

The need for additional ADHD medications in Saudi Arabia

Overview of ADHD treatment options:

In general, the types of medication for Attention Deficit Hyperactivity Disorder (ADHD) can be divided into two groups: stimulant and non-stimulant. The stimulant class of medications are considered to be the first-line treatment for ADHD in older children and adolescents, as well as the first-line treatment for adults with ADHD, or in some countries, for adults with ADHD who are continuing treatment from childhood. In pre-school aged children, most international guidelines recommend stimulant medication as a second-line treatment, with behavioral therapy taking precedence, although some prominent ADHD experts dispute this, preferring stimulant medication as the first-line treatment regardless of age, as long as the individual case is managed by a qualified and experienced physician.

In cases where one of the stimulant medication options are not effective: where there are unacceptable non-transient side-effects after dose titration, where there are comorbid psychiatric disorders or medical conditions whose symptoms may be exacerbated by stimulant medications, or in cases where patients or their parents choose not to use stimulant medication, then there are two main classes of non-stimulant medication that may be considered second-line and third-line treatment options for ADHD, as well as a number of medications which are sometimes used off-label for treatment of ADHD and comorbid conditions.

The main types of each medication are summarized in the table below:

First Line: Stimulant Medication	
<i>Methylphenidate</i>	<i>Brand names: Ritalin, Concerta</i>
<i>Amphetamine</i>	<i>Brand names: Adderall, Vyvanse</i>
Second Line: Non-Stimulant	
<i>(Bupropion, tricyclic antidepressants TCAs, and alpha-agonists)</i>	
Third Line: Non-Stimulant	
<i>Atomoxetine</i>	<i>Brand name: Strattera</i>

Medication Availability

Currently, the only ADHD medications available in Saudi Arabia are Concerta, Ritalin (short acting), and Strattera.

Saudi Arabia Needs Another Stimulant Option

I'd like to make the case for bringing additional types of stimulant medication to Saudi Arabia. To understand why they are not already available, we should first discuss the reason for this unavailability, then examine why this should change.

What factors influence the availability of medications?

I believe that the three main considerations are social, medical, and financial.

1 From a social perspective, one can only speculate; however, given the endemic proportions of fenethylamine (Captagon) abuse in the Kingdom, and considering the superficial similarities between fenethylamine and amphetamine-based ADHD medications such as Adderall and Vyvanse, which are all metabolised as dextroamphetamine, the most likely reason is the fear of diversion and abuse. This fear will complicate the approval of these medications with the Saudi Food and Drug Authority, which is a prerequisite to importing or manufacturing any medication in Saudi Arabia. However, it should be noted that the overarching problem with fenethylamine is one of cheap low-quality fenethylamine tablets being manufactured illicitly and smuggled into the country to fuel the street-drug market, and is not one of diversion of genuinely-prescribed medications. Furthermore, with newer formulations such as the smart drug Vyvanse the risk of diversion or abuse is virtually nil. I know that Adderall was declined by the SFDA years ago, so I have written a comparison of Adderall and Vyvanse below to demonstrate Vyvanse's more favorable therapeutic effect, as well as its much lower abuse potential.

2 From a medical perspective, one must consider the need for the medication based upon the benefits vs the risks of the medication compared to other existing medications. There is an overall need for more than one type of stimulant medication: there is a positive response rate to *either* amphetamine *or* methylphenidate indiscriminately at 41% and 44% respectively, for positive response to an individual stimulant only. This gives us an overall positive response to stimulant medication as a first-line treatment for ADHD of 85% (AACAP's ADHD Practice Parameters). A wider availability of an amphetamine alternative in addition to methylphenidate in Saudi Arabia would predict a better response in *nearly half of patients*. In Saudi Arabia, out of the two families of stimulant medication, only methylphenidate is available. This potentially leaves a large

number of patients with sub-optimal treatment and poorly-controlled symptoms. Ideally, there should be at least one additional medication from the amphetamine-family of stimulant medications. Which one will depend on the comparative effectiveness of the various options, as well as minimising abuse potential, and ensuring profitability.

- 3 The financial perspective is irrelevant at this stage, but is primarily concerned with factors that affect market-penetration and profitability. In my mind there is no question that there is sufficient demand, for example, but this would depend upon independent market research.

What's the difference between Adderall and Vyvanse?

