allows the classification of two subtype disorders: (i) predominantly inattentive where the child only meets criteria for inattention; and (ii) predominantly hyperactive–impulsive where only the hyperactive–impulsive criteria are met (3-5). Effective treatment depends on appropriate diagnosis of ADHD. A comprehensive medical evaluation of the child must be conducted to establish a correct diagnosis of ADHD and to rule out other potential causes of the symptoms. ADHD can be reliably diagnosed when appropriate guidelines are used (6-10).

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Epidemiology

The prevalence of ADHD is difficult to establish due to differences in diagnostic criteria over the past several decades, differences in perception of symptoms between informants, and cultural differences. In the United States, however, the estimated prevalence of ADHD among children is 8% to 10%. The DSM-IV-Text Revised estimates the prevalence in school-aged children to be 3% to 5% (11). Children with ADHD are the most common category of referrals to child and adolescent psychiatric health services. In elementary school-aged children, the ratio of boys to girls is typically 2 to 1 and up to as much as 9 to 1 in clinical settings, but approximates 4:1 in community epidemiological surveys (12). Teachers identify fewer girls than boys with ADHD symptoms. The male to female ratio ranges from 4:1 for the predominantly hyperactive-impulsive type and 2:1 for the predominantly inattentive type. Interestingly, even among children rated by teachers as meeting criteria for any subtype of ADHD, fewer girls than boys receive an ADHD diagnosis or stimulant treatment (13-15).

Diagnostic criteria

There are two groups of nine symptoms: inattention and hyperactivity-impulsivity (subdivided into two groups). Inattention includes failing to give close attention to details or making careless mistakes, difficulty sustaining attention, not listening, not following through, difficulty organizing, avoidance or dislike of sustained mental effort, losing things, easily distracted, and forgetful. Hyperactivity includes six symptoms: fidgety, out of seat, running or climbing excessively, difficulty playing quietly, on the go or as if driven by a motor, and talking excessively. The three impulsivity symptom criteria are: blurting out answers, difficulty awaiting turn, and often interrupting or intruding on others (6-8).

The predominantly inattentive type is more common in females and, together with the combined type, seems to have a higher impact on academic performance. Children with the predominantly hyperactive-impulsive behavior are more aggressive and impulsive than those with the other two types of ADHD and tend to be unpopular and highly rejected by their peers (11). The combined type causes more impairment to global functioning, compared to the other two types. The behaviors used to meet the criteria must be inconsistent with the patient's developmental level and intellectual ability and have been present for at least six months (12). Functional impairment must be present in two or more settings, with clinically significant impairment in social, academic, or occupational functioning. By definition, the diagnosis of ADHD cannot be made if the symptoms occur exclusively in the presence of a pervasive developmental disorder, schizophrenia, or other psychotic disorder or if they are better accounted for by another psychiatric disorder. Signs of ADHD may not be observable when the patient is in highly structured or novel settings, engaged in an interesting activity, receiving one-to-one attention or supervision, or in a situation with frequent rewards for appropriate behavior. Conversely, symptoms typically worsen in situations that are unstructured, minimally supervised, boring, or require sustained attention or mental effort (11,12). Core deficits include impairment in rule-governed behavior across a variety of settings and relative difficulty for age in inhibiting impulsive response to internal wishes or needs or external stimuli (6-8,10).

Assessment

The parent interview is the core of the assessment process. It is often difficult to confirm the diagnosis of ADHD by the interview with the child or adolescent alone since some children and most adolescents with ADHD are able to maintain attention and behavioral control while in the office setting (16). Many lack insight into their own difficulties and are not willing or able to report them accurately. Both parent and child interviews are used to rule out other psychiatric or environmental causes of symptoms. Structured interviews of parents may be useful in assuring coverage of ADHD symptoms, or a DSM-IV symptom checklist may be used. Standardized interviews of children and adolescents are less useful for ADHD symptoms but may aid in discovering alternative or comorbid diagnoses. Queries about family history of ADHD, other psychiatric disorders, and psychosocial adversity (e.g., poverty, parental psychopathology or absence, family conflict) are especially important because of their relationship to prognosis (16-18).

