Treatments for Attention Deficit Hyperactivity Disorder:

The psychopharmacology of Adderall in children and alternative treatments

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Introduction

The history of amphetamines stretches back over 5000 years, to ancient China. The first recorded use of amphetamine was the herb Huang by Chinese herbalists, which contained ephedrine. Huang was used to lower appetite and increase energy and wakefulness. By 1920, doctors began prescribing another amphetamine-like compound, Ephedrine, as a bronchodilator for asthma. However, there was so much demand for the drug that chemists began synthesizing a synthetic alternative: Amphetamine (Meyer & Quenzner, 2013). This new compound was first marketed in 1935 as a treatment for narcolepsy, and was subsequently used to great effect in WWII as an energy booster. After WWII, street use of amphetamines surged, peaking in 1970 before leveling off (Meyer & Quenzner, 2013).

Amphetamine and amphetamine-like compounds refer to a group of psychostimulants that include commonly recognized drugs such as methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and Adderall (Meyer & Quenzer, 2013). Adderall is a pure amphetamine salt, and can therefore be referred to as simply ‘Amphetamine’. Adderall is a combination of the D- and L-type isomers, referred to as dextroamphetamine and levoamphetamine respectively. Like other amphetamine-like compounds, Adderall increases energy, alertness and confidence, and can allow for sustained physical effort without rest or sleep (Meyer & Quenzner, 2013).

Adderall is frequently prescribed to treat Attention Deficit Hyperactivity Disorder (ADHD) in the United States. The diagnosis of ADHD is becoming more prevalent among children (ages 4 to 17) according to the Centers for Disease Control and Prevention. The number of children diagnosed with ADHD in the U.S. rose from 7.8% in 2003 to 11% in 2011.

ADHD can set back children in school and can cause behavioral problems. Children are diagnosed when they experience a lack of focus and behavioral problems across a multitude of different environments. Due to damage to self esteem, social interactions, and academics, many practitioners are attempting to diagnose and treat ADHD as early as possible. The Pediatrics Association recommends prescribing Adderall to children as young as six (Wolraich et al., 2011). While Adderall is effective in treating ADHD in the short-term, ADHD can last throughout childhood and into adulthood. The long term use of Adderall can lead to concerns over its side effects, including the risk of cardiovascular events and sudden death (Brown, 2013). Due to these side-effects, Canadian authorities have suspended the distribution of Adderall, and amphetamines have been banned from Japan and South Korea, in part due to their abuse potential (Strange, 2008).

Concerns over the long-term use of amphetamines or the inability to tolerate side-effects lead some patients to pursue alternative treatments for ADHD. The specific action of Adderall in the Prefrontal Cortex (PfC) accounts for its therapeutic benefits. Following an explanation of Adderall's psychopharmacological mechanism of action, we will explore its behavioral effects and then briefly review treatment options. In this paper, we will review Adderall use in both children and adults, and compare Adderall with other treatments for ADHD.

Structure & Chemistry

Amphetamine is a racemic methyl homolog of the mammalian neurotransmitter phenylethylamine. Its structure is similar to the catecholamine neurotransmitters: they each share an aromatic ring with a propyl group and an amino group (Heal, Smith, Gosden, & Nutt, 2013). Its two enantiomers are levoamphetamine and dextroamphetamine, respectively. Dextroamphetamine is the pharmacologically active enantiomer, and Adderall is a 3:1 mixture of the two amphetamine enantiomers in salt form. Because of its amino group, amphetamine can be made into a salt in acidic conditions, preventing it from passing through cell membranes. Accordingly, Adderall is generally delivered therapeutically in its salt form.

The similarities of amphetamine in structure to the catecholamine neurotransmitters, specifically the monoamines, allow for pharmacodynamic effects like the reversal of dopamine active transporter (DAT) and the inhibition of monoamine oxidase (MAO).

