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Pharmacologic Treatment of Attention Deficit Disorder in Children and Adolescents: Executive Function Agents, Stimulants, and Sympathomimetic Amines

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Abstract

In the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents, the prescriber may consider both stimulants and non-stimulant medications; in addition, there are some over the counter substances and adjunct medications that may be helpful in mitigation or resolution of symptoms. Behavioral, environmental and psycho-social approaches should be instituted in association with pharmacology and extra caution and conservatism should be used in all children and adolescent patients. When making clinical decisions, it is important to consider use of both immediate release and sustained release stimulant preparations, as well as to carefully consider first line agents as well as second line or adjunct agents. It has been long recognized that the prominent central nervous system neurochemicals intimately involved with ADHD symptoms affect dopamine and/or norepinephrine receptor systems.

Keywords: Attention-deficit/hyperactivity disorder; ADHD; Stimulants, dopamine; Norepinephrine; Children; Adolescents; Psychotropic medication

Introduction

For treatment of ADHD, stimulants affect dopamine and should be considered first line agents proven to exhibit the highest efficacy in mitigation of symptoms in most patients. Agents that affect dopamine and/or norepinephrine appear to impact ADHD. The Food and Drug Administration approved Atomoxetine and long-acting alpha-2 adrenergic agents for the treatment of ADHD. Other medications such as bupropion and tricyclic antidepressants may be used as off label options for symptoms. Amantadine has indirect effects and may be helpful in modulation of dysfunction of the dopamine system. Modafinil is prescribed for some patients who have failed trials of FDA-approved medication options. This article serves as a brief overview of pharmacology to be considered for the treatment of ADHD.

Stimulant Medications

Methylphenidate and amphetamine are common central nervous system stimulants, also known as sympathomimetic amines. These two are the medications of choice for the treatment of ADHD [1]. There are short acting and long acting options, and issues such as adherence, potential for abuse, diversion, and various side effects should be carefully considered when prescribing. ADHD and the use of stimulants are the most widely published topics in child and adolescent psychiatry. The literature in the area clearly and consistently shows that stimulants are superior in efficacy versus placebo in improving attention span, decreasing impulsivity, and reducing hyperactivity [2,3]. There is solid scientific evidence for the benefit of both short and long-acting formulations. Stimulants undergo metabolism in both the liver and the gastro-intestinal tract, and subsequently excreted by the kidneys.

Patient Case

Tony is a 7-year-old male who presented with his parents for evaluation due to "constantly getting into trouble." Since starting school one year ago he has had a difficult time staying in his seat, can't keep his hands to himself, and frequently gets into altercations on the playground. He has to stay in at recess to finish missing assignments. He needs constant redirection, yells out in class, and gets easily frustrated. His grades have begun to decline, and he has been lying to his parents about school assignments. He frequently blames his teachers, stating they did not tell him he had homework. His mom notes, "I'm so tired of constantly giving him consequences for forgetting his homework at school. It's had a negative impact on our relationship. He is constantly crying and screaming at me. I worry what his future looks like." Mom goes on to note he was always a difficult child who would frequently forget the rules, had a hard time playing quietly, and his room was always a mess.

During the appointment you note Tony has a hard time sitting still, frequently fidgeting in his chair. When he starts playing with the toys in the office he goes from one toy to the next without cleaning up and soon has every toy scattered across the floor. He frequently interrupts his mother and needs frequent redirection.

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Safety Considerations in the Use of Stimulants

Extra caution must be used in patients diagnosed with substance use disorders. Tolerance and physiological dependence are possible when stimulants are used chronically and in an abusive fashion.

A thorough and systematic informed consent discussion reviewing the risks, benefits and potential side effects is necessary prior to and throughout the prescribing process. For patients with the diagnosis of ADHD, the appropriate prescription of stimulants may prevent patients from using illegal substances due to effective treatment of impulsivity, elimination of the need to self-medicate, the reduced risk of depression and anxiety symptoms. Some parents and guardians may ask about the risk of future substance use in children prescribed stimulants, but there is no scientific literature showing that this subgroup is at greater risk than controls [1,2].

Serious cardiac conditions are a contraindication for the use of stimulants. Specifically, Adderall XR is documented to be associated with "serious cardiovascular adverse events and may cause sudden death in patients with pre-existing cardiac structural abnormalities." Children taking stimulants should always be monitored closely for chest pain, pre-syncope, syncope, and shortness of breath. Other contraindications to stimulants include known sensitivity to stimulants and glaucoma. Extra caution should be taken with patients who have history of tics, seizures, autism spectrum disorder, and psychosis. Care should be taken to identify a personal or family history of Bipolar Disorder; stimulants have the ability to induce hypomania and manic episodes in those who are vulnerable. Some patients with ADHD have baseline insomnia, so the medication trial may worsen this condition.

The most common adverse drug reactions and side effects associated with stimulants include insomnia, loss of appetite, nausea, abdominal pain or cramping, headaches, vomiting, mood lability, irritability, sadness, tearfulness, vital sign alterations such as tachycardia and blood pressure changes. Many of these may present during the initial stages of the trial or with dosage changes, and then may resolve.