Etiology

The causes of ADHD are unknown. Most children with ADHD have no evidence of gross structural damage in the central nervous system. ADHD does appear to run in families with approximately one-third of affected children having a first degree relative with a history of ADHD (17,18). Recent functional MRI brain studies indicate that the disorder may be caused by atypical functioning in the frontal lobes, basal ganglia,

corpus callosum, and cerebellar vermis. Pharmacological studies have also implicated dysregulation of frontal-subcortical-cerebellar catecholaminergic circuits in the pathophysiology of the disorder. Central catecholaminergic neurotransmission systems appear to be involved in the pathophysiology of ADHD. Effective medication treatments for ADHD appear to modulate dopaminergic and noradrenergic neurotransmission in the prefrontal cortex. Children with ADHD as a group show differences from unaffected children in the volumes of specific brain regions in imaging studies (i.e., frontal lobes, temporal gray matter, caudate nucleus, and cerebellum) (18). The cause of such differences is unknown and brain imaging is not useful as a diagnostic tool if used to differentiate youth with ADHD from those without. Traumatic brain injury has been associated with ADHD but probably accounts for ADHD in only a small percentage of affected children (18,19). Environmental factors may also be relevant. Exposure to maternal tobacco or alcohol use in utero may increase the risk of ADHD in offspring. Exposure to lead early in life has 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 (19-22).

Treatment

The three treatments that have been validated as being significantly effective for ADHD are: (1) medication management, (2) behavioral therapy, and (3) a combination of the two approaches (23). While there is no doubt that medication in the treatment of ADHD is effective, an estimated 30 percent of affected individuals do not adequately respond or cannot tolerate the medication. Considering the above facts, medications are short-acting drugs that require multiple administrations during the day with their impact dependent on compliance and the need to take treatments during school (23).

Medication management

Stimulant medications

Psychostimulant medications are the first choice in medications for ADHD. Approximately 70 percent of children treated show improvement in primary ADHD symptoms and in co-morbidity such as conduct disorder although the benefits may not hold beyond two years (23). Stimulant medication is by far the most commonly used treatment in managing children with ADHD. Ten to twenty percent of those who take such medication show clinically significant improvements in their primary ADHD symptom (24). Even when a favorable response is obtained, some children experience side effects with significant occurrence and severity to prevent continued use of stimulant medication. In light of these issues, many parents prefer not to use any form of medication in treatment of their child (24,25). The most common side effects are reduced appetite, insomnia, increased anxiety and depression, tics, and irritability (25). Another side effect associated with taking medications is the potential emotional impact on the child (24,25). The fact that stimulants are controlled substances continues to fuel worries in children and families. Child psychiatrists say that these fears are based on lingering concerns about the abuse potential of stimulant drugs by the child or family member, the possibility of diversion, and safety concerns regarding the use of a controlled substance by patients who are impulsive and frequently have antisocial tendencies (24,25). Currently, methylphenidate (MPH) and amphetamine are the drugs of choice (26,27). Methylphenidate is the most widely used and best studied stimulant medication. Dextroamphetamine (d - amphetamine) and mixed amphetamine salts (d, l – amphetamine) are also quite commonly used and have been reasonably well studied (28). Recent reports of sudden death in a handful of youth treated with amphetamine salts have generated understandable concern. It appears that the majority of reported cases occurred in youth with pre-existing structural cardiac abnormalities, but a few cases were not associated with such findings. At the present time, existing knowledge should be shared with patients and families, and a careful history of pre-existing cardiac problems, “drop attacks”, or family history of sudden death should be explored prior to initiating treatment with amphetamine salts. Pemoline use has been discouraged by reports of rare but potentially fatal hepatoxicity in association with its use (26).

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 (29,30). Consequently, given the current state of knowledge, it has been recommended that children who fail to respond to one stimulant should be tried on another. Approximately 40% of youth with ADHD will respond equally well to methylphenidate or amphetamine preparations, but about one-third will respond better either to methylphenidate or an amphetamine based preparation (31,32).

