Universidade de Lisboa

Faculdade de Farmácia

Overview of treatments for ADHD: pharmacological, complementary and alternative medicine and the associated safety problems

Maria Constança Frazão Salgueiro Boigues do Amaral

Monografia orientada pela Professora Doutora Cristina Luzia Dias de Mello Sampayo, Professora Auxiliar da Faculdade de Farmácia da Universidade de Lisboa

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Agradecer em específico,

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Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

O ponto-chave desta tese é explicar em que consiste esta Perturbação de Hiperatividade e Défice de Atenção (PHDA), a população mais afetada por ela, como pode ser diagnosticada e tratada, explicando a farmacodinâmica das terapias convencionais no cérebro das pessoas com PHDA e os problemas de saúde associados a estas terapias.

A PHDA é uma perturbação neurológica que afeta vários aspetos da vida de uma pessoa. Caracteriza-se por desatenção, hiperatividade e impulsividade. Pensa-se que a PHDA é causada por fatores genéticos, ambientais e neurobiológicos.

Observou-se que o número de receptores dopaminérgicos está envolvido no desenvolvimento da perturbação e que estes estão reduzidos no córtex frontal das pessoas com PHDA. Outros receptores que também parecem estar envolvidos são os receptores noradrenérgicos, uma vez que os efeitos favoráveis dos medicamentos utilizados para tratar a PHDA estão também relacionados com a atividade do recetor alfa-1 adrenérgico.

O diagnóstico é efectuado clinicamente com base em questionários, entrevistas clínicas e, por vezes, testes neuropsiquiátricos. As entrevistas e os questionários são efetuados com o doente, mas também com pessoas que estão presentes na vida do doente, como professores, pais, irmãos.

Um diagnóstico correto do doente e uma avaliação criteriosa são fundamentais para poder delinear um plano de tratamento correto. Antes de decidir sobre o tratamento, é necessário efetuar uma avaliação geral do estado de saúde do paciente.

Existem diferentes métodos para tratar esta doença, consoante as necessidades e os sintomas da pessoa. As abordagens de tratamento incluem a intervenção farmacológica, combinada, ou não, com a intervenção não farmacológica ou apenas não farmacológica.
Os tratamentos farmacológicos podem incluir quatro grupos de fármacos: os fármacos estimulantes, este grupo é o que tem mais efeitos adversos; os fármacos não estimulantes; os antipsicóticos e os antidepressivos.
Os tratamentos não farmacológicos podem ser divididos em dois grupos: as terapias psicológicas e as terapias complementares e alternativas.

É importante conhecer os diferentes tipos de PHDA e os diferentes tipos de tratamento que existem, a fim de proporcionar o tratamento mais adequado a cada doente e dar-lhes os melhores resultados possíveis e menos efeitos adversos associados à medicação.

Palavras-chave: PHDA, Sintomas, Epidemiologia, Intervenção farmacológica, Efeitos secundários

Abstract

The key point of this thesis is to explain what this Attention Deficit Hyperactivity Disorder (ADHD) consists of, the population most affected by it, how it can be diagnosed and treated, explaining the pharmacodynamics of conventional therapies in the brains of people with ADHD and the health problems associated with these therapies.

ADHD, is a neurological disorder, which affects several aspects of a person's life. It is characterized by inattention, hyperactivity, and impulsivity. ADHD is thought to be caused by genetic, environmental and neurobiological factors.

It was observed that the number of dopaminergic receptors is involved in the development of the disorder, and they are reduced in the frontal cortex of people with ADHD. Other receptors that also appear to be involved are the noradrenergic receptors, since the favorable effects of drugs used to treat ADHD, are also related to the activity of the alpha-1 adrenergic receptor.

The diagnosis is made clinically based on questionnaires, clinical interviews and sometimes neuropsychiatric tests. Interviews and questionnaires are carried out with the patient, but also with people who are present in the patient's life, such as teachers, parents, siblings.

A correct diagnosis of the patient and a thorough assessment is crucial to being able to outline a correct treatment plan. Before deciding on treatment, it's necessary to carry out a general assessment of the patient's health.

There are different methods to treat this disorder, depending on the needs and symptoms of the person. The treatments approaches include pharmacological intervention, combined, or not, to non-pharmacological or just non-pharmacological intervention.
The pharmacological treatments can include four groups of drugs: stimulant drugs, this group has the most adverse effects; the non-stimulant drugs; the antipsychotics and the antidepressants.
The non-pharmacological treatments can be divided into two groups: psychological therapies and complementary and alternative therapies.

It's important to know the different types of ADHD and the different types of treatment that exist in order to provide the most appropriate treatment for each patient and give them the best possible results and fewer adverse effects associated with medication.

Keywords: ADHD, Symptoms, Epidemiology, Pharmacological intervention, Side effects

Abbreviations

5-HT2A - Serotonergic Receptors
ADD - Attention Deficit Disorder
ADHD - Attention Deficit Hyperactivity Disorder
ADHD-C - Attention Deficit Hyperactivity Disorder type Inattention and Impulsivity-Hiperactivity
ADHD-H - Attention Deficit Hyperactivity Disorder type Impulsivity-Hyperactivity
ADHD-I - Attention Deficit Hyperactivity Disorder type Inattention
ADR - Adverse Drug Reaction
AS - Active Substance
CES1A1 - Carboxylesterase Enzyme
Cmax - Maximum Concentration
CNS - Central Nervous System
CYP - Cytochrome
DA - Dopamine
DAT - Dopamine Transporter
DAT1 - Dopamine Transporter Gene
DRD-4 - D4 receptor gene
DSM-III-R - Diagnostic and Statistical Manual of Mental Disorders vol 3
DSM-IV - Diagnostic and Statistical Manual of Mental Disorders vol 4
DSM-V - Diagnostic and Statistical Manual of Mental Disorders vol 5
EMA - European Medicine Agency
FDA - Food and Drug Administration
H1 - Histaminergic
MAO - Monoamine Oxidase
MDD - Major Depressive Disorder
MPH - Methylphenidate
MSNs - Medium Spiny Neurons
NAcc - Nucleus Accumbens
NE - Norepinephrine
NET - Norepinephrine Transporter
NICE - National Institute of Health and Care of Excellence
ODV - O-desmethylvenlafaxine
OROS - Osmotic Controlled-Release Oral Delivery
PA - Physical Activities
PPAA - A-phenyl-2-piperidine acetic acid
SAD - Seasonal Affective Disorder
SERT - Serotonin Transporter
SNRIs - Serotonin/Norepinephrine Reuptake inhibitors
TCAs - Tricyclic Antidepressants
VMAT2 - Vesicular Monoamine Transporter 2

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1. Introduction

The key point of this thesis is to explain what this Attention Deficit Hyperactivity Disorder (ADHD) consists of, the population most affected by it, how it can be diagnosed and treated, explaining the pharmacodynamics of conventional therapies in the brains of people with ADHD and the health problems associated with these therapies.

Objective

The main goals of this review is get to know the different types of ADHD and the different types of treatment that exist in order to provide the most appropriate treatment for each patient and give them the best possible results and fewer adverse effects associated with medication.

2. Method

PUBMED, Science Direct, Web of Science, NIH, NHS, Google scholar, NICE, INFOMED, Drugbank, were used to conduct a literature review during the month January to August 2024. The following search terms were used: [ADHD], [Treatments], [Symptoms], [Diagnosis], [Epidemiology], [Pharmaceutical interventions]

After searching for keywords on the indicated sites, articles with the most recent date were chosen, to have the most up-to-date data and information possible. All articles that were more than four years old, those that were older than 2020, were discarded. With the exception of the guidelines published by NICE (National Institute of Health and Care of Excellence), which were last updated in September 2019.

