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Neurotoxicity of lisdexamfetamine: Implications for neuronal health and central nervous system function

Maral Hasanzadeh[1], Amirreza Beirami[1], Amir-Hossein Bayat[2], and Abbas Aliaghaei[1]*

[1]Department of Biology and Anatomical Sciences, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Department of Basic Sciences, Saveh University of Medical Sciences, Saveh, Markazi, Iran

Abstract

Lisdexamfetamine (LDX) is a d-amphetamine prodrug with a long-acting therapeutic profile. It has become well-known in recent years due to its widespread use in treating several psychological disorders, such as attention-deficit/hyperactivity disorder and binge eating disorder. However, concerns have been raised about its potential neurotoxic properties, particularly with long-term use. Although direct evidence of LDX-induced neurotoxicity is limited, insights can be drawn from studies on the harmful impacts of its parent compound and related amphetamines, such as amphetamine and methamphetamine, on the central nervous system. The potential mechanisms through which these drugs exert their neurotoxic effects include mitochondrial dysfunction, oxidative stress, neuroinflammation, synaptic failure, and excitotoxicity, all of which contribute to neuronal injury and death. Furthermore, amphetamines have been shown to disrupt the blood–brain barrier, likely triggered by the aforementioned mechanisms, with neuroinflammation being the most significant factor. In this review, we aim to synthesize the available knowledge on the potential mechanisms behind LDX-induced neurotoxicity and emphasize the need for future studies to better understand the long-term side effects of LDX.

Keywords: Lisdexamfetamine; Central nervous system; Neuroinflammation; Attention-deficit/hyperactivity disorder

***Corresponding author:**
Abbas Aliaghaei
(aghaei60@gmail.com)

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1. Introduction

Lisdexamfetamine (LDX) is a prodrug of the central nervous system (CNS) stimulant substance d-amphetamine. It is the first chemically manufactured stimulant prodrug that offers a novel long-acting medication for several psychological conditions.[1] The most prominent advantage of LDX over other formulations is that, as a prodrug, it does not contain the active form of the drug, which could be altered during ingestion and absorption in the gastrointestinal tract. However, LDX has a complex drug delivery mechanism that involves the enzymatic hydrolysis of the prodrug to active d-amphetamine and the naturally occurring amino acid L-lysine.[2] Since 2007, LDX has been approved for treating attention-deficit/hyperactivity disorder (ADHD) in children aged 6 – 12 years, and in April 2008, the United States Food and Drug Administration

approved its use in adults as well.[3] In addition to ADHD, LDX is also used for treating binge eating disorder (BED).[4]

Amphetamine has two enantiomers: Levoamphetamine (l-amphetamine) and dextroamphetamine (d-amphetamine). D-amphetamine is a non-catecholamine sympathomimetic amine known for its CNS-stimulating properties. It blocks several critical neurotransmitter transporters at the synaptic cleft, including dopamine transporter, noradrenaline transporter, and vesicular monoamine transporter 2. It can also block the serotonin transporter, but with lower affinity. Furthermore, it functions as a mild monoamine oxidase (MAO) inhibitor.[5] In norepinephrine neurons, d-amphetamine is a far more potent catecholamine uptake inhibitor than l-amphetamine. However, both isomers are equally effective in inhibiting catecholamine uptake in dopamine neurons in the corpus striatum. D-amphetamine ultimately inhibits the absorption of catecholamines (i.e., norepinephrine and dopamine) into the presynaptic neuron, increasing their availability in the synaptic space.[1] The specific mechanism of action of LDX in ADHD and BED has not been fully explored; nonetheless, the clinical effects of LDX are thought to be linked to the pharmacological activities of d-amphetamine.[5] Human pharmacokinetic investigations have revealed that d-amphetamine exposure following oral LDX administration is monophasic, persistent, and dose-proportional, with minimal variability both within one patient and between patients. This facilitates dose optimization.[6] In addition, because LDX does not impact cytochrome P450 enzymes, it has a minimal risk of pharmacokinetic drug–drug interactions.[7]

