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Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents: Benefits and Challenges

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Abstract
Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting approximately 11 percent of the country’s children and adolescents, between the ages four to seventeen years. Stimulant medications such as methylphenidate and amphetamines are the first-line of treatment for ADHD. The increasing use of these stimulant medications has resulted in increased media attention and raised questions about their efficacy and safety. This review focuses on the history of stimulant use in ADHD, the disease’s pathophysiology, the long-term benefits of pharmacotherapy, and the possible subsequent adverse effects associated with prolonged stimulant use in children and adolescents suffering from ADHD. Furthermore, we will highlight the important role of the pharmacist in both the long-term management of ADHD patients and in preventing the misuse/abuse of prescription stimulant medications. In addition, we briefly discuss the role of non-stimulants in the treatment of ADHD. Overall, a detailed review of the available literature suggests that there is an urgent need to conduct well-designed, long-term studies to more clearly understand the benefits and adverse effects associated with stimulant and non-stimulant use in the treatment of ADHD in children and adolescents.

Background of ADHD
Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate levels of hyperactivity, impulsivity and lack of focus and attention to the task on hand. As of 2011, approximately 6.4 million children and adolescents between the ages 4 to 177 years have been diagnosed with ADHD in the United States. The prevalence of ADHD in children has steadily increased and varied by state ranging from 5.6 percent to 18.7 percent in 2011. Importantly, it has been found that children with ADHD, if left untreated, have poor academic performance, low self-esteem, frustration and problems with social relationships. Further, it has been observed that untreated children are at increased risk of developing several types of psychiatric disorders in adulthood such as conduct disorder, mood disorder, substance use disorder and anxiety disorder. Thus, it is extremely important to both diagnose and treat children and adolescents with ADHD.

The most common treatment option for ADHD is stimulants, such as amphetamines and methylphenidate. In many children, stimulants reduce hyperactivity and impulsivity to improve their ability to focus and learn. Additionally, long-term treatment with stimulants has shown to improve academic performance and reduce the incidence of psychiatric disorders in adulthood. Despite these beneficial effects of stimulants, there is some concern regarding potential side effects associated with chronic, long-term use. Non-stimulants are viable second-line agents for treatment of ADHD, which can be used to avoid the side effects of stimulants. The major focus of this review is on the benefits and challenges associated with use of stimulants in treatment of ADHD in children and adolescents. The use of non-stimulants in ADHD treatment is also briefly discussed.

History of Stimulants
Amphetamine was synthesized in the laboratory by G.A. Alles in 1927. Alles reported for the first time that amphetamines could produce insomnia or arousal. Subsequently, it was also shown that administration of amphetamines led to improved performance on intelligence tests, stress relief, concentration enhancement and better intellectual performance. In addition, amphetamine was investigated as a medication for asthma in the 1920s and was used in the United States in the early 1930s for congestion and respiratory disorders. During World War II, amphetamines were used as ‘energy pills’ for allied forces. Amphetamines could be obtained with or without a prescription in the ‘50s and ‘60s to treat obesity, depression, narcolepsy and encephalitic Parkinsonism treatment. The widespread use of amphetamines resulted in significant abuse of the medication for recreational purposes resulting in development of amphetamine dependence in otherwise healthy individuals. In order to stem the misuse/abuse of amphetamines, the government made amphetamine a schedule II drug in 1972, which limited its sale only to individuals for treatment of their medical condition and required patients to obtain a prescription in order to possess amphetamines. The classification of amphetamine as a schedule II drug ultimately resulted in a decline in amphetamine use for medical conditions, although its abuse for recreational purposes continued.

