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# An Analysis of ADHD Drugs: Ritalin and Adderall

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# An Analysis of ADHD Drugs: Ritalin and Adderall

## **Abstract**

Ritalin and Adderall are commonly prescribed drugs for the treatment of the attention-deficit hyperactivity disorder (ADHD) in children, adolescents, and adults. Our study summarizes the properties and applications of these chemical compounds: methylphenidate (Ritalin, MPH) and dextroamphetamine (Adderall) describing the similarities and differences in their modes of action. Inclusively, these drugs perform by altering catecholamine levels in the nervous system for increased stimulation.

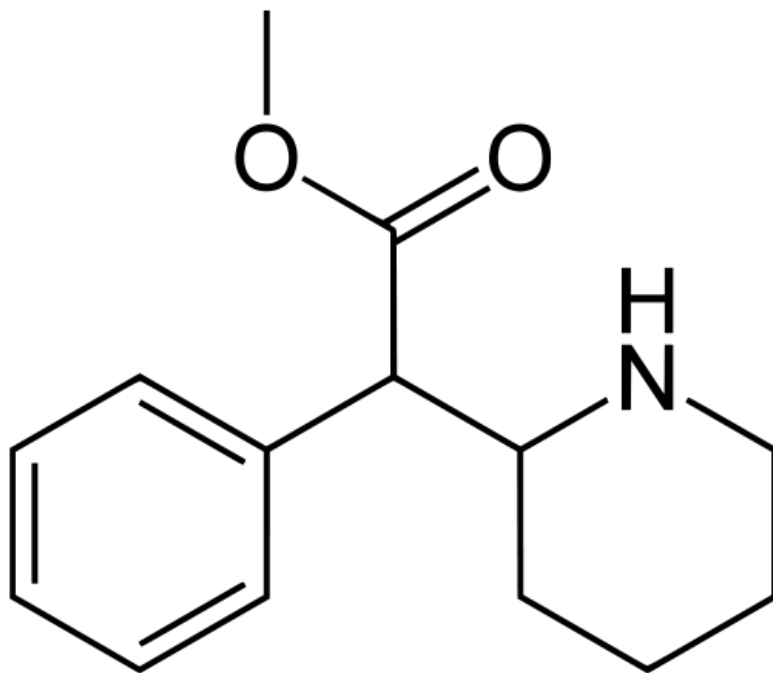
## **INTRODUCTION**

Attention-deficit hyperactivity disorder is a psychiatric condition that is treated with a class of drugs called psychostimulants whose major function is to increase activity of the central nervous system (CNS). The main region of exertion is the dopamine transporter (DAT) in the brain. Psychostimulants have been found to be the most effective drugs in reducing symptoms of inattention, hyperactivity, and impulsivity in patients with ADHD [1]. To gain an understanding of ADHD drugs, this paper will provide an overview of two commonly prescribed drugs: Adderall (dextroamphetamines) and Ritalin (methylphenidate), with emphasis on the chemical and physical properties, chemical structure, mode of action, dosage, and adverse effects.

## **PART I: CHEMICAL AND PHYSICAL PROPERTIES**

### **Ritalin**

The brand name Ritalin is made up of the chemical compound Methylphenidate (MPH) with the IUPAC (abbreviation from the International Union of Pure and Applied Chemistry) name methyl phenyl(piperidin-2-yl)acetate [2]. The molecular formula for MPH,  $C_{14}H_{19}NO_2$  and structural formula (pictured below) indicate that the chemical compound consists of the elements carbon, hydrogen, and nitrogen with a molecular weight totaling to 233.31 g/mol. MPH is a piperidine compound due to the presence of an amine group bonded within a carbon cycle. The melting point of this compound is 214 °C [2]. The finished product that makes up MPH is an odorless, white solid as crystalline powder [3].



