LISDEXAMFETAMINE IN THE TREATMENT OF ADHD

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Lisdexamfetamine is used to treat attention deficit hyperactivity disorder (ADHD) as part of a total treatment plan, including psychological, social, and other treatments. This article provides a brief overview of the pharmacology of lisdexamfetamine

Keywords: lisdexamfetamine, ADHD, attention deficit hyperactivity disorder, treatment, medication, psychiatry

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Table of Contents

Introduction

Lisdexamfetamine (L-lysine-dextroamphetamine; LDX) is a central nervous system stimulant. It affects chemicals in the brain and nerves that contribute to hyperactivity and impulse control. It is used to treat attention deficit hyperactivity disorder (ADHD) in adults and in children who are at least 6 years old. The relative safety and efficacy in children and adolescents has been borne out in several studies (Coghill et al., 2017). It provides an alternative option for the treatment of children and adolescents with ADHD who have not responded adequately to previous ADHD pharmacotherapies (Frampton, 2018). However, the safety and the efficacy of LDX in children with ADHD three to five years old have not been established. There is also not enough data on patients 65 years or older. Common brandnames include Tyvense®, Vyvanse®, Elvanse®, and Samexid®.

Long Duration

Lisdexamfetamine was developed with the goal of providing a long duration of effect that is consistent throughout the day, with reduced potential for abuse. Prodrug LDX levels seem to have a

rapid peak and then decline, while dextroamphetamine levels peak 3 hours later than LDX levels and persist throughout the day (Adler, Alperin, Leon, & Faraone, 2017)

The attachment of the amino acid lysine slows down the relative amount of dextroamphetamine available to the blood stream. A relatively sophisticated biochemical process is needed to produce dextroamphetamine from LDX, which can make potential misuse more difficult. Although its abuse potential may be lower than that of dextroamphetamine, as a stimulant it is still relatively high.

Pharmacology

Lisdexamfetamine is a substituted amphetamine and an inactive prodrug of the central nervous system (CNS) stimulant dextroamphetamine. Its chemical structure consists of dextroamphetamine coupled with the essential amino acid L-lysine.

Lisdexamfetamine itself is inactive prior to its absorption and the subsequent cleavage of the molecule's L-lysine portion by enzymes in the red blood cells, which produces the active metabolite dextroamphetamine. The conversion of lisdexamfetamine to dextroamphetamine is not affected by gastrointestinal pH and is unlikely to be affected by alterations in normal gastrointestinal transit times.

Amphetamine enters the presynaptic neuron across the neuronal membrane or through DAT. Once inside, it binds to TAAR1 or enters synaptic vesicles through VMAT2. When amphetamine enters through VMAT2, it collapses the vesicular pH gradient, which in turn causes dopamine to be released into the cytosol through VMAT2. When amphetamine binds to TAAR1, it reduces the firing rate of the dopamine neuron via potassium channels and activates protein kinase A (PKA) and protein kinase C (PKC), which subsequently phosphorylate DAT. PKA-phosphorylation causes DAT to internalize into the presynaptic neuron and cease transport. Amphetamine is

also known to increase intracellular calcium, an effect which is associated with DAT phosphorylation through a CAMKIIα-dependent pathway, in turn producing dopamine efflux.

Amphetamines thereby cause the release monoamine neurotransmitters (dopamine, norepinephrine, and serotonin, among others) from their storage sites in the presynaptic neuron, and prevent the reuptake of these neurotransmitters from the synaptic cleft.

Pharmacokinetics

The oral bioavailability of amphetamine varies with gastrointestinal pH. When the pH is basic, more of the drug is in its lipid soluble free base form, and more is absorbed through the lipid-rich cell membranes of the gut epithelium. Conversely, an acidic pH means the drug is predominantly in a water-soluble cationic (salt) form, and less is absorbed. Following absorption, amphetamine readily distributes into most tissues in the body, with high concentrations occurring in cerebrospinal fluid and brain tissue.

The half-life of amphetamine enantiomers varies with urine pH. At normal urine pH, the half-lives of dextroamphetamine and levoamphetamine are 9–11 hours and 11–14 hours, respectively. Highly acidic urine will reduce the enantiomer half-lives to 7 hours,

highly alkaline urine will increase the half-lives up to 34 hours. Roughly 90% of ingested amphetamine is eliminated 3 days after the last oral dose. Lisdexamfetamine is not as sensitive to pH as amphetamine when being absorbed in the gastrointestinal tract. The elimination half-life of lisdexamfetamine is generally less than 1 hour. CYP2D6 is one of several enzymes known to metabolize amphetamine or its metabolites in humans.

Effects on the nervous system

The effects of stimulants on attention and behaviour are mediated by dopamine and noradrenaline (norepinephrine) pathways. Through neuromodulatory influences over fronto-striato-cerebellar circuits, dopamine and noradrenaline play important roles in high-level executive functions often reported to be impaired in attention-deficit/hyperactivity disorder (ADHD). (del Campo, Chamberlain, Sahakian, & Robbins, 2011) Medications used in the treatment of ADHD (including methylphenidate, dextroamphetamine and atomoxetine) act to increase brain catecholamine levels.