Currently, amphetamines are medications of choice for the treatment of ADHD. The first amphetamine on the market was Benzedrine®, a racemic α-methylphenethylamine, registered by the pharmaceutical company Smith, Kline, and French. Later, the same company synthesized both the dextro-(d-) and levo-(l-) isomers and began to market d-amphetamine as Dexedrine® in 1937, as the more potent isomer. Clinical trials in the 1970s showed that both the l-isomer (Cydir®) and the d-isomer were clinically effective in the treatment of ADHD. The use of α-methylphenethylamine began to decrease dramatically after a report by Gross in 1976 showed that the racemate was less effective than d-amphetamine. Currently, l-amphetamine is only used in mixed salt ADHD medications which are a three to one enantiomeric mixture of d-amphetamine and l-amphetamine respectively. This mixture is available as immediate and extended-release Adderall®. Administering an extended-release stimulant allows for the patient to take the medication under the history of stimulant use in ADHD, the disease’s pathophysiology, the long-term benefits of pharmacotherapy, and the possible subsequent adverse effects associated with prolonged stimulant use in children and adolescents suffering from ADHD. Furthermore, we will highlight the important role of the pharmacist in both the long-term management of ADHD patients and in preventing the misuse/abuse of prescription stimulant medications. In addition, we briefly discuss the role of non-stimulants in the treatment of ADHD. Overall, a detailed review of the available literature suggests that there is an urgent need to conduct well-designed, long-term studies to more clearly understand the benefits and adverse effects associated with stimulant and non-stimulant use in the treatment of ADHD in children and adolescents.

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These neurotransmitters thus amplify signal: noise ratio and amino butyric acid (GABA)ergic inhibitory interneurons. The that are mainly responsible for suppressing excessive volun­
terest. In ADHD patients, synaptic levels of NE and DA in the receptors and thereby increases attention toward stimuli of interest (signal).10 At the same time, dopamine binds to D1 dopaminergic receptors and helps suppress activation of PFC ganglia is responsible for the hyperactivity symptoms, such as the globus pallidus, a major component of the basal ganglia. The basal ganglia consists of subcortical nuclei that are mainly responsible for suppressing excessive voluntary motor function through its communication with the PFC. Neuro-imaging studies conducted in children diagnosed with ADHD have reported a decrease in gray matter volume of the globus pallidus, a major component of the basal ganglia.11,12 It is hypothesized that the decreased functioning of the basal ganglia is responsible for the hyperactivity symptoms, such as tremors and jerking, commonly observed in ADHD patients. Overall, lesions or malformations in the PFC can dramatically decrease attention span and attenuate concentration while heightening voluntary motor function.

Pprefrontal cortex function is mediated by microcircuits of glutamatergic pyramidal cells interacting with gamma-aminobutyric acid (GABA)ergic inhibitory interneurons. The pyramidal cells are activated by N-methyl-D-aspartate (NMDA) synapses on dendritic spines and help maintain the necessary neurotransmission for working memory or inhibiting inappropriate motor behaviors. Intensity of the NMDA-mediated signaling is modulated/fine-tuned by endogenous neurotransmitters, such as norepinephrine (NE) and dopamine (DA). Increased stimulation of NE and DA receptors (i.e., α2 and D1, respectively) facilitates improved connectivity between different brain regions involved in attention and learning. Norepinephrine binds to α2A adrenergic receptors and thereby increases attention toward stimuli of interest (signal).10 At the same time, dopamine binds to D1 dopaminergic receptors and helps suppress activation of PFC circuits due to competing or distracting stimuli (noise).10,11 These neurotransmitters thus amplify signal: noise ratio and help in improving focus and attention toward stimuli of interest. In ADHD patients, synaptic levels of NE and DA in the PFC are decreased. These deficits can be corrected by administer-
ing stimulant and non-stimulant medications, which help in either increasing NE/DA concentration and/or increasing respective receptor stimulation.

