Lisdexamfetamine: an over(re)view

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Background: Lisdexamfetamine (LDX), a prodrug of *d*-amphetamine, is a pharmaceutical used in the treatment of neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD) [1]. **Objective:** Herein we aimed to comprehensively review LDX pharmacokinetics, pharmacodynamics, clinical efficacy, safety profile, and forensic implications. **Methods:** A literature search was conducted in PubMed without a limitation period using the keywords LDX, pharmacokinetics/dynamics, clinical use and efficiency, among others related. All types of articles were included. **Results:** LDX undergoes rapid absorption via peptide transporter 1 (PepT1) in the small intestine, achieving C_{max} within 1–2h [2-5], and is hydrolyzed in erythrocytes by an unidentified aminopeptidase, into *d*-amphetamine and *l*-lysine [5, 6]. Excretion occurs primarily via urine (96.4%), with minimal fecal elimination (0.3%) [2]. Pharmacokinetic studies indicate that LDX does not significantly alter the activity of CYP1A2, CYP2D6, and CYP3A4 [7], suggesting low potential for drug-drug interactions. Its stimulant activity results from trace amine-associated receptor 1 (TAAR1) activation, monoamine oxidase (MAO) inhibition, and reverse transport of the vesicular monoamine transporter 2 (VMAT2), dopamine transporter (DAT), norepinephrine transporter (NAT), and serotonin transporter (SERT), increasing dopamine levels in synaptic cleft [1, 8]. Common adverse effects of LDX include dizziness, somnolence, appetite suppression, headache, nausea, and fatigue [9]. Concerns regarding growth suppression arise mainly in the first year of treatment and diminishing thereafter [9, 10]. Although LDX exhibits a lower reinforcing potential than *d*-amphetamine [11], supra-therapeutic doses may induce similar abuse liability and toxicity. However, its higher lethal dose threshold (five times that of amphetamines) reduces overdose risk [12]. **Conclusions:** LDX therapeutic efficacy in ADHD is well-established, with superior outcomes relative to other stimulant medications. In forensic context, differentiating between therapeutic and illicit consumption remains a critical challenge. Given its potential applications beyond ADHD, further large-scale studies are warranted to elucidate the full scope of LDX's pharmacological and clinical utility.

Keywords: lisdexamfetamine; pharmacokinetics; pharmacodynamics; ADHD treatment; forensic toxicology.

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