Standard preparations of methylphenidate or amphetamine are relatively short acting, with durations of action ranging from 3 to 6 hours and thus require two or three administrations per day (26). The development of new stimulant formulations that allow for the rapid onset of action and a longer duration of effect have been important developments in the treatment of ADHD since their use can eliminate the need for multiple doses of a short acting stimulant across the day and avoids dosing during school. These preparations can be employed as the initial stimulant treatment for ADHD, eliminating the need to begin with a short acting preparation followed by conversion to a longer acting preparation (33).

Dexmethylphenidate extended release

Methylphenidate is a 50: 50 mixture of two isomers, dextro (d)-threo-methylphenidate and levo (l)-threo-methylphenidate. When taken orally, methylphenidate undergoes enteric and hepatic enantioselective de-esterification to ritalinic acid, resulting in a limited bioavailability of approximately 22–50% for d-methylphenidate and 1% for l-methylphenidate (34). Dexmethylphenidate (Focalin®) is the single d-isomer that was shown to be more potent than (d,l)-methylphenidate in reducing motor activity in rats and humans. Dexmethylphenidate was FDA approved in the US in 2001 for use in children aged ≥6 years with ADHD. Oral dexmethylphenidate extended release (XR) capsules have a bimodal pharmacokinetic profile because each capsule contains half the dexmethylphenidate dose as immediate release (IR) beads and half as enteric-coated, delayed-release beads (34,35). Following a single dose of oral dexmethylphenidate XR, the first dexmethylphenidate peak plasma concentration is reached at 1.5 hours, and a second peak is reached at 6.5 hours after drug administration. A single dose of dexmethylphenidate XR 20 mg is bioequivalent to two doses of dexmethylphenidate IR 10mg given 4 hours apart. The recommended initial treatment with dexmethylphenidate XR is a 5mg capsule each morning (26). Dosing may be increased by 5mg/week up to the maximum FDA-approved dose of 20 mg/day until optimal benefit is achieved. Regulatory approval was based on one double- blind study of 103 children and adolescents (aged 6–17 years) treated with dexmethylphenidate XR or placebo for 7 weeks. Flexible daily dosing (5–30 mg/day) for 5 weeks established maximum clinical benefit after which the optimal dosage was maintained for 2 weeks (36). Dexmethylphenidate XR has demonstrated superior efficacy to placebo and appears similar in efficacy to methylphenidate. Its advantage is a longer lasting effect at a lower dose than methylphenidate (26, 36). Benefit in reducing ADHD symptoms is typically observed within 30 minutes and lasts up to 10 hours at the FDA maximum recommended dose (20 mg/day) (26,35,37).

Methylphenidate osmotic-release oral system (CONCERTA®)

CONCERTA® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components (38,39). There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate.

Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice (38-40). The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA®. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that CONCERTA® extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized. Concerta is intended to provide rapid onset of effect and subsequent continuous delivery of drug with a smooth concentration-time curve (38-40).

A large multicentre, randomized, clinical trial was used to determine the safety and efficacy of Concerta in an outpatient setting (41). A total of 282 children with ADHD (ages 6–12 yr), were randomized to placebo (n=90), MPH IR t.i.d. (n=97), or Concerta once a day (n=95) in a double-blind, 28-d trial. Children in the Concerta and MPH IR groups showed significantly greater reductions in core ADHD symptoms than did children on placebo throughout the study. Concerta was

well tolerated. There was a mild appetite suppression but no sleep abnormalities.