Methylphenidate

### Adderall

The brand name Adderall is a chemical compound that is made up of powerful blends of the amphetamine (abbreviated form from alpha-methylphenethyl amine) salts dextroamphetamine and levoamphetamine, which are isomers of the original amphetamine molecule and come in a 3:1 ratio [4]. The blend consists of the following:

One-quarter racemic (d,l)-amphetamine aspartate monohydrate,

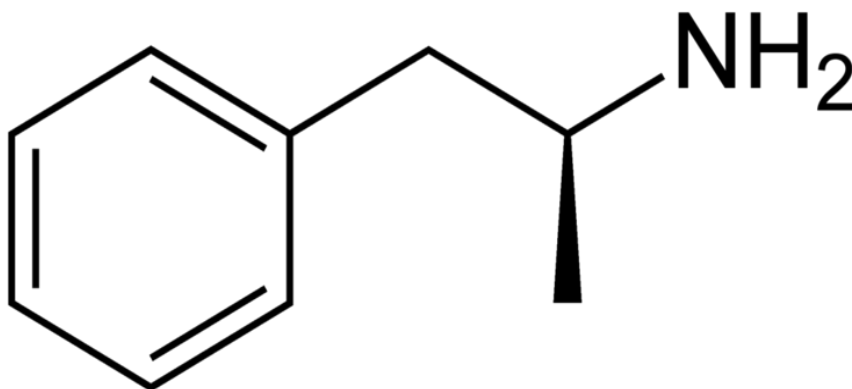
One-quarter dextroamphetamine saccharin,

One-quarter dextroamphetamine sulfate,

One-quarter racemic (d,l)-amphetamine sulfate [5].

The IUPAC name for dextroamphetamine is 1-phenylpropan-2-amine [5]. The molecular formula,  $C_9H_{13}N$  and structural formula (pictured below) show that the compound consists of the elements carbon, hydrogen, and nitrogen with a molecular weight totaling to 135.21 g/mol. The

chemical structure also reveals a benzene aromatic ring bonded with an amine side group. Before amphetamine is made into a salt or a solid for ingestion, it is a colorless liquid with a boiling point of 203-204 °C [6].



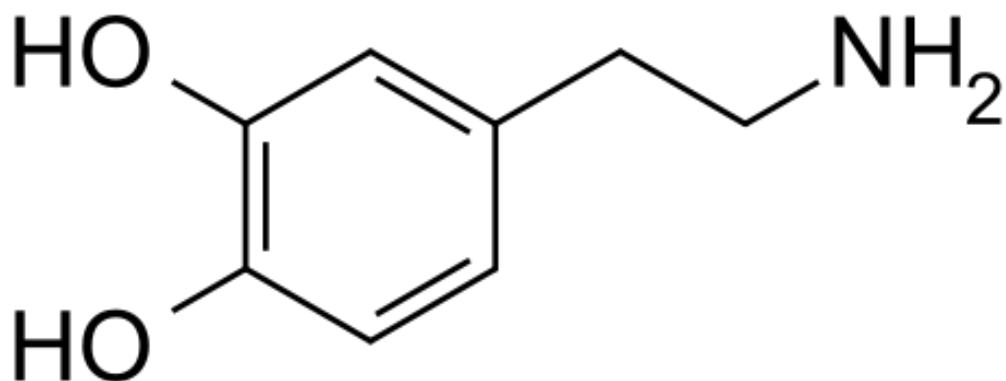
Amphetamine

## **PART II: MODE OF ACTION**

### **Dopamine**

The biggest player in improving symptoms of ADHD is a catecholamine neurotransmitter called dopamine. The molecule consists of a benzene ring with two attached hydroxyl side groups (see picture below). Studies suggest that a person with ADHD has a dopamine dysfunction and lacks the normal levels of the neurotransmitter [7]. Dopamine is biosynthesized in the body through an enzyme catalyzed process in which substrates are converted to more complex products [7,8]. Furthermore, dopamine is a precursor for the neurotransmitters norepinephrine (noradrenaline) and then epinephrine (adrenaline) in their biosynthetic pathways. This family of catecholamines is biosynthesized by nervous tissue and the adrenal gland [7]. After synthesis, dopamine is packaged into vesicles which are then released into the synapse in response to a presynaptic action potential. In the nervous system, a synapse is a structure that permits a neuron (nerve cell) to pass an electrical or chemical signal to another cell [9] via axons. Action potentials generate and travel along axons of neurons to activate synaptic connections