Like any other medication, LDX has been found to induce a wide range of side effects. The adverse effects associated with LDX are similar to those expected with other stimulants. The most prevalent side events after LDX administration in children, adolescents, and adults with ADHD include anxiety, irritability, insomnia, anorexia, weight loss, nausea, vomiting, upper abdominal discomfort, diarrhea, dizziness, and dry mouth.[8] Similarly, the most common side effects of this drug in individuals with BED include dry mouth, insomnia, jitteriness, elevated heart rate, decreased appetite, anxiety, and constipation.[8] Furthermore, LDX has been shown to be prone to abuse in some cases.[9] However, in abuse liability studies involving individuals with a history of stimulant dependence, LDX is linked to lower abuse liability responses compared to immediate-release dexamfetamine (Table 1).[10]

As previously stated, once converted into its active form, d-amphetamine, LDX significantly affects neurotransmitter dynamics in the brain, mainly by increasing dopamine and norepinephrine levels. However, it can be argued that prolonged and excessive activation of these pathways may lead to neurotoxicity. This argument is supported by several animal studies showing that chronic exposure to high doses of amphetamine, the active form of LDX, can impair synaptic plasticity and cause cognitive deficits.[14,15] These findings emphasize the need for further research into the long-term effects of LDX on neurons and other CNS cell lines. Accordingly, this review carefully examines the available evidence regarding LDX's potential neurotoxic effects, with an emphasis on neuronal health.

Table 1. Common adverse events (AEs) reported for lisdexamfetamine

Study	Sample	Common AEs	Severity	Onset time
Biederman *et al.*[11]	Children (*n*=52)	Insomnia, appetite loss	Mild to moderate	Week 1
Wigal *et al.*[12]	Children (*n*=129)	Irritability, headache	Mild	Early treatment
Weisler *et al.*[13]	Adults (*n*=191)	Respiratory infection, insomnia	Mild-to-severe	1st week

Table 2. Structure and activation pathway of lisdexamfetamine

Stage	Location	Conversion/action
Absorption	Small intestine	Absorbed via PEPT1
Hydrolysis	Red blood cells	Converted to d-amphetamine and L-lysine
Pharmacological effect	Brain	Inhibits reuptake and promotes release of DA/NE

Abbreviations: DA: Dopamine; NE: Norepinephrine; PEPT1: Peptide transporter 1.

2. Mechanism of LDX's action in the CNS

LDX is a prodrug composed of a peptide bond covalently linking d-amphetamine to the naturally occurring amino acid L-lysine, rendering the parent molecule pharmacologically inactive. After oral administration, LDX is actively absorbed in the small intestine via peptide transporter 1.[16] Studies have indicated that LDX is hydrolyzed in human blood, with bioconversion specifically occurring in red blood cells (RBCs).[16] The rate of LDX hydrolysis is hematocrit-dependent. However, significant conversion to d-amphetamine still occurs even when hematocrit levels are reduced to 10% or 25% of normal.[16] Moreover, the hydrolysis rate remains unchanged even when RBCs undergo lysis,[16] and the release of d-amphetamine from LDX is unaffected in blood from donors with defective RBCs caused by sickle cell disease (Table 2).[17]