Rebound effects may occur approximately five hours after the last dose of short acting agents. Symptoms of ADHD recur after the effects of the medication have worn off. In some patients, it is possible for the symptoms to be more exaggerated during these time periods. The presentation may include excitability, talkativeness, overactivity, insomnia, gastrointestinal upset and mild nausea. These symptoms are typically less pronounced with the use of long acting agents, but still may occur approximately 8-12 hours following the last dose.

Patient Case Continued

Mom denies any family history of unexplained death of a child, cardiac structural abnormalities, arrhythmias, myocardial infarction at a young age, cardiac artery disease or stroke. She denies any known cardiac history in Tony and reports he was healthy at birth no cardiac structural abnormalities and no history of heart murmurs or arrhythmias. He does have a history of stomachaches secondary to constipation, which can make him irritable. He has no other past medical history, including no history of seizures. Since there is no family history or personal history of cardiac concerns, his physician discusses the different types of stimulants with Tony's mother and prescribes a long acting Methylphenidate formulation to minimize rebound.

Stimulant Medications Approved for Use in Children and Adolescents

The most frequently prescribed medication class in childhood is stimulants. Zuvekas and Vitiello's twelve-year prospective study reviewing stimulant medication estimates that 3.5% of children in the United States in 2008 was prescribed stimulant medication; this was an increase from 2.4% in 1996 [1]. It is clear that more children today are prescribed stimulants than in previous years.

Of the stimulants approved for the use in treatment of ADHD, the two classes are typically the Methylphenidate (MPH) and the amphetamine classes of the MPH class [1], many of the medications contain both the D and the L enantiomers. The D enantiomer shows greater pharmacologic activity with respect to the efficacy of these medications; thus, Focalin XR was created specifically for its exclusive action on the D enantiomer. Amphetamines are non-catecholamine sympathomimetic amines with central nervous system activity [4,5]. Amphetamines two enantiomers (dextro-[D-] and levo-[L-] have very different levels of pharmacologic activity. The D-isomer is biologically more active than the L-isomer. There are individual variations among patient in the efficacy associated with each isomer. The medications known as "amphetamines" contain both the D and L enantiomers. Medications listed as "dextroamphetamine" contain only the D enantiomer. Adderall XR is a mixed salt amphetamine formulation with dextroamphetamine and amphetamine components.

Non-Stimulant Medications for the Treatment of ADHD in Children and Adolescents

Selective Norepinephrine Reuptake Inhibitors (SNRIs)

Atomoxetine Hydrochloride (Strattera) is an SNRI that selectively inhibits the presynaptic norepinephrine transporter [6]. It is thought that this is the mechanism that treats ADHD symptoms. Atomoxetine was approved by the FDA for the treatment of ADHD in 2002, and it remains one of the few non-stimulant medications approved for this specific diagnosis. By contrast to the rapid quieting of symptoms by stimulants, Strattera will take longer to achieve results.

Some patients do not tolerate stimulants, and others are not reasonable candidates due to abuse or risk of diversion (by either the patient, other family members, or alternate

caregivers). Atomoxetine may be a good option for patients with co-occurring ADHD and tics or anxiety disorders. Another circumstance to consider an atomoxetine trial is when patients fail trials of stimulants. Atomoxetine carries a Black Box Warning from the FDA and therefore all patients being prescribed this agent should be carefully monitored for suicidal thoughts, suicidal behavior, clinical worsening, and any other unusual changes in behavior.

Alpha-adrenergic agonists

The dopamine system is understood to be involved in executive functioning with regard to frontal lobe activity, but the norepinephrine system in some individuals diagnosed with ADHD appears to be related to behavioral and cognitive abnormalities [7,8]. Clonidine is a centrally acting antihypertensive agent. The only formulation with a pediatric indication for ADHD is clonidine hydrochloride extended release; this agent may be used as monotherapy and also as an adjunct to stimulants. IR Clonidine has been approved for use in the treatment of hypertension in older adolescents and adults. Studies are not available to prove the safety in children, but this agent is often prescribed off-label for the treatment of ADHD, anxiety, insomnia, tics, and aggression.

Clonidine is an alpha-2-adrenergic receptor agonist whose action is independent of norepinephrine levels. The three types of subtypes of alpha-2 receptors are 2A, 2B, and 2C. The 2A and 2C subtypes are both widely distributed throughout the central nervous system, including the prefrontal cortex. It is possible that alpha-2 agonists improve attention and behavior through direct stimulation of postsynaptic alpha-2A adrenoceptors. Alpha-2 agonists also bind to alpha-2B and alpha-2C receptors. All three subtypes are associated with sedation; hypotensive effects are related to subtype 2C. Clonidine binds to all three subtypes with some equanimity whereas guanfacine appears to be 15-20 times more selective for the alpha-2A-receptor subtype [8,9]. The most common side effects of clonidine include: sedation, irritability, sore throat, insomnia, nightmares, mood changes, constipation, stuffy nose, increased body temperature, dry mouth, hypotension and decreased pulse rate.