Methylphenidate transdermal system (MTS) (Daytrana®)

As a patch, the methylphenidate transdermal system (Daytrana®; Shire US Inc., Wayne, PA, USA) delivers methylphenidate into the systemic circulation directly through the skin, reducing first-pass metabolism by the liver (26). It was approved for use in children in 2006 and for adolescents in 2010 (26). The MTS combines MPH, acrylic polymers, and silicone adhesives in a formulation that concentrates the drug and facilitates its diffusion into the skin. The dose of MPH delivered is dependent on the surface area of the patch and the length of time that the patch is worn on the skin. The onset of action is considerably slower than for oral preparations. Heat is known to increase the rate of diffusion. After application, the elapsed time until MPH takes effect can be 2 hours. Behavioral efficacy has been measured at 2 hours and reported clinically at 1 to 2 hours (26). Findling *et al.* studied 270 children 6-12 years of age with ADHD in an intention-to-treat analysis, randomized in a 1:1:1 pattern to MTS, Osmotic-Release Oral System (OROS) MPH and placebo conditions in a parallel-group, dose-titration study (42). Average doses were 20-30 mg for MTS and 36-54 mg for MPH. Both active treatments resulted in an approximately twofold improvement in ADHD Rating Scale IV versus placebo (42). Similar improvements were found in the active treatment groups on the Connors Teachers Rating Scale. Significant improvements in the Connors Parent Rating Scale - Revised were found for morning and afternoon, but not at evening hours (42). However, an earlier study of patients with ADHD enrolled in a summer treatment program found that parents reported that treatment effects persisted into the evening despite a 3:30 pm patch removal time

Lisdexamfetamine dimesylate (Vyvanse®)

Lisdexamfetamine dimesylate (Vyvanse®; Shire US Inc., Wayne, PA, USA) is the first long-acting prodrug stimulant and is the most recent stimulant formulation approved for the treatment of ADHD in children aged 6–12 years and in adults. Indeed, Lisdexamfetamine (LDX) was approved by the FDA for treating ADHD in children in 2007 and was approved for use in adults in 2008 (26). Vyvanse® is a therapeutically inactive molecule. After oral ingestion, Vyvanse® is converted to l-lysine and active d-amfetamine, which is responsible for the therapeutic effect. The cleaved d-amphetamine then crosses the blood-brain barrier and exerts the known effects of amphetamine: occupation of the dopamine transporter, which thus diminishes reuptake of dopamine and norepinephrine, and also facilitates release of presynaptic dopamine into the extracellular space. However, rate-limitation of the cleavage slows the availability of d-amphetamine to the brain. The onset of action of LDX is slower than that of IR amphetamine, and efficacy has been observed to last 12 to 14 hours. It is available in 20- mg, 30-mg, 40-mg, 50-mg, 60-mg, and 70-mg capsules. The conversion rate of lisdexamfetamine to dextroamphetamine base is 0.2948, so a 30-mg strength LDX capsule is molecularly equivalent to an 8.844-mg dextroamphetamine base. The recommended starting dose for children and adults is a fixed dose of 30 mg with titration intervals of 10 mg. The approval of lisdexamfetamine was based on data from two controlled trials in 6- to 12-year-olds. As lisdexamfetamine maintains d-amfetamine inactive until metabolized, it is theorized to discourage the misuse and abuse that has been commonly associated with other stimulants (43). Additionally, lisdexamfetamine may benefit children who require a less varied absorption pattern than that of XR mixed amfetamine salts, with data supporting lisdexamfetamine having superior effect over placebo which lasts up to13 hours.(44) On the other hand, lisdexamfetamine duration of effect may be too long for some younger children.

Non-stimulant medications

Between 10 to 30% of those 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 (45). In such instances or when families are unwilling to consider a stimulant, non-stimulant medications may be appealing. Several non-stimulant medications that affect noradrenergic and/or dopaminergic pathways have demonstrated efficacy in the treatment of ADHD. Though effect sizes are probably somewhat comparable with methylphenidate in trials, less data has accumulated regarding the safety profile of nonstimulants in general. Nevertheless, this group includes drugs with noradrenergic, dopaminergic and serotoninergic properties such as venlafaxine, monoamine oxidase inhibitor (selegiline and moclobemide), buspirone, amantadine, cholinergic drugs, carbamazepine, neuroleptics and theophylline (45-49).