LDX has been shown to enhance impulse control in individuals with BED and ADHD.[18,19] It is believed that, like

other psychostimulants, LDX improves impulse control by modulating the prefrontal cortex (PFC), a brain area involved in self-regulation and inhibitory control.[20] LDX influences the pharmacological activity of seven human proteins. Its active form stimulates the CNS by inhibiting the activity of the synaptic vesicular amine transporter (encoded by *SLC18A2*), dopamine transporter (encoded by *SLC6A3*), noradrenaline transporter (encoded by *SLC6A2*), and serotonin transporter (encoded by *SLC6A4*). All of these targets are involved in presynaptic signaling, suggesting that LDX regulates three major neurotransmitter pathways: Dopamine, norepinephrine, and serotonin.[21] In addition, LDX activates the trace amine-associated receptor 1, which may help attenuate several maladaptive eating behaviors. It also functions as a neuro-maintenance agent by inhibiting oxidative enzymes MAO-A and MAO-B (Table 3).[21] Furthermore, LDX has been reported to modulate several inflammatory mediators.[22] Tumor necrosis factor (TNF) is induced following LDX treatment, suggesting a potential immunomodulatory role of the drug. Other cytokines stimulated by LDX include interleukin (IL)-4, IL-6, and IL-10. Notably, IL-4 and especially IL-10 exhibit anti-inflammatory properties, indicating that LDX may contribute to the regulation of the inflammatory response (Table 4).[21]

Table 3. Biochemical pathways involved in lisdexamfetamine (LDX) action

Pathway	Proteins/targets	Effect of LDX
Dopaminergic	DAT, VMAT2, MAO-A	Inhibits reuptake and degradation
Noradrenergic	NET	Inhibits reuptake
Serotonergic	SERT	Weak inhibition of reuptake
Immunomodulatory	Tumor necrosis factor -α, IL-4, IL-10	Modulates inflammatory response
Receptor-mediated	TAAR1	Regulates compulsive behavior

Abbreviations: DAT: Dopamine transporter; MAO: Monoamine oxidase A; NET: Noradrenaline transporter; SERT: Serotonin transporter; TAAR1: Trace amine-associated receptor 1; VMAT2: Vesicular monoamine transporter 2.

Table 4. Immune and inflammatory mediators stimulated by lisdexamfetamine (LDX)

Mediator	Immune role	Status with LDX
TNF-α	Pro-inflammatory	Increased
IL-1β	Pro-inflammatory	Possibly increased
IL-6	Dual role	Upregulated
IL-10	Anti-inflammatory	Mildly increased
IL-4	Anti-inflammatory	Mildly increased

Abbreviations: IL: Interleukin; TNF: Tumor necrosis factor.

One important consideration is that these mechanisms, and how each patient responds to LDX, may be further complicated by individual genetic differences. Therefore, pharmacogenomics studies are essential to clarify how LDX leads to improved outcomes or is better tolerated in specific genotypes.[23] To summarize, the pharmacological profile of LDX as a prodrug is complex: It must undergo hydrolysis to convert into its active form, d-amphetamine, which significantly affects neurotransmitter systems, particularly dopamine and norepinephrine. The mechanism of LDX action involves multiple proteins, such as neurotransmitter transporters and oxidative enzymes. Additionally, its modulation of inflammatory mediators, including TNF and IL-10, suggests a potential immunomodulatory role. However, the exact molecular mechanisms of LDX action, particularly how individual genotypes influence drug response, remain unclear.

3. Adverse events (AEs) associated with LDX

Numerous clinical trials have investigated the safety and efficacy of LDX, consistently identifying several common AEs associated with its usage. For instance, Biederman *et al.*[24] conducted a randomized crossover study comparing the efficacy of LDX and mixed amphetamine salts extended-release (MAS-XR) in a simulated classroom setting involving 52 children with ADHD aged 6 – 12 years. In the LDX group, the most frequently reported AEs were insomnia, decreased appetite, and anorexia, whereas MAS-XR was linked to reduced appetite, stomach discomfort, vomiting, and insomnia. In another large multicenter trial, Biederman *et al.*[11] studied 290 children with ADHD and found that over 95% of all AEs were mild to moderate, most occurring within the 1st week of treatment. Common AEs in this study included reduced appetite, insomnia, irritability, stomach discomfort, and headache. Similarly, Wigal *et al.*[12] conducted a randomized, placebo-controlled crossover study in 129 children, where the most commonly reported AEs were mood swings, irritability, headache, and loss of appetite. These findings are consistent with a longitudinal research by Findling *et al.*[25] which monitored 272 children treated with LDX over 12 months. The most frequent AEs, such as weight loss, reduced appetite, and insomnia, occurred mostly during the 1st month of therapy, with no significant AEs specifically attributed to LDX.

