

Pharmacology of Attention-Deficit/ Hyperactivity Disorder Treatments

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Abstract

There is a significant body of research on the topic of treatments for attention-deficit/hyperactivity disorder in children, adolescents, and adults. Major pharmacological treatments include stimulants (amphetamines and methylphenidate) and non-stimulants (atomoxetine and others). There are also forms of non-pharmacological treatment, including behavioral and psychosocial therapies. Studies have demonstrated the most improvement in functioning and reduction of symptoms because of a combination of pharmacological and behavioral treatment, however on its own, medication management has proven to be significantly more effective than behavioral therapy strategies. This review covers recent trends in Treatments and Pharmacology of Attention-Deficit/Hyperactivity Disorder.


Introduction

Currently one of the most frequently diagnosed disorders in childhood is ADHD. It was once believed that this disorder was linked only with children, however it is clear nowadays that there are a significant percentage of adults with ADHD as well. Patients with ADHD show abnormalities in the brain through magnetic resonance imaging (MRI) when compared to people without a diagnosis.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder, or ADHD, is among the most common neurological disorders diagnosed in the United States. Some estimates put it at up to 12% of the population, although many people go undiagnosed into adulthood Shier [1]. In order to be properly diagnosed with ADHD, a child or adolescent needs to have 6 or more symptoms present for at least 6 months. For adults, the number is reduced to 5 or more symptoms present for at least 6 months. The symptoms must be present in at least two different settings, interfere with functioning to some degree, and not be better explained by another mental illness, developmental disorder, or drug use. To be diagnosed in adolescents or adults, several symptoms must have been present before the age of 12 [2]. Even though ADHD is frequently diagnosed in childhood, many people are not diagnosed until adulthood, and up to two thirds of children with ADHD will continue to have the disorder into adulthood [3,4]. Girls are much less likely to be diagnosed with ADHD than boys are, mainly because girls are less likely to present hyperactive and behavioral symptoms that are more noticeable. Furthermore, ADHD presentation in young girls may be misdiagnosed as a learning or developmental disorder. There are three specific types of ADHD according to the Center for Disease Control: predominantly inattentive, predominantly hyperactive-impulsive, and combined presentation. To be diagnosed with predominantly inattentive or hyperactive-impulsive ADHD, a person must present enough symptoms to meet criteria for that specific type and not the other. Combined presentation is diagnosed if a person meets criteria for both inattentive and hyperactive-impulsive simultaneously Bitter [5].

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Adolescent and Adult ADHD

Scientists used to think that ADHD was a childhood specific disorder, and that symptoms either disappeared or were reduced significantly once a person reached adulthood. It is now understood that about one third to one half of children or adolescents with a diagnosis of ADHD will continue to experience the disorder into adulthood, although symptoms might be slightly different [6,7]. Research has shown that many of the hyperactive and disruptive symptoms characteristic of childhood ADHD will be less significant as patients age, most likely because people are more aware of their social presence and can control outbursts better. An adult with ADHD might still feel compelled to fidget and move around instead of staying seated, but they are more capable of suppressing these urges as an adult, especially in settings such as work or higher education. This is also why people are much more likely to be diagnosed with ADHD in childhood or adolescence, as their symptoms are probably more noticeable by others Greenhill [8]. Adolescents with a diagnosis of ADHD are increasingly likely to resist medication by the end of high school, with a majority reporting that their symptoms have gotten better, and that medication was no longer needed, even if evidence showed that this was not the case. Teenagers in general do not like to be told what to do and may feel increased stigma from peers for taking medication for a neurological disorder such as ADHD. This could result in them being hesitant to continue medication from their childhood, or to start medication if they had not been prescribed any previously. This information should be taken into consideration when assessing research on adolescent ADHD prescriptions and treatment [9,10].

Pharmacological Treatments

There is currently a variety of treatment options available for ADHD, including pharmacological treatments, psychosocial and behavioral treatments, as well as a multitude of combinations of these. Most professional practices recommend the use of combined medication and behavior therapy for treatment of children with ADHD. One of the largest ADHD treatment studies is the Multimodal Treatment of ADHD study, conducted by the National Institute of Mental Health originally in 1999. This study found a significant difference in improvement when children were treated with a combination of medication management and behavior therapy, as opposed to either treatment alone or the control group. Medication management was found to be more effective on its own than behavior therapy on its own, but the greatest result occurred when both were present together.