**Pharmacology**

Norepinephrine and DA are cleared from the neuronal synapses via uptake transporters located on presynaptic nerve terminals; therefore, the most efficient way to increase synaptic DA/NE levels is to block their uptake via these transporters. Central nervous system (CNS) stimulants, like methylphenidate and amphetamine, dramatically increase the amount of extracellular NE and DA available in the PFC via blockade and/or reversal of the norepinephrine uptake transporter (NET) and dopamine uptake transporter (DAT). In addition, amphetamines also disrupt vesicular storage of these neurotransmitters in the presynaptic terminal, allowing them to accumulate in the cytoplasm. Furthermore, amphetamine inhibits the degradative enzymes monoamine oxidase A and B (MAO-A, MAO-B), which allows cytosolic accumulation and promotes release in the synapse. In addition, the U.S. Food and Drug Administration (FDA) has approved non-stimulants for the treatment of ADHD such as atomoxetine, clonidine and guanfacine. Atomoxetine selectively inhibits the presynaptic reuptake of NE in the PFC, thus increasing synaptic NE levels. In contrast, guanfacine and clonidine are α2 adrenergic receptors ago-

ists and thus help in increasing activity of α2 adrenergic receptors. Non-stimulant medications are considered second -line treatments and are reserved for patients who are unresponsive to stimulants or in whom stimulants cannot be used, for example patients with cardiovascular abnormalities or patients predisposed to addiction/substance abuse. Overall, this stimulant/non-stimulant-induced increase in DA/NE receptor activity improves neuronal communication by amplifying the signal to noise ratio; and thus, ultimately results in improved attention and working memory. However, increasing concentrations of DA/NE is beneficial up to a certain point. Excessive increase in DA/NE levels results in suppression of neuronal firing in the PFC networks and can ultimately lead to worsening of ADHD symptoms. Thus, there is an "inverted U"-shaped dose dependent relationship between PFC function and DA/NE levels.

**Beneficial Effects of Chronic Stimulant Use**

Long-term use of stimulants in children and adolescents diagnosed with ADHD does have significant beneficial effects. These effects are apparent in children/adolescents who are between 6 and 18 years old taking methylphenidate and those who are older than 3 years old taking amphetamine. Studies have shown that there is a positive correlation between ADHD medications and academic performance in elementary school. Children, ages 9.11±1.22 years, who were treated with stimulants for at least one year outperformed their control counterparts in all tests measuring academic achievement. Additionally, longitudinal case-control prospective studies of ADHD patients (males and females aged 6-18 years) were conducted to assess the psychiatric consequences of long-term stimulant use. Results suggest that lifetime stimulant treatment may prevent psychiatric outcomes such as antisocial, addictive, mood and anxiety
disorders.\textsuperscript{16,17} Addiction and subsequent substance use disorder (SUD) is precipitated by untreated ADHD. For example, in a longitudinal study of boys (aged 6 to 17 years) with ADHD, incidences of SUD was compared in young adults without ADHD (Group 1), young adults with untreated ADHD (Group 2), and young adults with ADHD treated with stimulants (Group 3). Baseline SUD was initially recorded and remeasured after 4 years. In this study, SUD consisted of alcohol, marijuana, hallucinogen, stimulant and cocaine abuse. Rates of SUD were as follows: Group 1 (75%), Group 2 (25%) and Group 3 (~18%). Medicated children with ADHD were almost 85 percent less likely to develop a SUD. These data suggest that untreated ADHD patients could have an increased substance abuse potential and that pharmacotherapy may protect children from this risk.\textsuperscript{18,19} Therefore, it is important to treat ADHD to minimize this increase in substance abuse potential. Non-stimulants, commonly prescribed to adults and children with ADHD, have not been extensively studied in clinical trials to assess their long term efficacy.\textsuperscript{20} Overall, studies suggest that pharmacological treatment of ADHD in general can lead to improved quality of life.