The U.S. Food and Drug Administration (FDA) approved Stattera® (atomoxetine) (Eli Lilly and Co., Indianapolis, IN) in November 2002 as a new non-stimulant treatment for ADHD. Atomoxetine is a highly selective norepinephrine reuptake inhibitor that is the best studied and the only nonstimulant medication approved by FDA for treatment of ADHD in both childeren and adults (50-52). Unlike stimulant medications, atomoxetine does not appear to have abuse potential and is not a controlled substance. Atomoxetine increases concentrations of norepinephrine and dopamine in the prefrontal cortex, where dopamine is primarily inactivated by the presynaptic norepinephrine transporter, but not in other brain regions such as the striatum and nucleus accumbens, which may explain the drug's lack of abuse potential (45). Several studies have demonstrated the efficacy of atomoxetine for ADHD at total daily doses ranging from 1 to 1.8 mg/kg/day, with the drug producing improvements in ADHD symptoms, as well as in family and social functioning, in both short term and long term trials lasting as long as 24 months. The drug is generally started at 0.5 mg/kg/day, then increased after three or four days if tolerated to approximately 1.2 mg/kg/day. The maximum recommended dosage in children is 1.4 mg/kg/day or 100 mg, whichever is less. Unlike stimulants, which tend to show effects on core ADHD symptoms virtually immediately, patience is required when using atomoxetine, as some patients may still show improvements in one to two months after achieving the recommended dosage (50-52). The drug is reasonably well tolerated, with few serious safety concerns until two recent case reports of atomoxetine associated hepatotoxicity. Other than slight increases in pulse and blood pressure, cardiovascular effects are not generally clinically significant. Common side effects include weight loss, poor appetite, nausea, insomnia, fatigue, dizziness and irritability. Urinary retention and sexual dysfunction have been reported in adults. Atomoxetine is metabolized primarily by cytochrome P450-2D6 making t he roughly 7% of the Caucasian population who are poor metabolisers potentially more vulnerable to experiencing side effects on typical dosages, and making it necessary to consider dosage adjustments when using atomoxetine in combination with CYP2D6 inhibitors such as fluoxetine (53,54).

Several open and controlled trials of tricyclic antidepressants, such as desipramine, imipramine and nortriptyline have indicated the efficacy of TCAs in the treatment of ADHD. It has been reported that their activity in ADHD stems from their actions on noradrenaline and dopamine reuptake (25,45). Advantages of the TCAs include their relative long half-life eliminating the need to administer medication during school hours, absence of abuse potential, and putative positive effects on mood and anxiety, sleep, and tics (25,45). Nevertheless, TCAs show a narrower margin of safety than stimulants, along with a wider range of potential side effects (25,45).

Venlafaxine, an antidepressant with both serotonergic and noradrenergic properties, has been investigated as a possible treatment alternative in ADHD. It has no significant affinity for muscarinic, cholinergic, histaminic, or alpha-1-adrenergic receptors and has a relative short half life, and is given in divided doses (45). 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 treating the core symptoms of ADHD in children and adolescents and adults (55). Side effects include irritability, insomnia, and gastrointestinal disturbance. In addition, one recent double-blind randomized and active controlled trial reported the efficacy of venlafaxine in the treatment of ADHD (48).

While two open-label studies of fluoxetine in 51 children and adolescents with ADHD suggested that fluoxetine may be beneficial in the treatment of ADHD, the effectiveness of serotonin reuptake inhibitors (SSRIs) in the treatment of core ADHD symptoms is not supported by clinical experience. Lack of comparison trials, makes the role of the SSRIs in ADHD at best unclear (45,56).

A small number of studies with monoamine oxidase inhibitors (MAOIs) suggested that irreversible MAOIs and reversible MAOIs may improve ADHD symptoms. 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 by their potential to generate hypertensive crises via dietary violations (tyramine-containing foods) and drug interactions. Reversible MAOIs (e. g., moclobemide, selegiline) need to be further evaluated.