Pharmacokinetics

Adderall is typically taken orally. A standard dose is 5-15mg, with roughly a 30-minute metabolic period before behavioral effects begin to emerge. Amphetamine has a high lipid solubility when not in its salt form, and it is best absorbed through the small intestine. It is primarily metabolized by hepatic enzymes in the liver at a slow rate, and it leaves the body through urine. Amphetamine has a highly variable half-life of 7-30 hours. At lower stomach pH this half-life decreases because of the greater concentration of amphetamine in its salt form due to the alkaline amino group (Anggard, Jonsson, Hogmark, & Gunne, 1973).

Pharmacodynamics

Amphetamine's principal pharmacodynamic effect is on the catecholamines - specifically, dopamine, serotonin, and norepinephrine. It acts to increase the concentration of these monoamines in the synaptic cleft, and as such acts as an indirect agonist of the catecholamine system (Meyer & Quenzner, 2013). It does this through its affinity for various catecholamine transport proteins in the presynaptic membrane and axon terminal. This affinity causes competition by amphetamine for reuptake into the axon terminal with endogenous catecholamines. First, either amphetamine or a catecholamine binds to two Na+ ions and a Cl- ion; this molecular complex then takes advantage of the Na+ concentration gradient to enter the axon terminal through Dopamine Active Transporter (DAT), Norepinephrine Transporter (NeT), or Serotonin Transporter (SERT) depending on the neurotransmitter system being acted upon (Heal, Smith, Gosden, & Nutt, 2013). In addition to competing for reuptake, amphetamine acts to displace monoamines from the axon terminal cytosol (Heal et al., 2013). The net effect is to reverse the transporter through phosphorylation by protein kinases, such that the monoamine is pumped into the synaptic cleft rather than out of it. Amphetamine has its greatest effect on DAT, and as such dopamine is predominantly agonized (Heal et al., 2013).

Additionally, at high concentrations, amphetamine inhibits the catecholamine metabolism by monoamine oxidase. Monoamine oxidase (MAO) normally works to break down monoamines; amphetamine inhibits its action. This causes a greater concentration of monoamine in the cytosol, which in turn results in a greater concentration of monoamine in the synaptic cleft (Meyer & Quenzner, 2013). The net result of amphetamine's actions on MAO and DAT is an

increase in DA activation on D1 receptors and an increase in norepinephrine activation on Alpha-2a receptors.

The agonistic effects of amphetamine on DA and NE produce a therapeutic 'signal-to-noise' effect for ADHD patients in the PfC. Both the stimulus ('signal') on which patients are focused becomes more salient, and the extraneous stimuli ('noise') becomes less salient. Reversing DAT to pump DA into the synapse works to reduce the noise: more DA binds to D1 receptors, causing a decrease in cAMP by inhibition of adenylyl cyclase, cAMP's catalyzing enzyme. This decrease leads to an alteration in K+ channels that causes noise reduction (Meyer & Quenzner, 2013; Arnsten, 2009; Gamo Wang, & Arnsten, 2010). Additionally, blocking NeT causes a stronger signal. More NE in the synapse causes greater stimulation of postsynaptic a2a receptors. This causes an agonistic effect on the potency that transmitters like Glutamate have on PfC pyramidal cell synapses (Gamo et al., 2010). Network connections are therefore strengthened between neurons within a network, and the signal strength is accordingly increased.

Alternative Treatments for ADHD in Children

While Adderall is a well-known treatment for children with ADHD, there are a variety of other pharmacological and behavioral treatments available. For example, Methylphenidate, which includes Ritalin, is another psychostimulant which acts similarly to Adderall. According to clinical practice guidelines released by the American Academy of Pediatrics, Methylphenidate can be prescribed to children under six where Adderall is not recommended. They recommend behavioral treatment first, however (Wolraich et al., 2011). Many practitioners are aiming to

diagnose ADHD as early as possible in order to avoid negative impacts on social interaction and academics, and researchers agree that Methylphenidate is an effective treatment for this young age group. There have been very few long-term trials that extend beyond 12 months, despite the potential for children to continue taking methylphenidate (Attention Deficit, 2012).