**Acute and Long-Term Side Effects**

Central nervous system stimulants are considered first-line therapy as they have been shown to be more effective than non-stimulants in managing ADHD.\textsuperscript{21} The use of stimulants for treating ADHD has increased dramatically from decade to decade. One study has reported an increase in stimulant use for treatment of ADHD from 0.9 to 3.4 per 100 children between 1987 to 1997.\textsuperscript{22} However, like all other medications, stimulants are associated with acute and long-term side effects. Acute side effects of stimulants include nervousness, insomnia, decreased appetite, headache, stomachache, nausea and dizziness one hour after oral administration. These symptoms are possibly due to an increase in sympathetic activity resulting from increased NE levels.\textsuperscript{23}

In addition, long-term administration of stimulant medications is associated with possible negative mental and physical consequences. Addiction is one of the most common chronic side effects of stimulant use. Methylphenidate and amphetamine increase concentrations of NE and DA in the brain, which results in a sense of alertness, increased energy and euphoria. Abuse of stimulant medications by taking them more frequently, or in doses higher than prescribed, can result in stimulant dependence in ADHD patients. Certain genetic polymorphisms may also increase predisposition to stimulant abuse.\textsuperscript{24} These genetic quirks alter the function of certain proteins involved in the reward pathways - networks in the brain responsible for motivation and incentive drive. Specifically, ghrelin is a peptide responsible for activating appetite. Polymorphisms in the pre-proghrelin and GHS-R1A (GHSR) gene equate to weight gain and increased alcohol/smoking use in humans. A case control analysis showed that individuals with a single nucleotide polymorphism to the GHSR gene had a higher Addiction Severity Interview composite score of drug use.\textsuperscript{25} Genetic alteration in ghrelin is currently not a diagnostic indication for amphetamine dependence; however, the role it has on addiction should not be ignored. This observation allows for possible drug development for the treatment of such addictive behaviors. Because of the high incidence of abuse, stimulant medications come with black box warnings which remind patients of the risk of dependence and that illicit use of stimulants is strictly prohibited.\textsuperscript{24,25} Non-stimulants, although not medications of choice for treatment of ADHD, are safer alternatives to stimulants because they do not present the same risk for abuse and addiction.\textsuperscript{26}

Adverse cardiovascular events are widely associated with the chronic use of stimulants.\textsuperscript{27} Methylphenidate and amphetamine are sympathomimetics, analogs that stimulate the sympathetic nervous system, which if abused can lead to hypertension, tachycardia, vasoconstriction, arrhythmias, coronary artery disease, myocardial ischemia and cardiomyopathy. Therefore, adolescents with underlying cardiac abnormalities or with a family history of unexplained syncope, angina and other cardiac issues should take extreme caution with using CNS stimulants. Long-term studies exploring the relationship between methylphenidate/amphetamine use and cardiovascular events indicate that there were small but significant increases in blood pressure and heart rate without significant changes in the electrocardiograms after a six-month to one-year treatment.\textsuperscript{20} However, these studies conclude that these cardiac changes are predictable and quite benign. Ways to minimize cardiovascular events include avoiding stimulant abuse and only titrating the dose as needed for effective therapy. Patients should also avoid use of any other NE/DA reuptake inhibitors or MAO inhibitors as they can enhance the hypertensive effects of stimulants. Atomoxetine may also increase blood pressure with short and long-term treatment. Although, long-term use of extended release guanfacine leading to cardiovascular events is uncommon, it still remains contraindicated in children with clinically significant cardiovascular history.