Buspirone has high affinity to pre- and post-synaptic 5-HT 1-A receptors as well as a modest effect on the dopaminergic system plus alpha-adrenergic activity (45,46). An open clinical trial of 12 children with ADHD treated with buspirone 0.5 mg/kg/day (range 15 to 30 mg/day) in two divided doses suggested that it helps to reduce hyperactivity, impulsivity and oppositionality (57). However, results from a recent

multi-site controlled clinical trial of transdermal buspirone failed to separate it from placebo in a large sample of children with ADHD (45). A recent multicenter, open-label, 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. Bupropion and the α-adrenergic agonists clonidine and guanfacine also have proven to be efficacious in the treatment of ADHD (45).

A meta-analysis of clinical trials involving clonidine for ADHD treatment suggested that clonidine is effective as second-line therapy, although the effect size of clonidine is lower than that of the psychostimulants. This study also indicated that there was a high rate of side effects associated with clonidine treatment, the most common of which were sedation, irritability, sleep disturbance, hypotension, dry mouth, and dizziness (58). It has been reported that clonidine in combination with psychostimulant medication can reduce conduct symptoms associated with attention-deficit/hyperactivity disorder. This combination is well tolerated and unwanted effects are transient (59). An XR preparation of clonidine is currently in development for use in pediatric ADHD (26).

Guanfacine is less sedating and has a longer duration of action than clonidine, which may make it more convenient to use with children and adolescents. A randomized, placebo-controlled study of guanfacine in 34 children with tic disorders and ADHD suggested that guanfacine is well-tolerated when administered three times daily. Improvements in behavior were similar to or better than those reported for other nonstimulant trials, but they were lower than improvement levels observed with psychostimulant use (60). An XR formulation of guanfacine was approved on Sep. 4, 2009 by the US FDA to treat ADHD in 6-17 year olds (61). Guanfacine XR has a mean half-life of 18 hours in adolescents and 14 hours in children, with steady state daily plasma concentrations usually reached within 5–7 days when taking 1-4mg/day (61).

It has been shown that bupropion is effective in improving ADHD symptoms (45,62). Generally, bupropion appears to be less effective than stimulants (32), but more studies are needed. A double-blind, crossover study in 15 patients with ADHD (7 to 17 years old) found methylphenidate (mean dose 0.7 mg/kg/day) and bupropion (mean dose 3.3 mg/kg/day) both effective and not different in their overall efficacy as medications for ADHD. Bupropion appears to be well tolerated in most children and adolescents. Bupropion's side effects include irritability, insomnia, drowsiness, fatigue, headache, dry mouth, sweating, constipation, nausea, and dermatological reactions. While it does not have the cardiovascular risks associated with the tricyclic antidepressants or the substance abuse potential of the stimulants, concerns remain about an increased risk of seizures. Therefore, regular control examinations of the EEG are recommended (62).

Modafinil is structurally different from the psychostimulants and has been reported that is effective in improving the symptoms of ADHD (25). It has been suggested that a higher dose of modafinil may be needed in children than that used for treatment of narcolepsy.

Recent double blind clinical trials with placebo or active control found that modafinil significantly improved symptoms of ADHD both at school and at home and was well tolerated by children and adolescents (63, 64). Abrupt discontinuation of modafinil was not associated with symptoms of withdrawal or with rebound of ADHD symptoms (65).

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 including dopamine, noradrenaline, acetylcholine, 5-hydroxytryptamine, gamma-aminobutyric acid (GABA) and endorphins and has been shown to improve vigilance, attention and executive function, probably by its noradrenergic or dopaminergic effects (50). Although controlled clinical trials in children, adolescents, and adults with ADHD have indicated that nicotinic receptor modulation may be a potentially useful strategy for the treatment of ADHD, the therapeutic uses of nicotine are limited due to side effects. Nausea, stomach ache, itching under the patch and dizziness are the most frequently reported adverse effects associated with transdermal nicotine (66). Other cholinergic drugs, such as acetylcholinesterase inhibitors (donepezil) as well as novel nicotinic analogues (ABT-418), have also been used in treating ADHD. ABT-418, a novel cholinergic activating agent with structural similarities to nicotine, has been found to be a potentially useful agent for the treatment of adults with ADHD in a double-blind, placebo controlled, randomized, crossover study. 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 (25,67).