I've shown that from a therapeutic perspective, we must have at least one amphetamine-based ADHD medication. The most ubiquitous members of this family of stimulant medications internationally, and ones that are approved by the FDA in the USA as well as the relevant authorities in numerous other countries are brand names Adderall and Vyvanse. Below, is a comparison between the chemical differences of the two formulations, neither of which is currently available in Saudi Arabia. It's written with a lay-audience in mind, as I don't know who the key person at the SFDA is that we need to approach, and whether or not they have a background in chemistry.

What's the difference in composition?

Adderall is a non-racemic (see below) mixture of some of the solid salts of dextroamphetamine and levoamphetamine:

<p>37.5% - <i>Dextroamphetamine Sulfate</i> 25.0% - <i>Dextroamphetamine Saccharate</i> 12.5% - <i>Dextroamphetamine Aspartate Monohydrate</i> 12.5% - <i>Levoamphetamine Aspartate Monohydrate</i> 12.5% - <i>Levoamphetamine Sulfate</i></p>
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Vyvanse is Lisdexamfetamine dimesylate which is converted by enzymes in the blood to dextroamphetamine.

To understand what this means, we first need to understand the difference between the base chemicals dextroamphetamine and levoamphetamine, which are basically the two types of the chemical amphetamine.

What is “amphetamine”? A brief chemical primer:

Amphetamine is the contracted form of the longer chemical name: alpha-methylphenethylamine. It refers to the base form of amphetamine that exists as a colorless volatile liquid at room temperature that is made up of equal parts of two related chemicals: levoamphetamine and dextroamphetamine.

These two chemicals are what are known as isomers: chemicals which share the same molecular formula but whose atoms are arranged differently. When pairs of isomers are physically structured so that their molecules are geometric mirror-images of each other they are called stereoisomers. In general, when a pair of stereoisomers are individually asymmetrical – much like your left and right hands are mirror images of each other yet in themselves asymmetrical – they are called Chiral [/'kaɪərəl/] molecules. Conversely, symmetric isomers whose mirror images are identical when superimposed are called Achiral molecules. It's worth noting that the property of chirality has numerous configurations depending on the overall molecular structure, the properties of individual ligands, and the number of chiral centres (centres of asymmetry). Chiral centres are most commonly carbon atoms.

The environment which these stereoisomers are in may itself contain reagents that are also chiral or achiral. Extending the hands metaphor, a chiral environment may be thought of to contain gloves (hand-specific) whereas an achiral environment may contain bracelets (not hand-specific). Based upon this distinction, stereoisomers are further divided into two types which distinguish between the comparative chemical (reactive) and physical (melting range, solubility, etc.) properties of the two pairs of isomers when they are in an achiral environment. Thus, stereoisomers that have the same properties in an achiral environment are called enantiomers (which usually have a single chiral centre) and stereoisomers that have different properties are called diastereomers (which usually have multiple chiral centres). Within a chiral environment, both enantiomers and diastereomers may exhibit different properties.

A chemical reaction that produces a chiral chemical will always yield a mixture of equal parts of both enantiomeric isomers. In chemistry this 1:1 mixture of enantiomers is called a racemic mixture. Through stereospecific (enantioselective) synthesis an enantiopure mixture – containing only a single enantiomer – may be produced.

Naming conventions

Pairs of chiral molecules are often referred to as left- and right-handed, and there are different non-equivalent naming conventions [e.g. Rectus (R)/Sinister (S), L/D (small caps), levo (l-)/dextro (d-)] relating to the optical properties of pairs of stereoisotopes;

however, in this context we can label these left- and right-handed pairs as “levo” and “dextro”, or l- and d- for short.

Difference between pairs of enantiomers in a chiral environment

Pairs of enantiomers often show different chemical reactions with other substances that are also enantiomers. Many biologically active molecules are chiral, including naturally occurring amino acids and sugars. In biological systems, most of these compounds are of the same chirality: most amino acids are l- and sugars are d-.