To summarize, the most common AEs reported in LDX clinical research across both pediatric and adult populations are reduced appetite, insomnia, headache, and irritability. These side effects typically emerge early in therapy and tend to diminish over time. The potential neurotoxicity of LDX may be linked to the same mechanisms that underlie these AEs, including overstimulation of dopaminergic and

norepinephrine pathways. Long-term exposure may also induce oxidative stress and neuroinflammation, raising concerns regarding its continued usage, particularly in vulnerable populations such as children and individuals with pre-existing conditions. Although the temporal pattern of AE development does not align with this theory, as most AEs appear early, evidence on long-term exposure remains scarce. Therefore, additional longitudinal studies are necessary to gain a more comprehensive understanding of these risks.

4. LDX-associated neurotoxicity

LDX is associated with potential neurotoxic effects on the CNS. While direct information on the mechanisms of LDX-induced neurotoxicity is limited, it is critical to examine the broader class of stimulant medications to which it belongs, as it is a prodrug of d-amphetamine. This class includes amphetamine and methamphetamine, both of which have well-documented neurotoxic effects. Previous studies have shown that chronic exposure to stimulants can cause oxidative stress, mitochondrial malfunction, and an imbalance between excitatory and inhibitory neurotransmission. In addition, preclinical and clinical investigations have identified neuroinflammation and blood–brain barrier (BBB) disruption, raising concerns regarding the long-term safety of LDX. Together, these factors create a neurotoxic environment that can lead to neuronal death and will be discussed in detail below.

4.1. Oxidative stress and mitochondrial dysfunction

Oxidative stress is a key factor in amphetamine-induced neurotoxicity.[26] Given LDX's structural similarity to amphetamine, it is plausible to assume similar mechanisms are involved. Administering a high dose of amphetamine and its analogs has been shown to increase free radical production, while pretreatment with antioxidants reduces dopaminergic deficits caused by amphetamine.[27] Furthermore, previous studies have reported that overexpression of superoxide dismutase, a free radical scavenger, inhibits the neuronal impairments caused by methamphetamine.[28] Taken together, these findings suggest that the formation of reactive oxygen species (ROS) mediates the harmful effects of amphetamine administration. However, amphetamines can induce oxidative stress via several distinct pathways.

Research has revealed that amphetamine and methamphetamine significantly influence mitochondrial function.[29] Under normal physiological conditions, mitochondria are the main source of intracellular ROS.[30] ROS are generated by the electron transport chain complexes on the inner mitochondrial membrane and by monoamine oxidase on the outer membrane. Therefore, one of the primary mechanisms through which amphetamines may increase ROS production is by changing basal mitochondrial activities.[31]

In addition, given that amphetamines promote dopamine release, another probable source of ROS is dopamine autoxidation through the Fenton reaction, which employs iron as a cofactor.[32] It has also been proposed that increased intracellular dopamine levels may result in the formation of reactive dopamine quinones,[32] which subsequently produce ROS. A third proposed mechanism involves calcium homeostasis. Amphetamines elevate intracellular calcium levels and activate nitric oxide synthase, leading to increased production of reactive nitrogen species like peroxynitrite, which may further contribute to oxidative stress.[27]

As a result of these mechanisms, reactive chemicals are produced and subsequently oxidized, ultimately disrupting the function of various cellular components such as proteins, lipids, and nucleic acids. This oxidative damage may also result in microglial activation.[33] Excessive stimulation of microglia appears to contribute to some of the neurotoxic effects of amphetamines, including the degradation of dopaminergic nerve endings.[34] Furthermore, microglial activation is often followed by astroglial activation, which leads to elevated levels of pro-inflammatory cytokines, as discussed in the next section (Tables 5 and 6).[33,35]