Diet (nutrition) and ADHD: Zinc and acetyl-L-carnitine

As a trace element, zinc is a cofactor of many cardinal enzymes. In addition, it is an important modulator of neuronal excitability (68). Most recent findings show that the dopamine transporter is regulated by zinc, which directly interacts with the transporter protein (68). So far, it is well known that zinc deficiency is linked to problems in cognitive development evident by alterations in attention, activity, neuropsychological behavior and motor development (68). Akhondzadeh et al. assigned 44 patients with ADHD to either methylphenidate plus zinc or MPH plus placebo in

a double-blind, placebo-controlled trial in order to evaluate the effects of zinc as an adjunct to MPH (68). The zinc sulphate group received 1 mg/kg/day MPH plus zinc sulfate (15 mg/day elemental zinc) and the placebo group received 1 mg/kg/day MPH plus sucrose for 6 weeks. At the end of 6 weeks, with 40 eligible patients remaining for analysis, the zinc group outperformed the placebo group on measures of both ADHDS scores rated by parents and teachers.

Carnitine (L-3-hydroxytrimethylamminobutanoate) is an endogenous compound with well-established functions in intermediary metabolism (5,6). Acetyl-L-carnitine (ALC) is an obligate for optimal mitochondrial fatty acid oxidation. A study conducted by van Oudheusden and Scholte showed that carnitine therapy has significant beneficial effect on hyperactive–impulsive behavior in school-age boys with ADHD without showing any adverse side effects. Nevertheless, Akhondzadeh et al used Acetyl-L-carnitine as an adjunctive therapy in the treatment of attention-deficit/hyperactivity disorder in children and adolescents in a placebo-controlled trial (69). They reported that administration of ALC as adjunctive therapy in the treatment of ADHD in children and adolescents has no beneficial effect. Nevertheless, in this study, those in the ALC group experienced fewer adverse events than the placebo group in particular regarding headaches and irritability (69).

Alternative medicine

Approximately 70% of children treated show improvement in the primary ADHD symptoms and in co-morbidity such as conduct disorder, although the benefits may not hold beyond two years (70). Despite the well-established efficacy and safety of stimulants for ADHD, alternative medicines are still needed for several reasons (70). 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 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 (71-72). Herbal medicines have been shown to ameliorate ADHD related behaviors in individuals without this disorder (70-72). For example, Ginkgo biloba is somewhat effective for dementia and memory impairment. A review of 40 controlled trials of Ginkgo biloba found at least a partial positive outcome in nearly all subjects who had cerebral insufficiency (eg, 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 and may help to reduce hyperactivity due to boredom and lack of focus (73). However, a recent double blind, randomized and active controlled trial does not support the application of Ginkgo biloba in the treatment of ADHD (74). A study by Akhondzadeh et al., showed that Passiflora incarnata may be a novel therapeutic agent for the treatment of attention deficit hyperactivity disorder. In addition, a tolerable side effect profile may be considered as one of the advantages of Passiflora in the treatment of attention deficit hyperactivity disorder (75).

Discussion

Pharmacotherapy continues to be the mainstay of treatment for ADHD. Despite the efficacy of short-acting stimulants, they can “wear off” during the day, which may increase symptoms of inattention during late morning or afternoon activities (11). Therefore, multiple doses during the day may be required to achieve continuous symptom management. Generally, longer-acting formulations may eliminate the need for in-school medication administration and provide ongoing clinical effect during the school day (25,45). Within the past few years, several second generation, extended-release, long-acting stimulants have been developed and evaluated for treating children with ADHD (45). Despite the promising results for the use of non-stimulant drugs in the treatment of ADHD, more large scale randomized clinical trial trials with placebo and stimulants control are needed to better define the role of alternative pharmacological medications in the treatment of ADHD. Polypharmacy with stimulant and

non-stimulant medications including herbal medicines should be investigated in controlled clinical trials as specific subgroups may have differential response. In conclusion, these pharmacological developments provide additional treatment options for ADHD children and adolescents, with ongoing work towards additional novel interventions of pediatric ADHD.

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