3. Clinical types of ADHD their prevalence and symptoms

ADHD, Attention-deficit hyperactivity disorder, is a neurological disorder, which affects several aspects of a person's life. It is characterized by inattention, hyperactivity, and impulsivity. [1]

To understand more, it's important to explain these characteristics:
- Inattention or lack of attention means that the person has difficulty staying focused, carrying out tasks to the end, and being organized. This is not due to a lack of understanding.
- Hyperactivity means that the person is unable to sit still even on the least appropriate occasions, shows restlessness and talks a lot.
- Impulsivity means that the person acts without thinking or has no control of their own. It can also include wanting immediate gratification, interrupting people during conversations, and making decisions without taking future consequences into account. [2]

According to the most prevalent characteristics this disorder can be classified in three different subtypes: ADHD-I, where inattention predominates; ADHD-H where hyperactivity-impulsivity predominates and ADHD-C where both symptoms of inattention and hyperactivity-impulsivity are present.

3.1. Pathophysiology of the disorder

The pathophysiology of this disorder is not entirely known. ADHD is thought to be caused by genetic, environmental and neurobiological factors. [3]
There is evidence that genetics can be an important factor, due to the fact that ADHD usually runs in the families. Its heritability may vary from 70% to 80%, being a very high percentage. Other possible factors and risks that can contribute to ADHD are brain anatomy, premature delivery, low birth weight, lead poisoning and substance abuse during pregnancy. [4]
When looking at images of the brains of people with ADHD, consistent results are not found. What was observed was that the number of dopaminergic receptors is involved in the development of the disorder, as they are reduced in the frontal cortex of people with ADHD. [5]
In clinical studies it was found that children with ADHD have an irregularity in the dopamine transporter gene (DAT1), in the D4 receptor gene (DRD-4) and/or in the D2 receptor gene. [67]
Other receptors that also appear to be involved are the noradrenergic receptors[5] since the favorable effects of drugs used to treat ADHD, such as methylphenidate, are also related to the activity of the alpha-1 adrenergic receptor. [6 7]

In the brain, the frontal lobe is responsible for language usage, decision-making, organizing thoughts and behavior control via “directed attention”. The brain of people with ADHD shows a slower growth unlike people without ADHD, affecting their ability to pay attention. This may be due to the fact that the number of dopamine receptors is reduced in this area of the brain [5], thus affecting normal brain development. They are able to pay attention, however it's hard to focus their attention at the right moment. When faced with stimuli, they struggle to maintain the motivation, because of the incapacity to filter in an efficient way that stimuli. This highlights how attention problems in ADHD have to do with the difficulty of filtering, choosing stimuli, and maintaining focus and motivation. [4]

3.2. Diagnosis

There are different diagnosis criterias and these criterias have been changed and altered over time.

It is important to highlight that in 1798, Sir Alexander Chricton wrote in his book *On Attention and its Diseases*, one of the first documents that talked about the characteristics of attention disorders.
In the 30s of the 20th century, two doctors, Kramer and Pollnow, wrote about children who had a syndrome that closely resembles what we now describe as ADHD. This syndrome was known as “hyperkinetic disease of infancy”. It was only in 1980, with the publication of the DSM-III (Diagnostic and Statistical Manual of Mental Disorders vol 3), that the diagnosis of “attention deficit disorder” (ADD) originated. The number of symptoms to confirm the diagnosis were also reduced, as well as the onset age, that was before 7 years old. [3]

However, it was in 1987, with the publication of the DSM-III-R, that the ADHD we know today emerged and combined the subtypes of lack of attention and hyperactivity into a single diagnosis. Afterwards, the DSM-IV separated the diagnosis into three subclasses,

predominant inattention, predominant hyperactivity and the two combinations. Finally, in 2013, with the DSM-V, the definition of ADHD was expanded, with significant changes. [3]

It was defined that the age of onset is usually before 12 years of age, symptoms occur both at school, at work and at home, the disruption causes significant problems in social, occupational and academic functioning and the disorder is not caused by any other behavioral disorder. [5]

The diagnosis is made clinically based on questionnaires, clinical interviews and sometimes neuropsychiatric tests. [3] Interviews and questionnaires are carried out with the patient, but also with people who are present in the patient's life, such as teachers, parents, siblings.[5]

Questionnaires and clinical interviews collect a series of key questions that aim to understand signs and symptoms. Questions may include: "what symptoms do you have?", "when did these symptoms start?", "What's going through your head when you're sitting in your chair listening to the teacher explain at school?", "what is your experience when you have to read or focus on work for a long period of time?", "Do you often lose things, like your cell phone, keys?", "What happens when you have many tasks to do at the same time and you have a deadline?", "How much attention do you pay to the things you like compared to the things you like less?", "Do your teachers, parents or friends ask if you are paying attention? Do you need to ask them to repeat themselves? Do you sometimes pretend you understand the conversation but you really don't?"[3]

During the interview it is important to observe details in the person's behavior, such as if they move a lot in the chair, or if they "play" with their hands and fingers, if they are restless, if their backpack is disorganized, if the patient talks a lot and quickly, if they repeat things that have already been said or if they have forgotten the question they were asked.[3]

This will help to better understand the patient's verbal and non-verbal behaviors and thus be able to confirm a diagnosis.[3]

3.3. Epidemiology

Attention deficit disorder has different subtypes, as already mentioned. Depending on these subtypes, there are different prevalence rates.

The ADHD-I subtype is prevalent in 18.3% of all patients. Whilst ADHD-H is prevalent in 8.3% and ADHD-C is prevalent in 70%. It was also concluded that the ADHD-I subtype is more prevalent in females. Nevertheless, this disorder affects more males than females, represented in a 2:1 ratio.

Speaking of the prevalence of the disorder among adolescents and children, according to studies carried out, the prevalence of ADHD in children between 3 and 12 years of age is 7,6% and is almost equal in the three subtypes, in adolescents between 12 and 18 years of age is 5.6%, but the most predominant is the ADHD-I subtype.

It has also been discovered that the prevalence of this disorder depends on the diagnostic criteria that is used. The predominance of diagnosis in adolescents and children using the

DSM-V is superior compared to alternative diagnostic criteria. This may be due to the fact that DSM-V is the most recent, with the most up-to-date and accurate criteria. [8]

4. Therapeutic Options to manage ADHD

4.1 Baseline assessment before medication

According to the guidelines published by NICE, National Institute of Health and Care of Excellence, and Australian ADHD Professionals Association there are a number of things that are important to evaluate before giving medication.

First of all, it is necessary to confirm the diagnosis and whether it meets the criteria for starting treatment. It is essential to carry out an evaluation of mental health and social situation, such as: existence of other mental health and neurodevelopmental disorders, present educational or employment situation, risk evaluation of the substance abuse or drug deviation, care needs.[9] [10]

After this, a physical health examination is carried out, such as: medical history, considering that certain conditions are contraindicated for specific medications, current medication, weight and height (measured and documented in relation to the age, height, and sex norms), basal pulse and blood pressure (assessed using a cuff that fits well and compared to the typical age range), a cardiovascular examination. [9]

It's not required to perform an electrocardiogram before starting to take stimulants, atomoxetine or guanfacine, unless the person has a condition that is being treated with medication that may increase the risk of a heart attack or has the following characteristics: “History of congenital heart disease or previous cardiac surgery; History of sudden death in a first-degree relative under 40 years suggesting a cardiac disease; Shortness of breath on exertion compared with peers; Fainting on exertion or in response to fright or noise; Palpitations that are rapid, regular and start and stop suddenly (fleeting occasional bumps are usually ectopic and do not need investigation); Chest pain suggesting cardiac origin. Signs of heart failure; A murmur heard on cardiac examination; Blood pressure that is classified as hypertensive for adults.” [9]

Once this assessment has been completed and concludes that everything is fine and the patient is healthy, we proceed to the therapeutic options. There will be differences between the preferred medications chosen in children and adults and other factors.

There are different methods to treat this disorder, depending on the needs and symptoms of the person.