In summary, studies on amphetamines indicate that oxidative stress and mitochondrial dysfunction are key

Table 5. Mechanisms of action underlying lisdexamfetamine-associated neurotoxicity

Mechanism	Description
Dopamine release	Enhances dopamine release and inhibits its reuptake, increasing synaptic dopamine levels
Norepinephrine modulation	Blocks norepinephrine reuptake and increases its release, enhancing adrenergic activity
Serotonin interaction	Although not primary, LDX may indirectly affect serotonin systems, especially at high doses.
Excitotoxicity potential	Elevated glutamate release linked to d-amphetamine may contribute to neuronal excitotoxicity
Oxidative stress induction	Stimulant-induced ROS generation can damage neuronal structures and functions
Mitochondrial dysfunction	Oxidative stress may impair mitochondrial function and energy metabolism
Neuroinflammation	Stimulant-induced activation of microglia and cytokine release may promote neuroinflammation
BBB disruption	LDX, like other amphetamines, may compromise BBB integrity under certain conditions

Abbreviations: BBB: Blood–brain barrier; LDX: Lisdexamfetamine.

Table 6. Possible sources of reactive oxygen species production induced by lisdexamfetamine

Source	Mechanism
Mitochondrial activity	• Electron transport chain dysfunction • MAO-mediated dopamine metabolism
Dopamine autoxidation	Iron-dependent Fenton reaction leading to dopamine-quinone formation
Intracellular Ca^{2+} rise	NOS activation and RNS production

Abbreviations: Ca^{2+}: Calcium ions; MAO: Monoamine oxidase; NOS: Nitric oxide synthase; RNS: Reactive nitrogen species.

contributors in drug-induced neurotoxicity. Although direct evidence for LDX is lacking, its potential effects should be considered in light of findings from related compounds.

4.2. Neuroinflammation and immune response activation

Autoimmunity, which is strongly associated with oxidative stress, also plays an important role in amphetamine-induced neuronal damage. Neuroinflammation can disrupt neurobiological pathways that regulate cognitive processes, such as inhibiting long-term potentiation and synaptic plasticity, while also dysregulating several metabolic processes, such as the tryptophan-kynurenine pathway, neurotrophin metabolism, and the hypothalamic–pituitary–adrenal axis.[36] Several studies have shown that the stimulant drug methamphetamine increases levels of at least one classic pro-inflammatory cytokine, including TNF-α, IL-1β, and IL-6, in various brain regions, such as the PFC, nucleus accumbens, ventral tegmental area, hypothalamus, and striatum.[37-40]

However, other studies found that these cytokines are not significantly altered in the hippocampus, PFC, or nucleus accumbens after a single administration of stimulants (amphetamine and methamphetamine).[41] Several other studies report asymmetric results across brain regions,[37,42,43] suggesting that drug-induced cytokine alterations are likely region-dependent and primarily affect dopaminergic neurons. It is also worth noting that additional factors, such as dosage, administration methods, treatment duration, and cytokine quantification methodology, may explain discrepancies across studies. For instance, dosage appears to play a significant role in this heterogeneity, with studies using low doses of stimulants generally showing no changes in cytokine levels,[43,44] whereas higher doses are associated with increased levels of classic cytokines.[37-40]

Although *in vivo* investigations on the pro-inflammatory effects of LDX are limited, a recent *in silico* study has provided some insight. Using a systems biology-based virtual model of LDX, researchers investigated the molecular pathways affected by the drug.[45] This model suggests that LDX-induced impairment of dopamine signaling may regulate neuroinflammation by influencing various molecular targets, including cytokines such as TNF-α, IL-6, IL-1B, and interferon gamma receptors, as well as immune cells including microglia, T cells, and monocytic cells.