between each other. Regulation of neurotransmitters such as dopamine is achieved through cell-cell signaling via synapses. At a chemical synapse, one neuron releases neurotransmitter molecules into a small space (the synaptic cleft) that is adjacent to another neuron. These molecules then bind to the receptors on the receiving cells side of the synaptic cleft to the post synaptic area. Finally, the neurotransmitters must be cleared out of the pre synaptic area efficiently in order to be prepared for succeeding signals [10]. The dopaminergic neuron dopamine modulates both pre and post synaptic neurotransmission [7]. It is naturally released in rewarding experiences. Moreover, dopamine has many functions of regulation in the brain including cognition, voluntary movement, motivation, punishment, sleep, mood, attention, working memory, and learning [10]. For example, an individual affected with Parkinson's disease experiences dysfunctions in their motor and cognition because the dopamine generating cells no longer operate appropriately. Dopamine neurotransmitter plays a crucial role in the ability of a person to function and perform all essential daily activities. A synthetic form of dopamine has been made, however ingesting the synthesized dopamine drug has no direct affect to the CNS (central nervous system) because it cannot pass the blood brain barrier (BBB). For this reason, chemical compounds that are smaller molecules such as MPH and amphetamines are medically used to increase levels of dopamine and related neurotransmitters in the brain.



Dopamine

### Ritalin

MPH is a chain substituted amphetamine derivative that primarily acts as a norepinephrine-dopamine reuptake inhibitor [2]. It is well absorbed from the gastro-intestinal (GI) tract after oral administration and reaches peak concentrations in the brain within approximately 2 hours [11, 12]. MPH targets the dopamine transporter (DAT) with the affected area being the prefrontal cortex in the brain [13]. The main mechanism of action is the modulation of the catecholamines, norepinephrine and dopamine. This is achieved by the enantiomers d-threo-methylphenidate and l-threo-methylphenidate which bind to DAT [14]. A norepinephrine-dopamine reuptake inhibitor increases the amount of norepinephrine and dopamine neurotransmitters in the brain by partially blocking DAT, inhibiting it from completely removing the dopamine from the synapse [2]. Generally, the inhibition of DAT stops the presynaptic neuron from reabsorbing dopamine and norepinephrine, which increases the amount of dopamine in the synapse. Persons affected by ADHD tend to have lower levels of dopamine neurotransmitters in their synapses and the inhibition of DAT during treatment stimulates the

release of dopamine and norepinephrine into the synapse. MPH has the capability to occupy about 50% of the dopamine transporters [2]. Because MPH is a small molecule, it passes through the BBB in the mode similar to those of cocaine, but the MPH is less intoxicating and its duration of action is longer. Stimulation of dopaminergic activity greatly increases levels of dopamine, which ultimately increases attention and motivation, while decreasing distractibility and motor hyperactivity [13].

### **Adderall**

Adderall is administered orally and absorbed from the GI (gastrointestinal) tract with peak concentration in the brain reached approximately in 3 hours [15]. During its metabolic process, the aromatic ring in amphetamine oxidizes to form alpha-hydroxyamphetamine, which then undergoes deamination to form phenylacetone, and finally, oxidizes to form benzoic acid [15]. Similar to MPH and cocaine, amphetamine is a small molecule allowing it to pass the BBB easily. Dextroamphetamine affects the central nervous system by increasing dopamine levels while levoamphetamine affects the peripheral nervous system by increasing norepinephrine [16]. Since dextroamphetamine consists of three quarters of the salts in Adderall, it greatly impacts the prefrontal cortex of the brain. In reducing ADHD symptoms, the key function of Adderall is to block the reuptake of norepinephrine, dopamine, and serotonin into the presynaptic neuron and increase the release of these monoamines into the synaptic space [15]. Like MPH, it is able to enhance dopaminergic activity by binding to DAT and prolonging the availability of neurotransmitters in the synapse by slowing down their removal [16]. Additionally, amphetamine enters the presynaptic neuron building a membrane potential to force dopamine molecules out of their storage vesicles and expel them into the synaptic space. This action is performed by making the dopamine transporters work in reverse [7]. Subsequently, amphetamine



