

Adderall: On the Razor's Edge of ADHD Treatment, Enhanced Academic and Physical Performance, Addiction, Psychosis, and Death

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Abstract

Adderall, as a drug combination, is medically-approved for treating attention-deficit/hyperactivity disorder (ADHD) and narcolepsy. The active ingredients of Adderall are central nervous system stimulants, affecting neurotransmitters and promoting the synthesis of specific neuropeptides. Pharmacological effects include increased physical energy, improved mental aptitude, hyperexcitability, and mood elevation. In ADHD, Adderall increases arousal, wakefulness, and motivation to execute a task, promoting goal-directed behavior. Regarding physical performance, amphetamine (Adderall) improves endurance and reaction time. Thus, Adderall is banned for use among professional and Olympic athletes. As well as benefits, Adderall has numerous mild to severe adverse effects (including death) and can result in physical and psychological dependence. The sudden cessation of the drug may cause paranoid delusion, psychosis, hallucinations, mood swings, suicidal ideation, panic attack, and tremor. Also, long-term use can result in tolerance to the drug. Adderall has high abuse potential as a recreational agent. It is misused as an academic-enhancer—known as “smart pills”—by students. Although medically-approved for managing symptoms of ADHD and in treating narcolepsy, Adderall has a high abuse and addiction potential and should be taken only if medically prescribed. Realistically, however, Adderall's off-label and unprescribed use will likely continue; if so, it should be taken with extreme caution and vigilance.

Keywords: Amphetamine; Attention; Cocaine; Dopamine; Ecstasy; Hyperactive; Neurotransmitter; Smart Pills

Abbreviations

ADHD: Attention-Deficit/Hyperactivity Disorder; CART: Cocaine- and Amphetamine-Regulated Transcript; CDC: The Centers for Disease Control and Prevention; CNS: Central Nervous System; DEA: Drug Enforcement Agency; IOC: International Olympic Committee; IR: Immediate-Release; MDA: Methylenedioxymphetamine; MDMA: Methylenedioxymethamphetamine; MLB: Major League Baseball; NBA: National Basketball Association; NCAA: National Collegiate Athletic Association; NFL: National Football League; WADA: World Anti-Doping Agency; XR: Extended-Release

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Introduction

Adderall is a combination of medications (amphetamine and dextroamphetamine) medically-approved for treating attention-deficit/hyperactivity disorder (ADHD) and narcolepsy. First synthesized in 1920, the drug was primarily used to allay fatigue and improve alertness during the Second World War. Chemically, the drug is a mixture of four salts—two amphetamine and two dextroamphetamine salts—in equal proportions [1–3]. The amphetamine salts are aspartate monohydrate and amphetamine sulfate, whereas the dextroamphetamine salts are dextroamphetamine sulfate and dextroamphetamine saccharate [3].

Amphetamine and dextroamphetamine, the active ingredients of Adderall, are central nervous system (CNS) stimulants. They increase neurotransmitter (dopamine and norepinephrine) activities and trigger epinephrine, serotonin, and histamine release. They also promote the synthesis of specific neuropeptides, such as cocaine- and amphetamine-regulated transcript (CART) peptides [1,4]. Amphetamine and dextroamphetamine bind to the same biological receptors but with different binding affinities. Thus, the potency of the two active ingredients is different. Compared to the racemic amphetamine, the drug combination has more potent CNS effects due to a higher dextroamphetamine concentration [3,5]. The drug is available in two formulations: immediate-release (IR) and extended-release (XR) [5,6] (Figure 1).



Figure 1: Image of extended-release (XR) 25mg Adderall capsule. Source: public domain.

Discussion

Absorption

Following oral administration, amphetamine is rapidly absorbed by the small intestine, and the peak plasma concentration is achieved within 1–2 hours. Food intake accelerates its absorption. The significant metabolites of amphetamine are p-hydroxy ephedrine and p-hydroxy amphetamine. Amphetamine elimination is mainly through urine. Following a single oral dose, amphetamine is detected in urine for about 48h. The time to reach the peak concentration varies between individuals, but most likely occurs between 3h and 12h after drug intake [3].

Pharmacological effects: cognitive performance

Physiological effects of amphetamine include increased physical energy, improved mental aptitude, hyperexcitability, and mood elevation. The drug's adverse effects include anxiety, indifference, irresponsible behavior; increased irritation, restlessness, dehydration, tremor, insomnia, loss of appetite, and depression; these effects being primarily dose-dependent [7].

