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Lisdexamfetamine: From Pharmacology to Forensic Implications

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Abstract

Background: Lisdexamfetamine dimesylate (LDX) is a prodrug of *d*-amphetamine used in the treatment of neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD) [1]. **Objective:** This systematic review aims to provide a comprehensive overview of LDX pharmacokinetics, pharmacodynamics, clinical efficacy, safety profile, and forensic considerations. **Methods:** A literature search was conducted in PubMed without a limitation period using the keywords "lisdexamfetamine", "lisdexamfetamine dimesylate", "LDX", "ADHD", "pharmacokinetics", "pharmacodynamics", "forensic implications", "abuse", "clinical applications", "clinical efficacy", and "adverse effects", either individually or in combination. All types of articles were included. A total of 113 articles were selected. **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]. It is primarily eliminated in the urine (96.4%), with minimal fecal elimination (0.3%) [2]. 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 activation, monoamine oxidase inhibition, and reverse transport of the vesicular monoamine transporter 2, dopamine transporter, noradrenaline transporter, and serotonin transporter, increasing neurotransmitter levels in the 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 demonstrates established therapeutic benefits in ADHD, often yielding superior outcomes compared with other stimulant medications. In forensic settings, distinguishing between prescribed use and illicit intake remains a significant challenge. Considering its potential applications beyond ADHD, further large-scale investigations are needed to fully define LDX's pharmacological, toxicological, and clinical profile.

Keywords: lisdexamfetamine dimesylate; *d*-amphetamine; attention-deficit/hyperactivity disorder

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