The treatments can be pharmacological, non-pharmacological and both combined.

4.2. Pharmacological treatment

Starting with pharmacological treatments, it can be separated into three groups.

First group are the stimulant drugs, these are the ones that will interfere with the dopamine (DA) neurotransmitters and norepinephrine (NE) neurotransmitters (reuptake inhibitors), some examples are methylphenidate hydrochloride (most used one), lisdexamfetamine dimesylate, dexmethylphenidate hydrochloride, and others. [11]

Second group are the non-stimulant drugs, which are selective norepinephrine reuptake inhibitors (atomoxetine) and alpha 2 adrenergic receptor agonists (guanfacine, clonidine).[11]

Third group consist in other drugs or off-label drugs, like antipsychotics, some examples are risperidone, aripiprazole, olanzapine, and antidepressants like bupropion, venlafaxine, desipramine. [11] These medications are used not to directly treat ADHD, but rather the comorbidities that some individuals have or develop, due to the disorder or due to the side effects of the aforementioned medications. [11]

4.2.1. Drug targets

The most common drugs target used in ADHD trials are: “sodium-dependent noradrenaline transporter inhibitors (21 agents), sodium-dependent dopamine transporter inhibitors (17 agents), D2 dopamine receptor agonists (10 agents), sodium-dependent serotonin transporter inhibitors (9 agents), neuronal acetylcholine receptor agonists subunit alpha-4 (7 agents), neuronal acetylcholine receptor agonists subunit beta-2 (7 agents), 5-hydroxytryptamine receptor agonists 2A (6 agents), synaptic vesicular amine transporter inhibitors (5 agents), neuronal acetylcholine receptor agonists subunit alpha-7 (4 agents), alpha-2C adrenergic receptor agonists (4 agents), alpha-2A adrenergic receptor agonists (4 agents) and histamine H3 receptor antagonists (4 agents).” The pharmacological agents using these drug targets will act as reuptake inhibitors, regulating the neurotransmission of noradrenaline, dopamine and serotonin and thus normalizing their levels in the brain. It was noted that most of the agents act on the noradrenaline transporter, the dopamine transporter and the serotonin transporter, all of which are sodium-dependent. The main class of drugs approved to treat ADHD are stimulants and they mainly act on these targets. [11]
Patients who are not suitable for treatment with stimulants have the option of treatment with non-stimulant drugs like alpha 2 adrenergic receptor agonists and selective norepinephrine reuptake inhibitors, which will promote the neurotransmission of DA and NE.[11]

Another interesting target is the histamine H3 receptor. Studies say that histamine exerts a significant regulatory effect on different brain functions, such as cognitive functions, memory, motivation, arousal, goal-directed behavior, the sleep-wake cycle, control of pituitary hormone secretion and is involved in various behavioral and neuropsychiatric diseases. Genetic and pharmacological targeting of the histamine H3 receptor is thought to alter the level of anxiety, aggression, memory, social behavior and circadian rhythms and to have therapeutic effects on cognitive symptoms in brain disorders. [11]This target has immense potential, yet it is not used for the treatment of ADHD, because the results of clinical trials are not great. [11]

4.2.2. Stimulant drugs

The first group of drugs most commonly used to treat ADHD, belongs to the class of stimulants. These drugs are the ones that will act on the central nervous system, increasing the synaptic cliff concentration levels of certain neurotransmitters, such as dopamine (DA) and norepinephrine (NE), in the nucleus accumbens (NAcc) or striatum. [11]

The nucleus accumbens (NAcc) is a subcortical brain region found in the ventral striatum. The NAcc is mostly constituted of medium spiny neurons (MSNs) that express either dopamine receptor D1 (D1-MSNs) or D2 (D2-MSNs). It is commonly described as the brain's pleasure center due to its key function in pleasant emotion and feelings of reward. It has also an important role in motivation, behavior, and a limbic-motor link.[12]

This group of drugs may not be suitable for all patients. Stimulants are contraindicated in people with cardiovascular disease or a history of substance abuse [9]. They are also not used in people who cannot tolerate the adverse effects.

4.2.2.1. Methylphenidate (MPH)

Methylphenidate is a racemic mixture composed of two isomers the d- and l-isomers, where the d-isomer is more pharmacologically active. [6 7]

Chemical formula: C14H19NO2

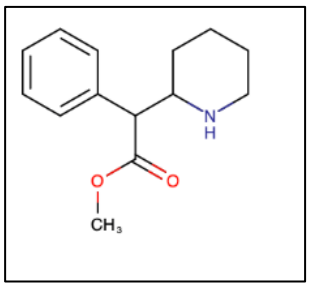

Figure 1- Methylphenidate chemical structure [7]

Chemically comes from phenethylamine and benzylpiperazine. [6]

Methylphenidate is usually the first line medication to treat children from 6 years old and adults with ADHD. Is commercialized by the names of Concerta, Rubifen, Ritalin, Biphentin, etc. [6]

This medication is going to obstruct, in the presynaptic neurons, the reuptake of two neurotransmitters, dopamine and norepinephrine. It will block the transporters of these neurotransmitters, raising the concentration of NE and dopamine in the synaptic gap. The favorable effects of the methylphenidate are also related to the activity of the alpha-1 adrenergic receptor. [67] This is what creates the stimulant effect in the central nervous system (CNS) in the prefrontal cortex. [67] When given higher doses there is an augmentation of the

NE and DA outflow inside the brain causing some effects such as locomotor-activation and impaired cognition. On the other hand, when given lower doses, the DA and NE neurotransmitters are selectively activated in the prefrontal cortex, therefore it will help to maintain the focus and decrease the disease symptoms.

When taken, MPH is quickly absorbed in the gastrointestinal tract [7,13]. It can be administered with or without food,[6] reaching its maximum initial concentration at 1 up to 2 hours post-dose. Maximum plasma concentrations are achieved after about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease. It is metabolized in the liver, by an enzyme called carboxylesterase CES1A1, turning methylphenidate into ritalinic acid (a-phenyl-2-piperidine acetic acid, PPAA), in a procedure called de-esterification. It is eliminated via urine mainly in the form of PPAA (60-90%). The half-life is 3,5 hours [7,13]

As mentioned previously, methylphenidate is commercialized by different brands with different names, the difference between these brands is not just the names, but the way the active substance is released. Depending on this, there are different dosages. [6,7]

Concerta®, developed by the pharmaceutical Janssen-Cilag, are extended-release tablets. The active substance (MPH), is going to be liberated in a patented system called OROS, Osmotic Controlled-Release Oral Delivery. OROS is composed of a trilayer core, osmotically active, surrounded by a semipermeable membrane with an immediate-release drug layer, meaning that 22% of the dose has an immediate release, the other 78% has a gradual release. This technology, used in other medicines of prolonged release, is based on a layer technique that prevents it from being immediately undone by stomach acids, having the desired prolonged effect. [7,13]

The immediate-release drug layer, which represents 22% of the active substance, when it arrives at the stomach, an aqueous organ, dissolves in an hour, liberating the first dosage of the methylphenidate. Then the semipermeable membrane is perforated by the water into the core of the tablet, there, the osmotically active polymeric excipients will expand, creating an aperture which allows the slow liberation of the drug over 6-7 hours. Concerta can also give a continued effect during a period of 10 to 12 hours, for that reason the dosage is once a day, in the morning. These tablets must be taken whole, they cannot be chewed, crumbled or broken, as they would lose their properties. Within 48-96 hours, it is eliminated via urine (78%-97%) as ritalinic acid and feces (1%-3%) in the form of metabolites. [7,13]

The dosages that exist are: 18 mg, 27 mg, 36 mg, 54 mg. Depending on the weight of the person the dose used is going to be different. However, when the treatment starts and it's the first time using this medication, the first dose used is always 18 mg. After a while and a continuous evaluation, the dose may increase according to the person’s needs and growth (weight). The dosage can be adjusted in increments of 18 mg. In general, dosage adjustments can be made at intervals of approximately one week. It is necessary to take the patient weight into account, because if not, the side effects can be more pronounced and that is not ideal. The maximum daily dose of this form of methylphenidate in kids is 54 mg, in adults is 72mg.