ADHD stimulants, including amphetamine, increase arousal and wakefulness and motivate ADHD patients to execute a task (task saliency), resulting in goal-directed behavior [8,9]. Studies exploring self-reported use of illicit drugs have demonstrated that about 5–35% of college students abuse ADHD drugs, more for enhancing academic performance than recreational purposes [8–11]. However, high-dose amphetamine can impair working memory and diminish cognitive abilities [8,12].

Spencer, *et al.* (2015) reviewed currently available evidence on amphetamine and found that the drug improved cognition, working memory, long-term episodic memory, inhibitory control, and attention span in normal, otherwise healthy individuals [7]. They reported that stimulation of dopamine receptors (D1 subtype) and adrenoceptors ($\alpha 2$ subtype)—located in the prefrontal cortex—is crucial to cognition enhancement associated with amphetamine use in healthy adults [7].

In a systematic review, Bagot, *et al.* (2014) examined neurocognitive effects of prescription CNS-stimulant drugs among non-ADHD young adults for their abuse potential in improving academic performance [13]. The review included 14 studies with participants aged between 12 and 25 years. The study considered three prescription stimulant drugs: modafinil, methylphenidate, and amphetamine. The findings demonstrated that amphetamine significantly improved the ability to consolidate information, leading to improved recall. Moreover, it improved working memory in adults [13].

Pharmacological effects: physical performance

Amphetamine improves endurance and reaction time, primarily through reuptake inhibition and the release of dopamine in the CNS [14,15]. Amphetamine and other dopaminergic drugs improve power output by facilitating a rise in the core body temperature by overriding the feedback inhibition process (“safety switch”) that occurs under normal physiological conditions [15,16].

At a therapeutic dose range, amphetamine does not decrease athletic performance, but a higher dose can cause an increase in body temperature and a rapid breakdown of muscle mass [10]. Thus, amphetamine use is prohibited (unless indicated medically) for athletes participating in any sporting event, and different national and international authorities regulate or prohibit its use [17].

The effect of amphetamine use among athletes was first investigated in 1959 [18]. Athletes tend to abuse amphetamine for their potential in improving performance. Amphetamine improves anaerobic performance with a modest effect on aerobic performance. Published studies reveal that amphetamine improves the reaction time, especially when the athlete is fatigued, increases muscle strength and endurance, facilitates metabolism by stimulating fat metabolism, and increases endurance. However, at higher doses, the drug tends to promote aggressiveness. Amphetamine in healthy individuals was reported to increase muscle strength, acceleration, alertness, athletic performance under anaerobic circumstances, and reaction time and delays the onset of fatigue [14,15].

Prohibition in professional and high-level sports

Several sporting authorities, including the National Football League (NFL), Major League Baseball (MLB), National Basketball Association (NBA), National Collegiate Athletic Association (NCAA), International Olympic Committee (IOC), and World Anti-Doping Agency (WADA) have banned the use of Adderall among athletes participating in sporting events [17,19]. The athletes are screened daily for the presence of prohibited substances, including amphetamine, by accredited laboratories. In competitive sports, amphetamine comes under Category S6, and its presence in urine is considered a severe doping offense [18].

Adverse effects

Common adverse effects associated with Adderall use are restlessness, difficulty in falling asleep, interrupted sleep, headache, dizziness, hoarseness, slowing of speech, visual change, alteration in sexual performance or desire, seizure, constipation, nausea, vomiting,

diarrhea, hallucination, paranoia, and exacerbation of pre-existing mental illnesses (such as bipolar disorder, depression, or anxiety) [20]. In some patients, severe adverse drug reactions of excessive body temperature, myocardial infarction (heart attack), or cerebrovascular accident (stroke) may occur [21,22]. Adderall (amphetamine) can produce both physical and psychological dependence. Thus, sudden cessation of the drug may cause withdrawal syndrome characterized by paranoid delusion, psychosis, hallucinations, mood swings, suicidal ideation, panic attack, and tremor [20,23].

In athletes, heatstroke and sudden cardiac arrest are the two most significant risks associated with Adderall use [24]. There have been reports of amphetamine-induced sudden cardiac arrest among cyclists during competition [25]. Amphetamine is known to mask pain caused by a sport-related injury, making the athlete oblivious to an underlying injury and risk of further harm. Increased aggression and reduced fatigue might lead to misjudgment of circumstances and sporting fouls [26].