Enzymes, which are chiral, often distinguish between the two enantiomers of a chiral substrate. As described above, one could imagine an enzyme as having a glove-like cavity that binds a substrate. If this glove is right-handed, then one enantiomer will fit inside and be bound, whereas the other enantiomer will have a poor fit and is unlikely to bind as effectively or at all. This can produce a marked difference in the effects of two enantiomers on biological organisms. In drugs, for example, often only one of a drug's enantiomers is responsible for the desired physiologic effects, while the other enantiomer is less active, inactive, or sometimes even responsible for adverse effects. This is why some drugs are synthesized with only one enantiomer to enhance the pharmacological efficacy or reduce side effects.

Chemical properties of amphetamine

The two isomers of amphetamine, levoamphetamine and dextroamphetamine, are enantiomers, having a single chiral Carbon and sharing the same physical and chemical properties in an achiral environment. Usually, amphetamine contains equal parts of dextroamphetamine and levoamphetamine, but it can be produced in different ratios such as a 3:1 ratio in Adderall or in an enantiopure form such as in the compound lisdexamfetamine.

Difference between dextroamphetamine and levoamphetamine

Both amphetamine enantiomers are non-catecholamine sympathomimetic amines with CNS stimulant activity; they are thought to increase the release of monoamines into the extra neuronal space, to inhibit the reuptake of norepinephrine and dopamine into the presynaptic neuron, and also – possibly – to inhibit monoamine oxidase (MAO) with a greater magnitude of increases than reuptake inhibitors atomoxetine or bupropion.

Although both amphetamine enantiomers affect the levels of dopamine and norepinephrine, each one affects the levels of the neurotransmitters to a different degree. Dextroamphetamine is approximately 3 to 4 times more potent in releasing dopamine and has an overall greater effect on dopamine than norepinephrine, whereas levoamphetamine is equally or slightly more potent in releasing norepinephrine

and has an overall more balanced action to increase both dopamine and norepinephrine. Levoamphetamine is also 3-7 times less potent as a dopamine reuptake inhibitor and has a relatively greater effect on the peripheral nervous system.

In a racemic amphetamine mixture, the effects of dextroamphetamine on dopamine levels are unaffected by the presence of levoamphetamine; however, in the 3:1 mixture of mixed amphetamine salts (Adderall), the presence of levoamphetamine modulates the activity of dextroamphetamine and prolongs its effects.

In the case of lisdexamfetamine, the activity of enantiopure dextroamphetamine is already rate-limited and sustained by the gradual enzymatic conversion of lisdexamfetamine to dextroamphetamine.

In both cases, this modulation of the metabolization of amphetamine is what produced the desired therapeutic effect; whereas in the chemically-related types of amphetamine which are commonly abused as a street drug, there is no such modulation.

In practical terms

Lisdexamfetamine was developed with the goal of providing a long duration of effect that is consistent throughout the day, with reduced potential for abuse. After oral ingestion, lisdexamfetamine is broken down by enzymes in red blood cells to form L-lysine, a naturally occurring essential amino acid, and dextroamphetamine. This rate-limited sustained enzymatic conversion of lisdexamfetamine to dextroamphetamine slows down and modulates the relative amount of dextroamphetamine available to the blood stream, and because no free dextroamphetamine is present in lisdexamfetamine capsules, dextroamphetamine does not become available through mechanical manipulation, such as crushing or simple extraction.

Peak plasma for lisdexamfetamine is 1 hour, compared to 3 hours for Adderall (short-acting) and 7 hours for Adderall (long-acting), and lisdexamfetamine maintains its maximum effect for at least 12 hours, whereas the effect of Adderall XR shows a clear decline after 6–8 hours. Furthermore, the functional effect of lisdexamfetamine is greater as the plasma concentration of dextroamphetamine falls, whilst with immediate-release dextroamphetamine as soon as the plasma concentration of the drug starts to decline, so does its pharmacological effect.

This shows that there are two advantages of Vyvanse over Adderall:

a) Lower abuse potential, b) More stable and sustained pharmacological effect

Conclusion

It is essential to have at least one methylphenidate-based ADHD medication and one amphetamine-based ADHD medication available as first-line treatments of ADHD by qualified physicians. Given that there is currently no amphetamine-based medication in Saudi Arabia, and given that Vyvanse is demonstrably the best option from a therapeutic and sociological perspective, it is essential that steps are taken to approve Vyvanse by the SFDA.

Sources:

Adderall XR® and Vyvanse™ from The Mental Health Clinician (mhc.cpnnp.org)

Amphetamine, past and present – a pharmacological and clinical perspective

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