Rubifen, developed by Rubió laboratories S.A., are immediate release tablets. The dosages that exist are: 5 mg, 10 mg, 20 mg, and the maximum daily dose of this form of

methylphenidate is 60 mg per day. Unlike Concerta, these pills can be split in half through the groove and will have an immediate and fast release. The effect of this drug will reach its maximum blood concentration in 1-2 hours after the administration. Within 2 hours, it is eliminated via urine and feces in the form of metabolites. For that reason, the method of administration and dosage is different, it can be up to three times a day. The first dose used, when the treatment starts, is 5 mg up to one or two times a day, in the morning (breakfast) and at lunch. Then the dosage can be increased, according to the person's needs, at a rate of weekly increments of 5 to 10 mg. The total daily dose must be administered in several doses. This is the treatment method chosen to treat children and adolescents, it is not widely used in adults.[14,15]

This brand also has another type of release, other than immediate release, that is commercialized by the name of Rubifen Retard, extended-release capsule. The capsules can be swallowed whole or alternatively, they can be administered by dispersing the contents of the capsule (granules) in a small amount of food. In this case, the food with the granules must be swallowed and not chewed. Capsules cannot be crushed, chewed or divided.
The specific dosage of Rubifen Retard simulates the twice-daily administration of an immediate release formulation of methylphenidate. Around 50% of the total amount of active substance is in the unmodified, immediate-release form, while the remaining 50% is released after approximately 4 hours. Within 48 to 96 hours, it is eliminated via urine and feces in the form of metabolites. [16] The recommended starting dose in kids and adults who have never taken methylphenidate is 20 mg once a day. For patients starting to take methylphenidate, it is from 20 mg that the desired effects are seen. However, in children, if the doctor thinks it's appropriate to start with a lower dose, you can start with 10 mg or opt for rubifen immediate release. The difference in the doses of this drug is not the initial dose, but the dose adjustment, in adults this adjustment can be made by increasing by 20 mg weekly. In children, the dose can be adjusted by increasing by 10 mg weekly. The dosages that exist are: 10 mg, 20 mg, 30 mg, 40 mg, 60 mg and the maximum daily dose of this form of methylphenidate in kids is 60 mg, in adults is 80 mg.[16]

Ritalin LA, developed by InfectoPharm drugs and Consilium GmbH, is an extended-release capsule. Is the same as Rubifen Retard. The dosages that exist are: 20 mg, 30 mg, 40 mg. [17]

4.2.2.2. Lisdexamfetamine dimesylate

Lisdexamfetamine dimesylate is a prodrug of dextroamphetamine, also known as d-amphetamine, a CNS stimulant, which is covalently connected to the amino acid L-lysine (fig. 2). It is used to treat children from 6 years old and adults with ADHD.[18,19]

Chemical formula: C17H33N3O7S2

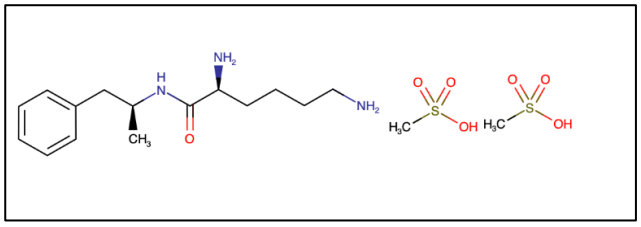

Figure 2- Lisdexamfetamine dimesylate chemical structure [18]

The mechanism of action is the same as the methylphenidate, it's an inhibitor of the DA and NE transporters, but it's also an inhibitor of the vesicular monoamine transporter type 2 (VMAT2) with a weak affinity to the serotonin transporter (SERT) and it's also weak monoamine oxidase inhibitor (MAO) [19,20]

When taken, lisdexamfetamine is quickly absorbed in the gastrointestinal tract [19,20] and can be administered with or without food.[21]. It reaches its blood maximum concentration at 3.5 hours post-dose. It is metabolized through hydrolysis by red blood cells, transforming into dextroamphetamine and l-lysine in the blood. Dextroamphetamine is also metabolized into other metabolites, such as hippuric acid. It is important to highlight that lisdexamfetamine is not metabolized by cytochrome P450 enzymes.[19,20] In 120 hours, 96% of the dose radioactivity is eliminated via urine in different metabolites, like amphetamine, hippuric acid and intact lisdexamfetamine. Only 0.3% was eliminated by feces. The half-life is 11 hours.[19,20]

Lisdexamfetamine is commercialized by a brand named Elvanse. [21]

Elvanse, developed by Takeda Pharmaceuticals International AG Ireland Branch, are capsules. These are composed of lisdexamfetamine dimesylate and dexamfetamine. The initial dose is 30 mg taken once a day, in the morning.[21] The dosages that exist are: 30 mg, 50 mg, 70 mg and the maximum recommended dose is 70 mg per day. The capsules can be swallowed whole or alternatively, they can be administered by dispersing the contents of the capsule (powder or compact powder) in a soft food like yogurt or in a liquid like water or orange juice. The capsule cannot be divided.[21]

4.2.2.3. Dexmethylphenidate hydrochloride

Dexmethylphenidate is the dextrorotatory version (d-enantiomer) of methylphenidate (fig. 3), which was launched in 2002. [22]

Chemical formula: C14H19NO2

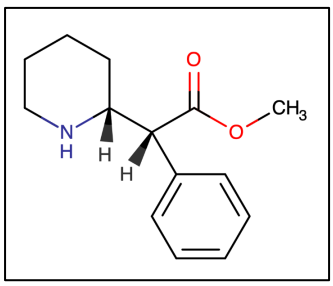

Figure 3- Dexmethylphenidate hydrochloride chemical structure [22]

Its mechanism of action is the same as the methylphenidate. This enantiomer may prevent the reuptake of dopamine and norepinephrine in synapses and is more pharmacologically active than the racemic combination.[22]

When taken, dexmethylphenidate hydrochloride is quickly absorbed in the gastrointestinal tract. It reaches its maximum concentration at 1-1,5 hours post-dose. It will be metabolized, by the enzyme carboxylesterase 1A1 present in the liver, into ritalinic acid. Another route can be used, but to a lesser extent, being transformed into the inactive metabolites 6-oxo-methylphenidate and p-hydroxy-methylphenidate.[22]
After 48 hours, dexmethylphenidate is eliminated mainly through the kidneys, 90% of the dose is gathered in the urine and 3,3% is gathered in the feces. The half-life is 5,69 hours after administered orally.[22]

Currently, this active substance is not approved in Europe by EMA, but is approved in the USA by the FDA and is commercialized under the brand name Focalin.

4.2.3. Non-stimulant drugs

The non-stimulant drugs most commonly used are: selective norepinephrine reuptake inhibitor (atomoxetine) and alpha 2 adrenergic receptor agonists (guanfacine, clonidine).[11]

Its mechanism of action consists of increasing dopamine (DA) and norepinephrine (NE) neurotransmitters in the brain, but not in the nucleus accumbens (NAcc).