also has the power to inhibit the enzyme that is responsible for the breakdown of neurotransmitters called monoamine oxidase [16]. Inhibiting this process leads to the accumulation of dopamine, norepinephrine, and serotonin. The potency of dextroamphetamine in Adderall greatly and rapidly increases levels of the monoamine neurotransmitters in the synapse, ultimately reducing symptoms of inattention, impulsivity, and hyperactivity.

### **PART III: DOSAGE AND ADVERSE EFFECTS**

#### **Ritalin**

MPH is available in immediate release form (Ritalin), sustained release form (Ritalin SR), and extended release form (Ritalin LA). The immediate release form is available as 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets and can last anywhere from 3 to 5 hours [17, 18]. The immediate release tablet is taken two to three times daily with an average dosage of 20 to 30 mg a day [17]. The recommended starting dosage is 5 mg and is adjusted based on the response of the individual [17]. Ritalin SR is available as 20 mg, 40 mg, and 60 mg and is taken once or twice daily. Ritalin LA is available as 20 mg, 30 mg, 40 mg, and 50 mg capsules [17]. Ritalin LA is taken once daily in the morning and can last anywhere from 8 to 12 hours [17, 18]. All forms of MPH are not recommended to exceed 60 mg per day [19]. The dosage prescribed to a patient is determined by their severity of symptoms, body weight, and rate of metabolism. The common adverse effects associated with taking MPH are rapid heart rate, palpitations, nervousness, restlessness, insomnia, dry mouth, constipation, nausea, diarrhea, loss of appetite, weight loss, and elevation of blood pressure [17]. MPH should not be used in children under six years old nor in persons with high blood pressure or any form of heart disease, persons who are nervous or have severe insomnia, persons who are taking monoamine oxidase inhibitors and persons who have a history of addiction to drugs and alcohol [20]. The Food and Drug Administration (FDA)

also issues an additional “Black Box” warning label which means that medical studies indicate these drugs carry a significant risk of serious, or even life-threatening, adverse effects [20]. Ritalin is classified as a schedule II substance by the FDA because it shares the same abuse potential as cocaine and morphine that may lead to severe psychological or physical dependence [20]. There is little research on the long term effects of using MPH. It is possible to build up a tolerance where the person using the drug will need to take larger doses to achieve the same effect [20]. Overtime, the body may become dependent on the drug to function normally. The withdrawal symptoms that could arise include tiredness, panic attacks, crankiness, extreme hunger, depression and nightmares. These symptoms are mostly psychological and stopping the drug suddenly can cause extreme fatigue and severe, even suicidal, depression in adult patients [20]. A person should never stop taking MPH abruptly but should do so gradually.

## **Adderall**

Adderall is available in instant (Adderall IR) and extended release form (Adderall XR). The instant release tablet is taken 2 to 3 times daily; 4 to 6 hours apart each time, and can be taken with or without food [21]. The doses available for Adderall IR tablets are 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, and 30 mg breakable tablets. The daily maximum recommended dose is 40 mg, but some patients may initially require 60 mg [22]. In contrast, Adderall XR is taken only once daily in the morning and can be taken with or without food [21]. The doses available for Adderall XR capsules are 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg capsules, which are not breakable [21]. The daily maximum recommended dose is 30 mg, but some patients may require more [22]. Adderall IR and XR are both metabolized by the liver; IR lasts 4 – 6 hours and XR lasts 8 – 10 hours [22]. Patients normally start at a low dose and gradually increase as tolerated. The most common adverse reactions in children ages 6 to 12 are loss of appetite, insomnia,