Psychostimulants are widely accepted as effective treatments for ADHD, but it is estimated that between 30% to 50% of patients prescribed stimulant medications stop using them because of negative side-effects or a lack of effectiveness (Strange, 2008). Other patients may be at a high risk for Adderall abuse or may have existing health issues such as anxiety that make psychostimulants a poor choice. There are three non-stimulant medications which are approved by the FDA to treat ADHD: Atomoxatine (brand name Strattera), Guanfacine (Intuniv), and Clonidine (Kapvay) (FDA, 2016).

Atomoxatine was the first non-stimulant medication approved to treat ADHD in the US (Strange, 2008). Atomoxatine is a selective norepinephrine reuptake inhibitor and it can be prescribed for children, adolescents and adults (Atomoxatine, 2009). In clinical trials, Atomoxatine was no less effective when other disorders were present, which is important for patients who suffer from multiple disorders. Unfortunately, Atomoxetine is not as effective as extended release mixed amphetamine salts or extended release Methylphenidate. Where Adderall can cause insomnia, Atomoxatine, Guanfacine and Clonidine can cause drowsiness (Atomoxatine, 2009; Strange, 2008). Atomoxetine has received a black-box warning from the FDA for increased risk of suicidal thoughts in children and teens, although this was seen in only a small percentage of participants in clinical trials (Atomoxatine, 2009).

Both guanfacine and clonidine are Alpha-2 agonists, which act on Alpha-2 adrenergic receptors, although they bind to certain Alpha-2 receptors differently (Strange, 2008). Atomoxetine use was also associated with increased heart rate and blood pressure, although Garnock-Jones and Keating noted that the increase is not clinically relevant (Garnock-Jones and Keating, 2012). Conversely, guanfacine and clonidine are associated with decreased blood pressure and heart rate. According to a literature review, these side effects are milder with guanfacine use than clonidine. Guanfacine may be a good choice for children who have ADHD and tic.

Some families also pursue behavioral therapy to help manage their child's symptoms at home and at school. Behavioral training for parents appears to be effective for children under six, with benefits noted for at least six months and up to two years in some studies (Attention Deficit, 2012). Benefits increased with more parental training (Attention Deficit, 2012). After the age of six, the American Academy of Pediatrics states that children can be prescribed FDA approved ADHD medication (Wolraich et al., 2011), and therefore in this age group, there is not enough research to suggest that behavioral therapy alone is effective long-term (Attention Deficit, 2012).

Adderall in Children

Adderall is prescribed in children experiencing hyperactivity, such as fidgeting or constant movement; impulsivity, such as interrupting others; and inattention, such as poor attention to detail. When children begin taking Adderall, their once-disruptive behavior begins to diminish. Some behavioral benefits include psychomotor depression, high alertness and attention, and enhanced concentration (Berman, Kuczenski, McCracken, & London, 2009). In

one meta-analysis, Faraone and Biederman (2002), examined six studies on the efficacy of Adderall. In this meta-analysis, Adderall was shown to be successful in treating symptoms of aggression, hyperactivity, inattention, impulsivity, and global ratings. Faraone and Biederman (2002) also found that Adderall showed enhanced parent, teacher, and clinical ratings who were also blind to whether children were taking a placebo or Adderall.

The short-term effects of Adderall on children are often seen as a suppression of the previously mentioned behaviors. However, there is very little research on the long-term effects of Adderall in children. In one study (Firestone, Musten, Pisterman, Mercer, & Bennet, 1998), researchers discuss that this stimulant may enforce obsessive-compulsive, over-focused, or precautionary behaviors in children who were once hyperactive and/or inattentive. There is also some concern about cardiovascular problems, particularly by parents of children taking Adderall. In Brown's (2013) article, over a ten-year observational period, children were not at an increased risk for developing prehypertension or hypertension. However, researchers did find that children had an increase in heart rate while on amphetamines (Brown, 2013). Another behavioral symptom that may be seen in children while taking Adderall is social withdrawal (Firestone et al., 1998). Many children show reduced social interactions and responsiveness, and reduced spontaneity and behaviors that are unobtrusive, depressed, languid, and apathetic. In addition to this, common side effects of Adderall in children include insomnia, decreased appetite, delayed growth, headaches and stomachaches, and irritability (Firestone et al., 1998).