They are used in patients who are not suitable for stimulant medication, either because of health problems (cardiovascular diseases), or because they cannot tolerate the adverse effects, or because there is a risk of addiction and improper use. [11]

4.2.3.1. Atomoxetine

Chemical formula: C17H21NO

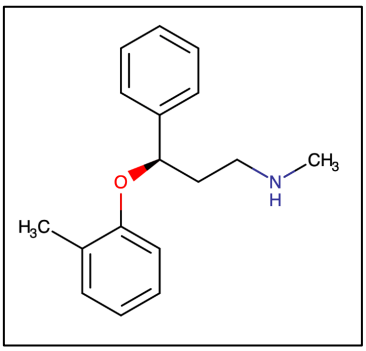

Figure 4- Atomoxetine chemical structure[23]

Atomoxetine is a potent and highly selective inhibitor of the presynaptic norepinephrine (NE) transporter, used to treat Attention deficit hyperactivity disorder (ADHD) in children 6 years of age and older, without directly affecting serotonin or dopamine transporters. Being a selective norepinephrine reuptake inhibitor, is going to increase the levels of NE and also

dopamine (DA), by inhibiting the presynaptic norepinephrine transporter, preventing the reuptake of NE throughout the brain and inhibiting the reuptake of dopamine in specific regions of the brain, the prefrontal cortex. They do the same as the stimulant drugs, but with a difference, in this case the neurotransmitters are not increase in the nucleus accumbens (NAcc) or striatum. [23,24]

Atomoxetine has minimal affinity for other neurotransmitters, transporters or receptors. It has two major oxidative metabolites: 4-hydroxyatomoxetine and n-desmethylatomoxetine. 4-hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter, but unlike atomoxetine, this metabolite also exerts some inhibitory activity on the serotonin transporter. However, any effect on this transporter is thought to be minimal. N-desmethylatomoxetine has substantially lower pharmacological activity compared to atomoxetine.[23,24]

It is rapidly and almost completely absorbed after oral administration, reaching peak plasma concentrations (Cmax) approximately 1 to 2 hours after ingestion. The absolute oral bioavailability of atomoxetine following oral administration ranged between 63% and 94% depending on interindividual differences in first-pass metabolism.[23–25] It is metabolized via the enzymes of the cytochrome P450 2D6 (CYP2D6), becoming the main oxidative metabolite 4-hydroxy-atomoxetine, which is quickly glucuronidated to 4-hydroxy-atomoxetine-O-glucuronide. The other metabolite is produced by CYP2C19 and other enzymes of the CYP450, forming N-desmethyl-4-hydroxyatomoxetine. Depending on the CYP2D6 of the patient, the half life can be up to 3 to 5,6 hours. Atomoxetine is excreted mainly in the urine as 4-hydroxy-atomoxetine-O-glucuronide.[23–25]

Atomoxetine is commercialized by a brand named Strattera. Strattera, developed by Eli Lilly and Company, are capsules of 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg. It can be administered as a single dose in the morning. Patients who were unable to achieve a satisfactory clinical response when taking Strattera as a single daily dose may benefit from taking it twice a day, evenly dividing the dose between the morning and late afternoon or early evening. The initial dose should be maintained for a minimum of 7 days before increasing the dose, titrating it according to clinical response and tolerability.[26]
The dosage for the pediatric population up to 70 kg body weight: It should be started at a total daily dose of approximately 0.5 mg/kg. The recommended maintenance dose is approximately 1.2 mg/kg/day. For the pediatric population weighing more than 70 kg: It should be started at a total daily dose of 40 mg. The recommended maintenance dose is 80 mg. In adults: the treatment should be started at a total daily dose of 40 mg. The recommended daily maintenance dose is approximately 80 mg to 100 mg. The maximum daily dose is 100 mg.[26]

Stattera, exists in oral solution, the dose is 4 mg/ml. Pharmacokinetic studies have demonstrated that atomoxetine capsules and oral solution are bioequivalent.[26]

4.2.3.2. Guanfacine

Chemical formula: C9H9Cl2N3O

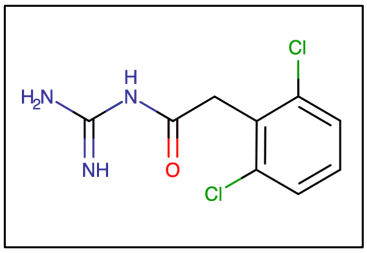

Figure 5- Guanfacine chemical structure[29]

Guanfacine is a selective alpha A2 adrenergic receptor agonist. It acts by modulating signaling in the prefrontal cortex and basal ganglia through direct modification of noradrenaline synaptic transmission in alpha2A adrenergic receptors. [27]Guanfacine also acts by inhibiting the opening of K+ channels by cAMP-PKA in the prefrontal spines, thus reinforcing the network's connectivity, increasing the prefrontal cortex neuronal firing and improving the prefrontal cortex cognitive functions, thereby improving ADHD symptoms.[28] Effects on the circulatory system and heart are non-desire effects of its mechanism of action in reducing the sympathetic nervous system. Is indicated for the treatment of ADHD in children and adolescents aged 6-17 years in whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

Guanfacine Is rapidly absorbed, with maximum plasma concentrations being reached approximately 5 hours after oral administration in pediatric patients. It is metabolized by CYP3A4/5-mediated oxidation, with subsequent phase II reactions of sulfation and glucuronidation. The main circulating metabolite is 3-OH-guanfacine sulfate, which lacks pharmacological activity. Is eliminated via urine in people who have a normal renal function. [27,29]

Guanfacine is commercialized by a brand named Intuniv. Intuniv, developed by Takeda Pharmaceuticals International AG Ireland Branch, are extended-release tablets of 1 mg, 2 mg, 3 mg, 4 mg.[27]. The recommended starting dose for all patients is 1 mg of guanfacine, taken orally, once a day in the morning or evening. The dose may be adjusted in increments of no more than 1 mg per week. The dose should be individualized according to the patient's response and tolerability. Depending on the patient's response and tolerability to Intuniv, the recommended maintenance dose range is 0.05-0.12 mg/kg/day.[27] The tablets should not be crushed, chewed or divided before swallowing as this increases the rate of guanfacine release. Treatment is only recommended in children who are able to swallow the whole tablet without any problems.[27]

Guanfacine can be administered with or without food but should not be administered with high-fat meals due to increased exposure. However, it should not be administered together with grapefruit juice.[27]

4.2.3.3. Clonidine

Clonidine, is an imidazole (fig. 6) that acts like an alpha-2 adrenergic agonist indicated to treat illnesses like hypertension and is helpful to treat ADHD. It Is a third line treatment.

Chemical formula: C9H9Cl2N3

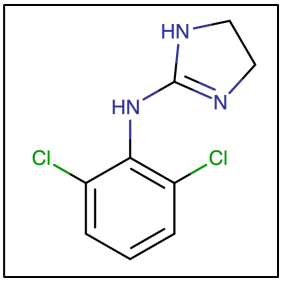

Figure 6- Clonidine chemical structure [32]

Clonidine, acts primarily on the central nervous system, resulting in a reduction in sympathetic response, specifically, the reduction of circulating adrenaline, and a decrease in peripheral vascular resistance, renal vascular resistance, heart rate and blood pressure. Renal vascular output and glomerular filtration rate remain unchanged. There is no interference with normal postural reflexes and, consequently, symptoms of standing are mild and infrequent. “The stimulation of alpha-2 adrenoceptors in the locus coeruleus may be responsible for the hypnotic effects of clonidine as this region of the brain helps regulate wakefulness”. This pharmacodynamic property is one of the things that helps the symptoms of impulsivity and hyperactivity in ADHD.

Clonidine is well absorbed and has a minimal first-pass effect. Plasma concentrations are reached 1-3h after oral administration.[30,31] The metabolism of this molecule is not well understood, but it is known to be metabolized by CYP2D6, CYP1A2, CYP3A4, CYP1A1 and CYP3A5 through hydroxylation, transforming in 4-Hydroxy-clonidine. It's eliminated by the urine and feces [30–32]

The pharmaceutic form used to treat the symptoms of ADHD is extended-release tablets in 0.1 mg.