Other Non-Food and Drug Administration Approved Medications

Bupropion

Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL) holds FDA approval for Major Depressive Disorder for adults, but it also used off label for this disorder and for ADHD in children and adolescents [9]. Bupropion is a norepinephrine-dopamine reuptake inhibitor and a nicotinic receptor antagonist. When prescribing for ADHD, it may be used as a sole agent or as an adjunct with other ADHD psychotropic medications. The decrease or resolution of ADHD symptoms may take weeks with the use of bupropion, and it also has a black box warning for suicidal ideation so this must be carefully discussed in the informed consent process. Of note, bupropion has several important contraindications, including anorexia, bulimia, and seizure disorders.

Tricyclic antidepressants

Tricyclic antidepressants (including amitriptyline, imipramine and nortriptyline) affect multiple receptor systems and therefore may improve conditions and disorders including but not limited to depression, anxiety, insomnia, ADHD, nocturnal enuresis, abdominal pain and headache prophylaxis [9,10]. Because TCAs affect many receptor systems, there is increased risk of side effects. Anticholinergic side effects are fairly common, and serious side effects include seizure activity, coma, and death (as in overdose). There is also a black box warning regarding suicidal ideas; this class of medications is rarely prescribed in the child and adolescent patient population.

Modafinil

Narcolepsy medications include modafinil (Provigil), but Provigil may also be prescribed for shift-work sleep disorder and obstructive sleep apnea. It has also been used off label as an adjunct agent for ADHD symptoms.

Alternate Substances/Over the Counter Options for the Treatment of ADHD in Children and Adolescents

Caffeine

Caffeine is a mild stimulant with some evidence of treating frontal lobe function deficits. There is no evidence in the relevant literature that caffeine is therapeutically useful in the treatment of ADHD.

Amantadine hydrochloride

Amantadine has been known for its efficacy in the treatment of sequelae of brain injuries including disinhibition, behavioral dysregulation and agitation [10]. This may be the result of a direct or indirect effect on the central dopamine system. Amantadine is a water-soluble acid salt that is FDA-approved for the treatment of influenza A and for Parkinson's disease. It is also used for extrapyramidal side effects of antipsychotics, pseudo-parkinsonism, akathisia, and neuroleptic malignant syndrome.

It may be helpful for patients who are status/post traumatic brain injury and/or have moderate to severe intellectual disability and present with behavioral dysregulation and impulsivity. For patients with symptoms of agitation and aggression during coma-recovery treatment, amantadine may be helpful for disinhibition, behavioral instability, abulia, and hypoarousal, especially in the first several months of the recovery period. Amantadine should not be discontinued abruptly if neuroleptics are co-administered because patients are at high risk of catatonia and neuroleptic malignant syndrome.

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Omega-3 fatty acids

Liririnen (Vayarin) is a prescription medical food that contains phosphatidylserine omega-3 and can be used for dietary management of ADHD [11]. There is a possible connection between ADHD and low levels of omega-3 fatty acids. Omega-3 fatty acids are well tolerated and no known serious side effects or adverse reactions have been identified. They have been studied in the treatment of many psychiatric disorders, including ADHD. Bozzatello et al. reviewed data from clinical trials, systematic reviews, and meta-analysis published between 1980 and 2015. They concluded that overall efficacy is lacking. Although it holds some promise, there is inconsistency among the existing literature regarding methods, dosing and formulation. More research is needed.

Vitamin D

Vitamin D is a natural compound that has a relationship with ADHD that is unclear but requires further investigation. Khoshbakht et al. found in a meta-analysis that there is a possible connection between the disorder and Vitamin D levels [12]. Children with ADHD had lower serum concentrations of 25-hydroxyvitamin D compared to their healthy child counterparts [13]. It is possible that perinatal suboptimal Vitamin D concentrations were significantly associated with a higher risk of ADHD in adult years. Although more research is required, some parents decide to add this over the counter option as the potential benefits outweigh the risks.

Conclusion

Stimulants should be considered first line agents in the treatment of Attention Deficit Hyperactivity Disorder unless there is a specific contraindication or a compelling reason to use alternate medications. Non-stimulant medications are also another option for this symptom set. There are both immediate release and sustained release preparations, and these options should be carefully considered with regard to adherence, scheduling, tolerability, efficacy, among other factors. Agents that modulate dopamine and/or norepinephrine appear to improve or resolve the symptoms of ADHD. When only partial symptom relief is attained, adjunct agents should be considered. Off-label, Over the Counter and Novel agents may be considered in treatment refractory patients. Under all circumstances, behavioral, environmental and psycho-social approaches should be instituted in association with pharmacology and extra caution and conservatism should be used in all children and adolescent patients.

Author's Note

The patient scenario presented in this article is a composite case written to illustrate certain diagnostic characteristics and to instruct on treatment techniques. The composite case is not a real patient in treatment. Any resemblance to a real patient is purely coincidental.

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