Adderall in Adults

A multitude of researchers interested in Adderall in adults focus its misuse. These health issues may concern parents, but the doses taken by abusers tend to be larger than the doses prescribed to children. Researchers are especially interested in the misuse among college-age and older individuals. One common theme of research is the misuse of Adderall to increase academic performance. However, one study (Lakhan & Kirehgessner, 2012), indicated that amphetamines do not increase academic performance but do help individuals maintain sustained focus and attention. This result has been found both in individuals with and without ADHD. One finding worth noting is that Adderall may augment traits of distractibility and selective attention due to the drug's increase in impulsivity if the user does not have ADHD-like traits (Lakhan & Kirchgessner, 2012). Those who do misuse Adderall or misuse it for long periods of time face serious health risks, including psychosis, seizures, and cardiovascular problems. More specifically, the most common cardiovascular problems are hypertension, tachycardia, and myocardial infarction (Lakhan & Kirchgessner, 2012). However, in Brown's (2013) article, which compares cardiovascular events in children and adults taking Adderall, these cardiovascular events occur after prolonged use of high doses or abuse of the drug. Researchers also proposed that Adderall-induced psychosis may be due to an excess of dopamine. Furthermore, other risk factors of psychosis include dependency, using in high doses, and the preceding symptoms of psychosis (Meyer & Quenzer, 2013). Individuals taking Adderall are highly likely to develop a tolerance or sensitivity to it.

Conclusion

Many families pursue behavioral therapy for home and school in addition to ADHD medication, but the best treatment depends on the individual and their needs and symptoms. While researchers tend to conclude that Guanfacine is more effective than Clonidine in treating ADHD, a review of 223 studies published between 1980 and 2010 stated that guanfacine was not well tolerated long-term; in one study only 20% of participants were still taking guanfacine after 12 months (Attention Deficit, 2012), although another review stated that only 12% discontinued taking it in clinical trials (Bernknopf, 2011). Non-stimulant drugs are often prescribed as a secondary option after Adderall, if adverse side-effects are not well tolerated. Guanfacine may be better for patients who have a tic and ADHD according to one review (Strange, 2008). Guanfacine also has a longer half life, and because of this, blood pressure and heart rate don't drop as much as with Clonidine use (Strange, 2008). Atomoxetine is an effective non-stimulant and is usually well-tolerated. Only a small number of patients discontinued use in clinical trials (Garnock-Jones & Keating, 2012). A combination of treatments has also been suggested by some researchers, such as prescribing either Guanfacine or Atomoxatine with a psychostimulant to combat insomnia (Strange, 2008).

Parents of children with ADHD should keep in mind that every treatment will have its adverse side effects; lowered appetite may be responsible for lower growth rates associated with ADHD medications, for example (Attention Deficit, 2012). Left untreated, however, children with ADHD are more likely to have issues with friendships, have difficulties at school, and have issues with their parents (FDA, 2016). Children with ADHD are more likely to get injured

(Strange, 2008), and teenagers with ADHD are two times as likely to have an auto crash if untreated (FDA, 2016).

The long-term effectiveness of pharmacological as well as behavioral treatments were not well-studied; in many articles, researchers referred to a drug as a good "short-term" treatment. The long-term effectiveness and adverse side-effects associated with long-term use need to receive more attention from researchers since ADHD can continue into adulthood, and children may take medications for years at a time. There may also be gaps in our current understanding of environmental influences on ADHD. There are higher incidences of ADHD with lower socioeconomic status, a relationship which is not well understood (Attention Deficit, 2012). It's also been noted that boys are more likely to have been diagnosed with ADHD, which may be due to the way that boys are raised (FDA, 2016).

Our understanding of ADHD continues to evolve as we're able to diagnose it sooner, as more environmental effects are accounted for in studies, and as children diagnosed with ADHD grow into adulthood. Further research may reveal that certain treatments are more effective for specific symptoms or types of ADHD, helping researchers to establish the best ADHD treatments.

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