Methylphenidate and dexamfetamine both act by inhibiting the reuptake of dopamine and norepinephrine. However, dexamfetamine, but not methylphenidate, also has a direct-acting effect on dopamine release. This effect by dexamfetamine on both reuptake and release of monoamines may be important where inattentive symptoms predominate and may explain why amfetamine salts seem to be more effective than methylphenidate, as evidenced by a significantly greater effect size. (Steer, Froelich, Soutullo, Johnson, & Shaw, 2012)

Since LDX does not bind to sites responsible for noradrenaline and dopamine reuptake, the drug requires enzymatic hydrolysis before it becomes pharmacologically active.

Structural Changes

Long-term amphetamine exposure at sufficiently high doses in some animal species is known to produce abnormal dopamine system development or nerve damage, but, in humans with ADHD, pharmaceutical amphetamines appear to improve brain development and nerve growth. Reviews of magnetic resonance imaging (MRI) studies suggest that long-term treatment with amphetamine decreases abnormalities in brain structure and function found in subjects with ADHD, and improves function in several parts of the brain, such as the right caudate nucleus of the basal ganglia.

ADHD

Reviews have indicated that long-term continuous stimulant therapy for ADHD is effective for reducing the core symptoms of ADHD including hyperactivity, inattention, and impulsivity, thereby enhancing a patient's functioning in everyday life and increasing his or her quality of life. Many patients with ADHD cannot live up to their potential in school, college and at their workplaces. More severe forms of ADHD usually mean that even finishing basic schooling is a gargantuan task which often fails without medication. Significant improvements with treatment can also be seen in relationships. Improvements have also been observed in social behaviour, driving, non-medicinal drug use, obesity, occupation, self-esteem, service use, and overall social functioning.

Long-Term Effectiveness

A review of key articles on long-term outcome of symptoms, comorbidity, substance use, executive functioning, academics, side effects, neurobiology, functioning, and quality of life led to the

conclusion that stimulants are very effective medications in the short term when used optimally. When administered properly with careful titration, follow-up, and dose adjustment, stimulants are also relatively safe. While long-term randomized, placebo-controlled studies do not seem feasible, long-term naturalistic studies are limited by absence of controls. (Craig, Davies, Schibuk, Weiss, & Hechtman, 2015) There thus remains a question mark in regard to the long-term effectiveness. From a neurobiological perspective, an upregulation of dopamine transporter availability during long-term treatment with methylphenidate may decrease treatment efficacy and exacerbate symptoms while not under the effects of the medication. (Wang et al., 2013)

Depression

Stimulants have long been considered possible treatment options for MDD, in part because of the role of dopamine in the pathophysiology of depression and its associated symptoms, such as anhedonia and lethargy.

Lisdexamfetamine has been studied as augmentation for medication of major depressive disorder. In a randomized, placebo-controlled study with 143 adults with mild MDD and executive dysfunction, it was reported that augmentation of the antidepressant therapy significantly improved executive dysfunction and depressive symptoms in participants with mild MDD. The safety profile of LDX was reported as consistent with prior studies in adults with ADHD. (Madhoo et al., 2014) However, in a randomized, placebo-controlled, double-blind study conducted at 76 sites across five countries (USA, Argentina, Chile, Australia, and the UK) between 2011 and 2014 augmentation up to 70 mg did not provide clinical benefit over placebo in adults with inadequate responses to antidepressant monotherapy. (Richards et al., 2017)

Dependence and withdrawal

There are various side effects and contradictions, some of them frequent, which should be looked up in the relevant literature.

Misuse and abuse of stimulants is unfortunately a widespread phenomenon, making it even more imperative to use common criteria and effective processes in making a diagnosis that is as reliable and valid as possible. The diagnosis of ADHD in adults has been discussed by the author more in depth elsewhere (Haverkampf, 2018)

Some symptoms that can point to the presence of a simulant abuse are as follows:

- Anxiety and excited speech (may look like an acute panic attack)
- Anorexia (can be severe)
- Confusion
- Depression
- Increased pulse rate (tachycardia) and blood pressure (even overt hypertension)
- Increased wakefulness and physical activity
- Irritability

- Infections from intravenous drug use (endocarditis, hepatitis, HIV, others)
- Memory loss
- Paranoia and aggressive tendency (even violent behaviour)
- Profound insistence on prescription refill
- Psychosis
- Tremors and convulsions
- Worsening academic performance

Psychosis

A severe amphetamine overdose can result in a stimulant psychosis that may involve a variety of symptoms, such as delusions and paranoia. However, it appears rare or even very rare that a psychosis would result from a normal therapeutic dose in a patient with ADHD.

Information

As with any other medication, there should be as much openness and transparency as possible between prescriber and patient. Both need to be well informed. Any existing somatic or mental health conditions should be explored, including cardiovascular conditions, depression, bipolar disorder, psychosis, suicidal thoughts or

behavior, high blood pressure, a family history of heart disease or sudden death, kidney disease, coronary artery disease, blood circulation problems in the extremities, drug or alcohol addiction and several more.

DISCLOSURE

The author reports no conflicts of interest in this work.

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