Effects of stimulants on growth are a major issue of debate in the treatment of ADHD children. Stimulants have been observed to decrease growth rate in newly medicated patients. Some formulations, such as the transdermal and osmotic controlled release oral delivery system methylphenidate, have been proven to affect rate of weight gain and linear growth.\textsuperscript{20} These data, however, need to be confirmed by further studies. Atomoxetine has also showed minimal effect on height.\textsuperscript{20} An increase in tics/Tourette's syndrome is sometimes observed in children with ADHD who are being treated with stimulants. However, there is no current data that support the exacerbation of tics/Tourette's syndrome is due to use of stimulant medications. One possible reason for the above observation could be that half of the children with chronic tics/Tourette's syndrome potentially qualify as an ADHD patient as well.\textsuperscript{20} Nevertheless, developing children and those with comorbid conditions such as Tourette's must be closely monitored during the course of stimulant treatment. Interestingly, a meta-analysis of nine studies demonstrated that tics and symptoms of Tourette's symptoms are effectively attenuated upon administration of non-stimulant medications such as a2 agonists and atomoxetine in children with comorbid ADHD.\textsuperscript{28} Regardless, stimulants such as methylphenidate appear to provide the best alleviation of ADHD symptoms.
A study has reported dopaminergic and serotonergic toxicity in primates after six weeks of treatment with amphetamine at doses used to treat ADHD patients. This study prompts a concern that chronic therapeutic doses of amphetamines can lead to similar toxicity in ADHD patients. Koessler et al. suggests that these neurotoxicities may not be observable in ADHD patients due to the fact that diseases such as Parkinson’s disease require 80 to 90 percent depletion in dopaminergic neurons before signs and symptoms appear. Despite these alarming reported amphetamine-induced toxicities in primates, it is possible that such toxicities may not appear in ADHD patients due to a few key reasons. Unlike primates, humans are able to prevent the neurotoxic accumulation of amphetamines through their extensive metabolism. Also, human and nonhuman subjects such as primates may differ in their sensitivity to amphetamine-induced toxicity. Finally, it is possible that amphetamine-induced toxicity may be observed only in healthy human subjects who abuse amphetamine for recreational purposes and do not actually suffer from ADHD. Patients suffering from ADHD have a deficiency of dopamine and norepinephrine and therefore may be less vulnerable to amphetamine-induced toxicity compared to healthy subjects. In summary, further studies are required to fully understand the implications of chronic stimulant exposure in ADHD patients.

The Role of the Pharmacist in Management of ADHD and Abuse

With pharmacists being the most accessible health care professionals, it is crucial for pharmacists to know both diagnostic and treatment guidelines. Guidelines for diagnosis have been established by the American Association’s Diagnostic and Statistical Manual, also known as DSM-5. In regard to treatment, the National Collaborating Center for Mental Health recommends that initial treatment begins with stimulants, and more specifically methylphenidate. When a patient initiates this therapy, it is important for pharmacists to ensure the patient is starting with a low dose with the potential to titrate up as needed. Supplemental treatment such as behavioral therapy should also be initiated. In regard to these guidelines, it is crucial for pharmacists to understand that there is no specific treatment algorithm for the treatment of ADHD. Stimulants are considered first-line whereas non-stimulants can be used as second-line therapy. Regardless of which treatment option is initiated, the therapy should start with low doses with the intent to titrate up as needed and always be supplemented with nonpharmacologic management such as behavioral therapy and parent training.

Considering that ADHD is a chronic disease that is diagnosed in childhood and continues well into adulthood, there is a need to carefully monitor and manage the therapy in these patients to maximize the beneficial effects and minimize the adverse effects. The pharmacist can play a pivotal role in the long-term management of these patients. The first goal of therapy should be to manage the patient's symptoms such as hyperactivity, inability to concentrate and lack of attention. As described above, stimulant medications compared to non-stimulant medications are more effective in managing ADHD patients. Also, another important goal of the pharmacist should be to minimize acute and long-term side effects resulting from medications prescribed for ADHD. This can be achieved through appropriate patient education and counseling. Patients must be made aware of the potential side effects such as tachycardia, palpitations, mood changes, agitation, insomnia and headaches. Furthermore, pharmacists need to stress to patients the importance of medication adherence. Medications must be taken as they are prescribed. Patients must also be made aware that taking the medication more frequently or in larger amounts can result in adverse long-term consequences such as development of drug dependence and/or neurotoxicity. Finally, it is important for the pharmacist to consistently monitor and record changes in weight, height and psychological status of these ADHD patients. The ultimate goal of ADHD treatment should be to improve the quality of life of the patient.