Adverse effects in long-term use

Prolonged use of amphetamine causes patients to develop tolerance to the drug. It may also cause physical dependence, often leading to severe withdrawal symptoms [27]. Amphetamine-dependent individuals demonstrate signs of increased aggression, psychosis, and anti-social behavior [26].

Summary (indications, contraindications, and prevalence of use)

In specific ADHD studies, Adderall alleviated symptoms of hyperactivity, impulsive behavior, and reduced attention span in 70–80% of pediatric patients and 70% of adult patients. The maximum benefit of the drug was achieved when the drug was used along with behavioral therapy. The drug is recommended to be taken in the morning due to its potential to interfere with sleep. Typically, Adderall is prescribed at low doses, which is increased gradually based on the response and tolerability [3].

Although chiefly approved for ADHD and narcolepsy, several off-label uses are strictly monitored by certain United States federal agencies due to its high abuse potential as a recreational agent and cognition- and performance-enhancer [28]. Adderall is misused as a recreational drug and academic-enhancer (“smart pills”) by students [29].

Since 1920, many drug derivatives—such as methamphetamine, dimethamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) or “ecstasy”, and selegiline—have been synthesized [30,31] (Figure 2). The use of amphetamines or its derivatives is banned in sporting events worldwide [32].

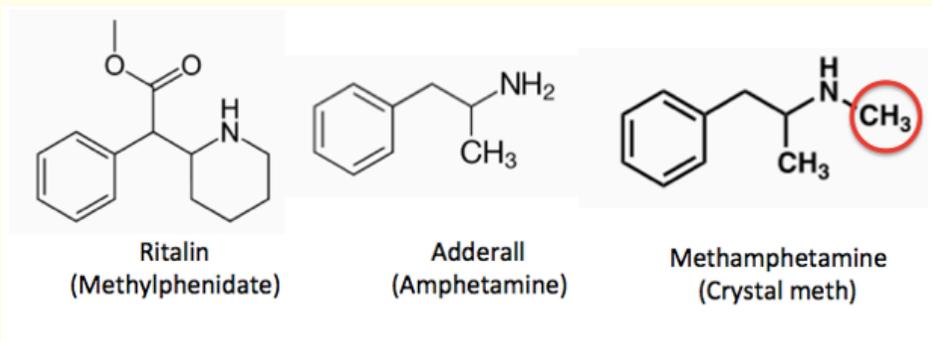


Figure 2: Comparative chemical structures of Ritalin (methylphenidate), Adderall (amphetamine), and “Crystal Meth” (methamphetamine). Source: public domain.

According to the United States Drug Enforcement Agency (DEA), approximately 50 million prescriptions for stimulant drugs, including Adderall, were dispensed in 2011, indicating a 40% increase in the prescription of stimulant drugs [26]. The Centers for Disease Control and Prevention (CDC) reported that about 10% of the American children (approximately 6 million) were clinically diagnosed as having ADHD and prescribed Adderall or similar drugs in 2015 [26]. However, the massive surge in such prescriptions has led to increased addiction to these drugs.

Conclusion

Adderall is medically-approved for managing symptoms of ADHD and treating narcolepsy. However, it has abuse potential as it enhances cognitive and physical performance. Adderall is misused as a recreational drug, academic-enhancer ("smart pills") by students, and performance-enhancer by athletes.

Long-term Adderall use and short-term use at higher doses result in mild to severe adverse effects, such as increased blood pressure, elevated core body temperature, precipitation of psychosis, hallucination, delirium, aggression, suicidal ideation, and insomnia. Although the drug may initially improve cognitive and physical performance to a certain extent, the performance gradually deteriorates due to the above-mentioned adverse events. Adderall use in athletes during stressful competitive events may precipitate sudden cardiac arrest, resulting in death.

Several international and national regulatory bodies have prohibited the use of Adderall among athletes participating in sporting events, and strict action is taken against those testing positive for the drug. Adderall may be beneficial if used for approved indications in a dose-titrated manner and behavioral therapy; however, higher doses for an extended period for any off-label use may lead to serious side effects. Its presence in body fluids is considered a doping offense.

Adderall has shown benefits in managing and treating ADHD and narcolepsy, and the rewards seem to outweigh the risks. Nevertheless, when it comes to enhancing physical and academic performance, taking "smart pills" seems "unsmart" and misguided, especially in the long-term, unless sensibly managed.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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