4.2.4. Antipsychotics

Antipsychotics aim to improve behavioral characteristics that some people with ADHD have, such as aggression, violence and others. They have an off-label use in ADHD. [33]

There are two types of antipsychotics, the first generation and the second generation.[33] The first generation, called by typical antipsychotics, are dopamine receptor antagonists (DRA), some examples are dibenzoxazepines, phenothiazines.[33] The second generation, called by atypical antipsychotics, are serotonin-dopamine antagonists, some examples are risperidone, aripiprazole, olanzapine.[33]

4.2.4.1. Atypical antipsychotics

The second generation is the most used to control behavioral disorders, thus improving attention and focus capacity.

Conduct disorders are caused by an hyperactivity of the central mesolimbic and mesocortical pathways, caused by the excess activity of dopaminergic D2 and serotonergic 5-HT2A

receptors. What atypical antipsychotics will do is reduce the excess activity of dopamine and serotonin on these receptors, ending hyperactivity by inhibiting their receptors in the brain. In other words, they are dopaminergic and serotonergic antagonists.[33]

Risperidone, is a selective monoaminergic antagonist with unique properties. It has high affinity for serotonergic 5-HT2 and dopaminergic D2 receptors. Risperidone also binds to alpha1-adrenergic receptors and, with a lower affinity, to histaminergic H1 and alpha 2-adrenergic receptors. [34]

It's used to treat many mental health and humor conditions, like schizophrenia and bipolar disorders. Is also indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder, in children over 5 years of age and adolescents with below average intellectual function or mental deficiency, diagnosed according to DSM-IV criteria, in which the severity of aggression or other behavioral disturbances requires pharmacological treatment. [34,35]

Risperidone is rapidly distributed. It is metabolized by CYP2D6 into 9-hydroxy-risperidone, which has pharmacological activity identical to that of risperidone. Risperidone and 9-hydroxy-risperidone together form the active antipsychotic fraction. Another metabolic pathway for risperidone is N-dealkylation. After oral administration in psychotic patients, risperidone is eliminated, after 24 hours through urine and feces with a half-life of approximately 3 hours.[34,35]

This active substance is present in several pharmaceutical forms: film-coated tablet (0.5 mg, 1mg, 2 mg, 3 mg, 4 mg), oral solution (1 mg/ml) and powder and vehicle for prolonged-release injectable suspension (25 mg/2 ml, 37.5 mg/2 ml, 50 mg/2 ml).
Some brand names: Risperdal, Okedi, Neclav.[35]

Regarding dosage in children and adolescents aged 5 to 18 years, weighing more than 50 kg, an initial dose of 0.5 mg per day is recommended. This dose can be adjusted individually in increments of 0.5 mg once daily, no more frequently than every other day, if necessary. The optimal dose for most patients is 1 mg per day. For patients weighing less than 50 kg, an initial dose of 0.25 mg oral solution once daily is recommended. The oral solution is the recommended dosage form to administer 0.25 mg. This dose can be adjusted individually in increments of 0.25 mg once daily. The optimal dose for most of these patients is 0.5 mg per day. [35]

4.2.5. Antidepressants

Antidepressants aim to improve symptoms of depression, anxiety, panic and other disorders which cause distraction and low motivation, in order to increase attention and focus capacity. This type of disorders normally are influenced by the reduced number of neurotransmitters that regulate well-being, happiness, sleep, mood, anxiety and nutrition. These neurotransmitters are serotonin, norepinephrine and dopamine. [36]

Antidepressants have an off-label use in ADHD. [36]There are several classes of antidepressants, the most used in ADHD are: Atypical antidepressants like bupropion,

Serotonin/Norepinephrine Reuptake inhibitors (SNRIs) like venlafaxine and Tricyclic Antidepressants (TCAs) like imipramine.[36]

Each class of antidepressant has a different mechanism of action, acting on different neurotransmitters, increasing their levels. The target neurotransmittets are serotonin, norepinephrine and dopamine.[36]

4.2.5.1. Atypical Antidepressant

Bupropion, is a selective inhibitor of the neuronal reuptake of catecholamines (noradrenaline and dopamine), with minimal effect on the reuptake of indoleamines (serotonin) and without an inhibitory effect on monoamine oxidase. [37]

It's used to treat major depressive disorder (MDD), seasonal affective disorder (SAD) and helps in smoking cessation.[37]

Bupropion binds to both the norepinephrine transporter (NET) and the dopamine transporter (DAT). Its pharmacological effects are achieved by slightly blocking the enzymes involved in the uptake of the neurotransmitters norepinephrine and dopamine from the synaptic cleft, hence prolonging their duration of action within the neural synapse and the downstream effects of these neurotransmitters. [37,38]

Bupropion is classified as atypical antidepressant because it has no substantial effects on histamine or adrenaline receptors, nor on serotonin receptors, like other antidepressants do. It is used off-label in ADHD in adults who have bipolar depression, to control mood changes, which may be caused by the side effects of first-line treatments such as stimulants.
It is important to remember that it is thought that dopamine in people with ADHD may be lower, compared to a person without ADHD. This is why this antidepressant is one of the most used in ADHD (when necessary), because it will increase dopamine levels, eliminating feelings of defeat and demotivation and improving the person's well-being and attention.[37,38]

Is extensively metabolized. Three pharmacologically active metabolites were identified in plasma: hydroxybupropion and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion. This fact may be of clinical importance, since its plasma concentrations are as high or higher than those of bupropion. Active metabolites are further metabolized to inactive metabolites and excreted in urine.[37,38]

Its formulation consists of modified-release tablets. The recommended starting dose is 150 mg once a day and the maximum daily dose is 300 mg. [37,38]

The onset of action of bupropion was observed 14 days after the start of therapy. As with all antidepressants the maximum antidepressant effect of bupropion may not be evident until several weeks of treatment.[37,38]

4.2.5.2. Serotonin/Norepinephrine Reuptake inhibitors (SNRIs)

Venlafaxine, is a serotonin and norepinephrine reuptake inhibitor (SNRIs), used to treat generalized anxiety disorder, social anxiety disorder, panic disorder, with or without

agoraphobia, major depressive episodes and prevention of recurrence of major depressive episodes. [39,40]

The mechanism of venlafaxine's antidepressant activity in humans is thought to be related to the potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have demonstrated that venlafaxine and its main metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of the neuronal reuptake of serotonin and norepinephrine. These neurotransmitters are essential in mood regulation.[39,4041]

It is also a weak dopamine reuptake inhibitor. This molecule and its active metabolite reduce the b-adrenergic response, both after acute (single dose) and chronic administration. Venlafaxine and ODV are very similar in terms of overall activity on neurotransmitter reuptake and receptor binding.[39,40]

It has no significant affinity for muscarinic, cholinergic, H1-histaminergic or 1-adrenergic receptors in rat brain in vitro. The pharmacological activity at the level of these receptors may be related to the occurrence of several undesirable effects observed with other antidepressant medications, such as anticholinergic, sedative and cardiovascular undesirable effects.[39,4041]

Venlafaxine undergoes an extensive hepatic metabolism. First, it undergoes biotransformation into its main active metabolite, ODV, by CYP2D6, then it is metabolized into N-desmethylvenlafaxine, a smaller and less active metabolite, by CYP3A4.
Its excretion is mainly done by the kidneys.[39,4041]

This active substance exists in different formulations: tablets, prolonged-release tablet, film-coated tablet, prolonged-release capsule and oral solution. The initial and maximum daily dose are defined depending on the type and degree of the disorder. It is recommended that venlafaxine be taken with food at approximately the same time each day.[39,4041]

5. Side effects and associated health problems

Medicines are created for a purpose, usually to treat a set of symptoms and treat a disease. They have a mechanism of action that will cause changes in the body's physiology, and with these changes come adverse effects.