As health care professionals, it is imperative to monitor patients for important parameters such as weight, growth, psychological status, efficacy of medication, compliance and adverse events such as cardiovascular issues and mental status alterations. To avoid these side effects and ensure quality of life for ADHD patients, it is crucial that pharmacists educate parents and other family members, as well as have them inform their teachers at school. This education will help with patient adherence as well as increase monitoring for adverse effects.

Another important role of the pharmacist in the management of ADHD patients is in preventing drug interactions. As a pharmacist, it is vital to review medication lists to ensure the patient is not at high risk for an adverse event. For example, a patient who is taking anti-arrhythmic medication may be at a greater risk for a cardiovascular event due to stimulant therapy for ADHD. It is important that pharmacists know and understand alternative pharmacologic and nonpharmacologic approaches for treatment of ADHD. In addition to nonstimulant medications, there are also many nonpharmacologic therapies, such as cognitive behavioral therapy, family therapy, parent training and social skills that can be useful in these situations. These can be aided by services offered through schools as well as follow-up visits with the prescriber. In summary, as health care professionals, it is imperative to assess the efficacy of medication and compliance, and to prevent adverse effects including potential drug interactions.

Due to the benefits of stimulants such as alertness and focus, there is a larger abuse potential in those with or without a prescription. Abuse of stimulant medications can lead to development of drug dependence in ADHD patients. This dependence can then lead to psychosocial alterations in patients who have already been diagnosed with another psychiatric disorder. This helps explain why ADHD medications have a black box warning and require strict monitoring. Pharmacists are the final line of defense against abuse and overuse of these medications and can monitor the exposures each month. Pharmacists can utilize tools such as Ohio Automated Rx Reporting System (OARRS) to track what controlled prescriptions a patient has, the quantity filled and...
how often they have filled a specific medication. Thus, this system may help control abuse by allowing pharmacists to identify abnormal filling tendencies of these medications and contact the prescribing doctor to ensure the integrity of the prescription. In addition to monitoring data that suggests abuse, it is important that the pharmacist look out for psychosocial behavioral changes and/or withdrawal symptoms.

Due to the pharmacological effects of stimulants such as increased alertness, increased energy and euphoria, there is a large potential for abuse of prescription stimulants by individuals without a prescription. In fact, abuse of stimulant medications is on the rise among college students for it is believed to improve performance on examinations. There are reports of prescription medications being sold to classmates because of their desired effects. Furthermore, there are reports that students are falsely reporting signs and symptoms of ADHD to their health care providers in order to obtain prescription stimulants.32 Despite regulations to monitor to whom these prescriptions are dispensed, it is much harder to regulate what patients do with their prescriptions. As described above, stimulant-induced neurotoxicities are more likely to occur in healthy subjects compared to patients with ADHD. Importantly, individuals abusing ADHD medications not prescribed to them will not be monitored and are therefore more vulnerable, compared to ADHD patients, to adverse consequences of these stimulant medications. In the future, all of the challenges associated with prescription stimulants such as abuse, misuse and malinger will need to be collectively addressed by pharmacists and other health care providers.29

Conclusion

There are warranted and appropriate uses of stimulants such as amphetamines and methylphenidate; however, these should be used with extreme caution. These stimulants have shown the ability to improve the patient’s quality of life when therapy parallels the strict guidelines such as those set by DSM. Appropriate therapy helps eliminate unnecessary exposure to adverse effects as well as misdiagnoses. Further, the role of non-stimulant medications needs to be further investigated to provide safe alternatives to ADHD therapy for those who have pre-existing conditions or sensitivities toward stimulants that disqualify them from stimulant therapies. Finally, it is imperative that the long-term effects, both beneficial and adverse, of stimulants and non-stimulants be evaluated in prospective cohort studies in order for prescribers and pharmacists to be aware that the added benefits of therapy outweigh the potential short-term and long-term risks.

References


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