Amphetamines

The use of amphetamines in a medical setting began around the 1930s when the over-the-counter drug Bensedrine was developed Ciccarone [11]. There are several different amphetamine-based treatments for ADHD currently, including d-amphetamine salts, dexamphetamine, mixed d- and l-amphetamine salts, d-methamphetamine salts, and lisdexamfetamine dimesylate [12,13]. Some amphetamine-based treatments must be taken twice

a day to be effective, and this causes problems with adherence due to having to take the medication during the school or workday. However, these issues with adherence led to more development of longer-acting forms of ADHD medication, allowing users to take the medication only once a day and resulting in higher rates of adherence. The newest amphetamine composition is lisdexamfetamine. Lisdexamfetamine, is created by linking d-amphetamine, to an amino acid, lysine Hodgkins [14]. The most common pharmacological treatments for ADHD in the united states are amphetamine and methylphenidate. These are seen as first-line treatments and have shown improvements in functional outcomes and reducing symptoms for patients with ADHD. In Europe and other areas outside the united states, dexamphetamine is described as a cost-effective treatment option, but studies and clinical trials on its effectiveness are not sufficient. The bulk of studies on amphetamine use as a treatment option for ADHD come in the form of micro dialysis studies in rats. These studies have consistently shown substantial dopamine increases in the striatum due to amphetamine as well as methylphenidate. Furthermore, these drugs increase norepinephrine levels in both the hippocampus and pre-frontal cortex in the brain.

Dexamphetamine Transfer in Breastfeeding Women

A study conducted in Australia in 2006 showed that a percentage of dexamphetamine from ADHD medication was transferred into breast milk from women taking the medication. The results from this study demonstrated that the percentage of dexamphetamine transfer to infants was relatively low (<10%) and therefore not an immediate risk to infants during breastfeeding. However, the study was small and further research needs to be done in order to fully evaluate the risks from dexamphetamine use while breastfeeding Ilett [15].

Methylphenidate

Methylphenidate is the other FDA-approved stimulant used for the treatment of ADHD, along with amphetamine. There have been many studies regarding the use of methylphenidate as an ADHD treatment, and they show that methylphenidate does result in a decrease of hyperactive and inattentive behaviors in children and adolescents [16]. There have also been studies done on the pharmacogenetics of methylphenidate response, however there is some conflicting evidence in this area [17,18]. In addition to being a common treatment option for ADHD, methylphenidate is also used for treatment of cancer, human immunodeficiency virus (HIV), and patients with a traumatic brain injury or stroke. Methylphenidate was first isolated in 1944 and is a central nervous system (CNS) stimulant. It increases dopamine levels in the CNS by binding to dopamine transporters and blocking reuptake primarily in the striatum. It has also shown to have effects on norepinephrine reuptake, and some researchers have suggested that methylphenidate's effects on behavior come because of multiple neurotransmitters, not just one Challman [19]. As with any medication, there are possible side effects associated with methylphenidate. The most common adverse effects reported are appetite loss, nausea, and headache.

Atomoxetine

Atomoxetine was the first nonstimulant to be approved for treating ADHD in children and adolescents. It has an overall lower effect size when compared to stimulants but may be beneficial to some patients as it is not a controlled substance and can have a longer effect length than amphetamines or methylphenidate. Clinical studies have shown approximately 50-60% of patients respond positively to atomoxetine, compared to approximately 70% with stimulants. "In contrast to both methylphenidate and amphetamine, atomoxetine increased noradrenaline levels in various brain areas, including the prefrontal cortex, but did not increase dopamine levels in the striatum or nucleus accumbens" Hodgkins [20]. All three forms of treatment show inhibition of monoamine uptake through binding to dopamine transporters and noradrenaline transporters.

Pemoline and Other Pharmacological Treatments

In 2005, the US Food and Drug Administration withdrew its approval of the drug pemoline for use as a treatment for ADHD. Pemoline is a stimulant of the central nervous system similar to amphetamine and methylphenidate, but it has a large risk of liver toxicity that ultimately resulted in the product being pulled from the market Reports of liver failure in those taking prescribed pemoline were as much as 25 times greater than the general population.