An adverse drug reaction (ADR), also known as an adverse effect or side effect, is defined as a harmful and unintended response to taking a medicine. It occurs despite the correct use of medicines, which means that in most cases it cannot be prevented. [42]

ADRs can be classified according to various criteria. In terms of their mechanism, there are two main groups: ADRs known as pharmacological and ADRs known as idiosyncratic.[42]

The so-called pharmacological ADRs are related to the therapeutic effects of the drug, resulting from an increased action in the body. They are generally predictable and dose-dependent reactions, i.e. they are more common with higher doses. They are the most frequent and usually the least serious. [42]

ADRs known as idiosyncratic do not result from the pharmacological actions attributable to the drug and are therefore unrelated to the dose used. They are mostly unpredictable and rare reactions, but they can be serious and have more serious consequences. They are often associated with genetic alterations that affect the body's response to medicines.
Allergic reactions fall into this group. The last ones manifest as a result of an inappropriate immune response to the presence of the drug in the body.[42]

In terms of their severity, ADRs can be classified as:
Mild - generally do not require any intervention.
Moderate - requires monitoring. It may be necessary to modify the treatment or add another drug to alleviate the ADR.
Severe - can result in significant damage and hospitalization, and endanger the person's life. The medication usually has to be stopped.
Fatal - are directly or indirectly related to death.[42]

In terms of their frequency, ADRs can be distinguished as follows:
Very common - affects at least 1 in 10 people treated with the medicine.
Frequent - affects at least 1 in 100 people treated with the medicine.
Infrequent - affects at least 1 in 1000 people treated with the medicine.
Rare - affects at least 1 in 10,000 people treated with the medicine.
Very rare - affects less than 1 in 10,000 people treated with the medicine.[42]

The risk of developing an ADR depends on the characteristics of the drug and the way it is used, namely the dose, duration of treatment and route by which it is administered. However, this risk also depends on some factors related to the person taking the medicine, namely:
Age - very young children and older people are more susceptible to developing ADRs.
Genetic factors - certain genetic alterations predispose to ADRs, in particular because they modify the effects of the drug on the body.
Illnesses - people with illnesses that, for example, reduce the function of the kidneys or liver, organs involved in eliminating medicines from the body, are at greater risk of ADRs.
Use of other medicines - taking several medicines at the same time increases the risk of ADRs.[42]

Reporting suspected adverse reactions after the drug has been authorized is important, as it allows for continuous monitoring of the drug's benefit-risk ratio.[42]

5.1. Side effects of stimulant drugs

The stimulant drugs act on the central nervous system, increasing the synaptic cliff concentration levels neurotransmitters, such as dopamine (DA) and norepinephrine (NE), in the nucleus accumbens (NAcc) or striatum. [11]
In addition to their therapeutic effects, several other undesired effects can happen as response to these drugs mechanism of action. The general side effects are: “Decreased appetite - possible therapeutic effect in specific users; Anxiety; Nervousness; Headaches; Weight loss; Insomnia; Psychosis; Pruritus; Paranoia; Sweating; Palpitations; Shortness of breath; Chest pain; Hypertension; Tachycardia; Seizures; Arrhythmias; ECG abnormalities: inappropriate sinus tachycardia, sinus arrhythmia, prolonged QT, premature ventricular

contractions, ventricular tachycardia; Cerebrovascular event; Sudden cardiac death."[43] To see more common and frequent side effects see Table 1.

Table 1- Very common and frequent side effects of stimulant drugs [13,14,21]

Organ system classes	**Adverse reactions**	
	Frequency	
	Very common	**Frequent**
Infections and infestations		Nasopharyngitis, Upper respiratory tract infection, Sinusitis
Metabolic and nutritional disorders		Anorexia, Decreased appetite, Moderate reduction in weight and height gain during prolonged use in children
Psychiatric disorders	Insomnia, Nervousness	Affective instability, Aggressiveness, Agitation, Anxiety, Depression, Irritability, Abnormal behavior, Mood swings, Tics, Initial insomnia, Depressed mood, Decreased libido, Tension, Bruxism, Panic attack
Nervous system disorders	Headache	Dizziness, Dyskinesia, Psychomotor hyperactivity, Drowsiness, Paresthesia, Tension headaches
Eye conditions		Accommodation disorders
Ear and labyrinth disorders		Vertigo
Heart disease		Arrhythmia, Tachycardia, Palpitations
Vasculopathies		Hypertension

Respiratory, thoracic and mediastinal diseases		Cough, Oropharyngeal pain
Gastrointestinal diseases		Upper abdominal pain, Diarrhea, Nausea, Abdominal discomfort and vomiting, Dry mouth, Dyspepsia
Hepatobiliary disorders		Alanine aminotransferase increased
Skin and subcutaneous tissue disorders		Alopecia, Pruritus, Skin rash, Urticaria, Hyperhidrosis
Musculoskeletal and connective tissue disorders		Arthralgia, Muscle stiffness, Muscle spasms
Diseases of the genitals and breast		Erectile dysfunction
General disorders and changes at the place of administration		Pyrexia, Growth retardation during prolonged use in children, Fatigue, Irritability, Feeling nervous, Asthenia, Thirst
Complementary diagnostic tests		Changes in blood pressure and heart rate (usually an increase), Weight loss

This table represents the most common and frequent adverse effects of stimulants in general, it does not mean that all stimulants cause all the adverse effects described above.

5.2. Side effects of non-stimulant drugs

The non-stimulant drugs increase dopamine (DA) and norepinephrine (NE) neurotransmitters in the brain, but not in the nucleus accumbens (NAcc). In addition to their therapeutic effects, several other undesired effects can happen as response to these drugs mechanism of action. The general side effects are: “Heartburn; belching; bleeding between periods and heavy bleeding during periods; chest tightness; cough; decrease in the frequency of urination and in urine amount; decreased appetite; decreased libido; difficulty having a bowel movement (stool) and in passing urine (dribbling); dizziness; dry mouth; fever; headache; inability to

have or keep an erection; indigestion; irritability; nausea; pain or tenderness around the eyes and cheekbones; painful urination; sleepiness or unusual drowsiness; stomach discomfort, upset, cramps, or pain; stuffy or runny nose; trouble breathing; trouble sleeping; dullness, tiredness, weakness; vomiting; constipation; weight gain."[44–46] To see more common and frequent side effects see Table 2.

Table 2- Very common and frequent side effects of non-stimulant drugs[25,27,31]

Organ system classes	**Adverse reactions**	
	Frequency	
	Very common	**Frequent**
Metabolic and nutritional disorders	Decreased appetite	Anorexia (loss of appetite)
Psychiatric disorders		Irritability, Mood swings, Insomnia, Agitation, Anxiety, Depression and depressive mood, Tics, Nightmares, Impaired ability
Nervous system disorders	Headache, Drowsiness	Sedation, Dizziness
Eye conditions		Mydriasis
Heart disease		Bradycardia
Vasculopathies		Hypotension, Orthostatic hypotension
Gastrointestinal diseases	Abdominal pain, Vomiting, Nausea, Dry mouth	Constipation, Dyspepsia, Diarrhea, Abdominal/gastric discomfort, Xerostomia, Parotid pain
Skin and subcutaneous tissue disorders		Dermatitis, Itching, Skin rash
Kidney and urinary diseases		Enuresis

Diseases of the genitals and breast		Impotence, Decreased libido
General disorders and changes at the place of administration		Fatigue, Lethargy, Chest pain, Irritability
Complementary diagnostic tests	Increased or decreased blood pressure, Increased heart rate	Weight gain or weight loss

This table represents the most common and frequent adverse effects of non-stimulants drugs in general, it does not mean that all non-stimulants drugs cause all the adverse effects described above.