abdominal pain, emotional liability, vomiting, nervousness, nausea, and fever [23]. In adolescents, the common adverse reactions are loss of appetite, insomnia, abdominal pain, weight loss, and nervousness [23]. Finally, in adults, the common adverse reactions are dry mouth, loss of appetite, insomnia, headache, weight loss, nausea, anxiety, agitation, dizziness, tachycardia, diarrhea, asthenia, and urinary tract infections [23]. Adderall should not be used in persons who have not tried other psychotherapy before, have high blood pressure or any form of heart disease, are very nervous or have severe insomnia, have a history of addiction to drugs or alcohol, take monoamine oxidase inhibitors, or have Tourette syndrome, which is one of several chronic tic disorders [24]. The FDA also issues a “Black Box” warning label which means that medical studies indicate these drugs carry a significant risk of serious, or even life-threatening adverse effects. Like Ritalin, Adderall is also classified as a schedule II drug by the FDA due to its high abuse potential. Amphetamines have the ability to induce anxiety disorders, psychosis, and sexual dysfunction [24]. Because amphetamines are very closely related to MPH, they have the same dependence, tolerance, and withdrawal characteristics. It is possible to build up a tolerance where the person using the drug will need to take larger doses to achieve the same effect [24]. Overtime, the body may become dependent on the drug to function normally. The withdrawal symptoms that could arise include tiredness, panic attacks, crankiness, extreme hunger, depression and nightmares [24]. These symptoms are psychological and stopping the drug suddenly can cause extreme fatigue and severe, even suicidal, depression in adult patients [24]. Again, a person should never stop taking Adderall abruptly but should do so gradually. Jack M. Gorman, M.D., professor of psychiatry at Columbia University and deputy director of the New York State Psychiatric Institute emphasizes: “Adderall is a very powerful drug that

undoubtedly works for ADHD, but there are alternatives with less abuse potential that should be tried first.” [24]

## **SUMMARY**

MPH and Adderall are both used for the pharmacological treatment of ADHD but differ chemically. Moreover, although the both drugs are similar in structure, metabolism, and clinical effects, they do differ in their mode of action. MPH is less potent and longer in duration of action [2]. In contrast, amphetamines have a quicker onset followed by a “speed crash.” Adderall has the ability to make DAT work in a reverse mechanism increasing catecholamine levels to a greater and quicker extent than Ritalin. The dosage charts of the two drugs also imply that Adderall has higher potency. Hence, the maximum recommended dosage for Ritalin is 60 mg compared to Adderall, which is 40 mg. Although dependency is possible with both Ritalin and Adderall, the potency of amphetamines in Adderall suggests a higher risk of dependency. It has greater ability to interfere with the natural mechanism of DAT, causing much lower levels of dopamine in the absence of the drug [2]. Comparable to cocaine, Ritalin and Adderall are classified as type II drugs by the FDA because they also have high risks of abuse potential. Furthermore, resembling cocaine, Ritalin and Adderall are also monoamine reuptake inhibitors of dopamine, norepinephrine, and serotonin. The similarities ADHD drugs have to street drugs such as cocaine gives rise to several controversies. However, Ritalin and Adderall are safe and effective to use in small doses because studies have proved them to be therapeutic under the proper regulations. Unfortunately, ADHD drugs are used as recreational stimulants to self-induce euphoria and can be used as a study aid, social aid or party drug [5]. The effects of long term usage of Ritalin and Adderall are not clear yet and remain under investigation. Although Ritalin and Adderall both act to stimulate the nervous system, there are several notable differences

between the two. It is not suggested for one to be better than the other because the effectiveness of each drug varies from person to person. The drug selected to use for treatment of ADHD symptoms is determined by a trained physician.

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