Drug Abuse

Over the recent years, diagnosis of ADHD has increased, and consequently the number of prescription stimulants has increased as well. While there is always risk of abuse and addiction, proper use of stimulants as prescribed does not lead to higher rates of substance abuse in adulthood. Many parents of children with ADHD are hesitant to give them prescribed medication, especially stimulants which are a controlled substance. Some may instead opt for nonstimulant medication or behavioral therapy alone. Another important consideration is that ADHD is a risk factor for substance abuse later in life, regardless of medication or treatment forms in childhood. Recently, the United States has seen an increased amount of people (particularly students) without a proper ADHD diagnosis or symptoms abusing ADHD medication. Students with a diagnosis benefit from the medication in the form of reduced symptoms and better academic and social functioning, whereas others abuse the medication to get ahead of their peers in school or occupational settings. Prescriptions for Adderall (mixed amphetamine salts) and other popular ADHD drugs has increased significantly in recent decades, and this may be a leading factor in their abuse. While there are guidelines for

Pharmacogenetics

Pharmacogenetics research is based in finding associations between specific genes in humans and response to medication. So far, research in pharmacogenetics for ADHD medications have been largely focused on methylphenidate. Other drugs have not been found to have significant effects in pharmacogenetic studies [21-23].

Methylphenidate

Methylphenidate is one of the most frequently used medications to treat ADHD in children, adolescents, and adults. Studies conducted with twins and family members have demonstrated a genetic component of ADHD presentation, and recently there has been more research looking for specific gene connection to ADHD. Although some individual studies have shown a possible gene link, the research is still new and further testing and evaluation needs to be done [24,25]. Currently there is no concrete evidence to show specific pharmacogenetics applications in ADHD medications.

Micro-dialysis Studies

A key amount of research regarding drugs used to treat ADHD is done through the use of rats, particularly spontaneously hypertensive rats Pillidge [26]. The neurobiological root of ADHD is largely associated with dysfunction of catecholaminergic systems in the prefrontal cortex and striatum. Some suggest that predominantly inattentive ADHD is a result of a dopamine system dysfunction, while the predominantly hyperactive-impulsive type is a result of subcortical structure dysfunction. The spontaneously hypertensive rats are hyperactive and impulsive and show a difference in dopamine transporter sites similar to humans with ADHD. They also have lower levels of norepinephrine in the prefrontal cortex [27]. Studies involving these rats is somewhat inconsistent but does result in improved behaviors such as conditional avoidance tasks and spatial learning tasks.

Non-Pharmacological Treatments

Medication is not always an option for those diagnosed with ADHD, especially considering the cognitive deficits that come along with ADHD which are associated with lower rates of medication adherence (due to memory deficits, oppositional issues, misplacement, etc.). Luckily, there are also clinically tested behavioral treatment options. Early diagnosis of ADHD in children is shown to decrease severity of symptoms later on in life, so it is important for parents and teachers to be aware of the signs and symptoms of ADHD in young children.

Behavioral Therapy

Especially for very young children (age 6 and younger), behavioral treatments for ADHD can provide a plethora of benefits [28]. A psychologist or mental health professional may coordinate with the parents or guardians of the young child to help reduce disruptive behaviors through behavior management therapy. These interventions can be done in the home or at school and give parents the knowledge and skills to help their child with their diagnosis. While behavior therapy can be very effective even through adolescence, it is much more difficult to implement for older children and/or adults [29]. It may be harder for parents of teenagers to engage with their children for behavioral parent training, and high school teachers are less willing to support treatment in a school setting. These barriers can make behavior therapy for adolescents almost impossible, and thus many adolescents refer to medication as a treatment option instead.

Differences in Pharmacological and Behavioral Treatments

As previously stated, research has shown a strong preference for a combination of pharmacological and behavioral treatment to combat childhood and adolescent ADHD. There is less research when it comes to the treatment of ADHD in adulthood, however a large majority of adults diagnosed with ADHD use medication only as treatment. Some people also choose not to use any specific treatment for their diagnosis of ADHD or attempt to self-medicate through the use of drugs and/or alcohol. Depending on the specific situation of an individual, their pharmacist or provider may choose to treat with a certain medication, with behavior therapy, or a combination of the two [30-41].

Conclusion

Although ADHD affects such a large proportion of the population compared to other psychiatric disorders, there are any ways that can be used to treat it. Research has shown a combination of medication management and behavior therapy to be the most beneficial, particularly in younger children. Pharmacological treatments such as amphetamines and methylphenidate are among the most effective drugs for ADHD treatment [42-57].

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