5.3. Side effects of antipsychotics

Antipsychotics will modulate DA and NE effects. In addition to their therapeutic effects, several other undesired effects can happen as response to these drugs mechanism of action. The general side effects are: “Extrapyramidal side effects; dry mouth, constipation, urinary retention, sedation; seizure threshold; abnormal heart rhythm, ventricular arrhythmia, torsades de pointes; prolongation of QTc interval, prolonged atrial and ventricular contraction; orthostatic hypotension; increased serum prolactin concentrations along with galactorrhea, breast enlargement, amenorrhea, impotence in men, and anorgasmia in women; allergic dermatitis and photosensitivity; weight gain and metabolic syndrome; dizziness; anxiety; temperature sensitivity to hot or cold temperatures and QTc prolongation; somnolence; agitation; headache; akathisia-like restlessness; hypersalivation; tachycardia.”[33] To see more common and frequent side effects see Table 3.

Table 3- Very common and frequent side effects of antipsychotic drugs [35]

Organ system classes	**Adverse reactions**	
	Frequency	
	Very common	**Frequent**
Infections and infestations		Pneumonia, Bronchitis, Upper respiratory tract infection, Sinusitis, Urinary tract infection, Ear infection, Influenza

Endocrine diseases		Hyperprolactinemia
Metabolic and nutritional disorders		Weight gain, Increased appetite, Decreased appetite
Psychiatric disorders	Insomnia	Sleep disorders, Agitation, Depression, Anxiety
Nervous system disorders	Sedation/drowsiness, Parkinsonism, Headache	Akathisia, Dystonia, Dizziness, Dyskinesia, Tremor
Eye conditions		Blurred vision, Conjunctivitis
Heart disease		Tachycardia
Vasculopathies		Hypertension
Respiratory, thoracic and mediastinal diseases		Dyspnea, Pharyngolaryngeal pain, Cough, Epistaxis, Nasal congestion
Gastrointestinal diseases		Abdominal pain, Abdominal discomfort, Vomiting, Nausea, Constipation, Diarrhea, Dyspepsia, Xerostomia, Toothache
Skin and subcutaneous tissue disorders		Skin rash, Erythema
Musculoskeletal and connective tissue		Muscle spasms, Musculoskeletal pain, Back pain, Arthralgia
Kidney and urinary diseases		Incontinence
General disorders and changes at the place of administration		Edema, Pyrexia, Chest pain, Asthenia, Fatigue, Pain
Complications of interventions related to		Falls

injuries and poisoning		

This table represents the most common and frequent adverse effects of antipsychotics in general, it does not mean that all antipsychotics cause all the adverse effects described above.

5.4. Side effects of antidepressants

In addition to antidepressants therapeutic effects, several other undesired effects can happen as response to these drugs mechanism of action. The general side effects include: “Sexual dysfunction; Headache; QTc prolongation; Hypertension; Headache; Diaphoresis; Bone resorption; Hepatotoxicity; Sedation, Weight gain; Seizures; Diarrhea; Nausea; Sedation, Priapism; Dry mouth; Urinary Retention; Constipation; QRS prolongation; Orthostatic Hypotension; Potential for serotonin syndrome; Significant potential for misuse.; Dissociative or perceptual changes and sedation; dizziness.” [36]
To see more common and frequent side effects see Table 4.

Table 4- Very common and frequent side effects of antidepressants[38,41]

Organ system classes	**Adverse reactions**	
	Frequency	
	Very common	**Frequent**
Immune system diseases		Hypersensitivity reactions such as urticaria
Metabolic and nutritional disorders		Decreased appetite, Anorexia
Psychiatric disorders	Insomnia	Agitation, Anxiety, Confusional state, Depersonalization, Abnormal dreams, Nervousness, Decreased libido, Agitation, Anorgasmia
Nervous system disorders	Headache, Dizziness, Sedation	Tremor, Dizziness, Taste changes, Akathisia, Paresthesia, Dysgeusia

Eye conditions		Vision changes, Eye disorder, Accommodation disorders including blurred vision, Mydriasis
Ear and labyrinth disorders		Tinnitus
Heart disease		Tachycardia, Palpitations
Vasculopathies		Increased blood pressure (sometimes severe), Flushing
Respiratory, thoracic and mediastinal diseases		Dyspnea, Yawning
Gastrointestinal diseases	Dry mouth, Nausea, Vomiting, Constipation	Abdominal pain, diarrhea
Skin and subcutaneous tissue disorders		Skin rashes, Itching, Sweating
Musculoskeletal and connective tissue		Hypertonia
Kidney and urinary diseases		Urinary hesitation, Urinary retention, Polakiuria
Diseases of the genitals and breast		Menorrhagia, Metrorrhagia, Erectile dysfunction, Ejaculation disorders
General disorders and changes at the place of administration		Fever, Chest pain, Asthenia, chills
Complementary diagnostic tests		Weight loss, Weight gain, Increased blood cholesterol

This table represents the most common and frequent adverse effects of antidepressants in general, it does not mean that all antidepressants cause all the adverse effects described above.

6. Non pharmacological interventions

Non-pharmacological interventions are very important for the development of people with ADHD.

Most children, adolescents and even adults with ADHD do not know how to study alone, nor do they have adequate study methods, which is why even if they study alone they cannot achieve good results, they are disorganized, which is why it is more difficult for them to carry out tasks and don't know how to make tasks more interesting to stay concentrated and focused.

Several different methods will provide the necessary tools for people to cope with their disorder and to have a better quality of life. These methods can be divided into two groups: psychological therapies and complementary and alternative therapies. [11]

Psychological therapies can address cognitive development and also behavior management. Several measures can be imposed: have private tutoring (where they teach how to study, how to have an appropriate study method, how to make diagrams and summaries), have an agenda (where they can organize the week, point out the tasks and deadlines, thus having a physical plan of the day to day, not depending only on mental planning, no longer taking the risk of forgetting the tasks), outline objectives and rewards (it will help to maintain focus and have motivation). Carrying out physical activities (PA), team sports, outdoor activities, dance classes, are also good options for cognitive development and behavior management, as they provide focus, organization and skills.[11]

As a result, a presumed mechanism of PA for treating ADHD symptoms is an increase in neurotransmission and availability of catecholamines in brain networks, which can lead to improvements in executive functioning. Many studies have demonstrated that it improves academic achievement, behavior issues, physical and emotional control, planning, and problem-solving skills. Some studies found significant improvements in anxiety and depressive symptoms, aggressive behaviors, and social issues.[11]

The complementary and alternative methods are based on dietary supplements, such as vitamins, fatty acids, amino acids, natural plants and mind-body techniques such as meditation.[11]

7. Combined interventions

The treatment of attention deficit hyperactivity disorder should be a combination of pharmacological and non-pharmacological interventions. In this way, better results will be achieved.

In this disorder, using medication alone on a daily basis will help, but it is not the most appropriate, as medication is only one part of the treatment for this disorder. Psychological therapy is very important for cognitive stimulation in these people and should always be complementary to pharmacological intervention.

Taking the medication every day as recommended by the doctor and leading a healthy, organized lifestyle are the keys to success.

8. Conclusion

ADHD is a disorder that affects many children and adults around the world. It's a disorder that can go unnoticed, ignored or undervalued by people who don't know about it or think it's not a real problem. People who suffer from this disorder are often misunderstood, blamed and labeled as lazy, disorganized, uninterested or dumb.

On the other hand, there are also people who know about this disorder and its pharmacological treatments, who take advantage of it in a bad way, such as parents who put pressure on their children to be better and adults who want to have a better mental performance, trivializing this disorder.

For these reasons is very important to know about this disorder and its characteristics. Knowing about it, will facilitate the way people act faced with the situation. Parents of young children, teachers, teenagers or adults educated about the disorder can recognize the symptoms and contact a doctor who will assess the situation.

A correct diagnosis is crucial to outlining a treatment. The treatment is not the same for everyone, it is always personalized, considering the needs and specificities of each person. There are many treatments available today, so there are plenty of options and solutions for people who need treatment.

In conclusion, ADHD is a disorder that was discovered many years ago, with many therapies available to improve the lives of these people, however it is still unknown by many and it is necessary to educate and talk about it so that it can be easier to detect the problem from a younger age providing the necessary treatments.

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