In addition to increasing the expression of pro-inflammatory cytokines, psychostimulants contribute to the development of neuroinflammatory processes by disrupting the structure and function of glial cells, leading to pathological events such as microgliosis and astrogliosis. For instance, microglial hypertrophy has been reported as a pronounced consequence of amphetamine exposure in the hippocampus of mice.[33] However, unlike pro-inflammatory cytokines, some brain areas rich in dopaminergic neuron bodies, such as ventral tegmental area and substantia nigra, have low sensitivity to amphetamine-induced microglial activation.[33] Additionally, chronic methamphetamine exposure has been shown to cause significant microglial activation, as evidenced by increased expression of ionized calcium-binding adapter molecule 1, a microglial activation marker, in the striatum and hippocampus of mice.[44]

Furthermore, substantial data suggest that both human amphetamine users and rats exposed to amphetamine exhibit diminished neuronal integrity and impaired glial responsiveness in the PFC.[33,46,47] In addition, methylphenidate, another widely prescribed psychostimulant, has been shown to induce widespread microglial activation with chronic exposure. In a study by Carias *et al.*,[48] such activation was observed across several brain regions, such as the somatosensory and motor cortices, insular cortex, thalamus, hippocampus, substantia nigra, and globus pallidus, both shortly after treatment initiation and even after its cessation. These findings indicate that similar mechanisms of glial activation may occur with LDX. However, as a prodrug, LDX may produce a more complex pattern of amphetamine-induced glial reactivity, necessitating further investigation.

In summary, neuroinflammation triggered by amphetamines, and likely LDX, underscores the drug's possible neurotoxicity. Although direct evidence remains limited, the pharmacological similarities among these compounds highlight the need for additional investigation into LDX's role in promoting neuroinflammation and immune response activation.

4.3. Excitotoxicity and neurotransmitter imbalance

Excitotoxicity refers to cell death caused by the detrimental effects of excitatory amino acids. Neuronal excitotoxicity often involves the damage and death of neurons due to

prolonged exposure to glutamate, the principal excitatory neurotransmitter in the CNS, resulting in excessive ion influx into the cell.[49] Consequently, the role of excitotoxicity in the neurotoxic mechanism of amphetamines may be ascribed to an amphetamine-induced elevation in striatal glutamate release. This is supported by evidence showing that the use of both metabotropic (e.g., 2-methyl-6-[phenylethynyl]-pyridine) and ionotropic (e.g., MK-801) glutamate receptor antagonists can mitigate the neurotoxicity caused by amphetamine and methamphetamine.[29]

As previously mentioned, d-amphetamine functions by inhibiting the reuptake of norepinephrine and dopamine into the presynaptic neuron while enhancing the release of these monoamines into the synaptic space. Although this mechanism contributes to the therapeutic effects of LDX at optimal doses and short-term exposure, its influence on neurotransmitter homeostasis at elevated doses and over prolonged periods remains poorly understood. Numerous animal studies have demonstrated that methamphetamine, which possesses a nearly identical chemical structure to d-amphetamine, can impair both the dopamine and serotonin systems.[50-52]

Furthermore, methamphetamine toxicity, especially following repeated high-dose administration, selectively affects specific neural systems, notably those within the limbic reward system (e.g., substantia nigra, striatum, and nucleus accumbens).[53] Chronic methamphetamine use may also diminish dopamine levels, receptor density, and dopamine transporter expressions.[52] Notably, postmortem studies have indicated that even recreational doses of methamphetamine can lead to substantial dopamine depletion.[54]

Overall, the pharmacological and structural similarities between LDX and other amphetamines suggest that excitotoxicity could be a concern with LDX usage. However, concrete proof is necessary. Further research is essential to clarify LDX's influence on neurotransmitter systems, particularly in the context of drug misuse.

4.4. Disruption of the BBB

Amphetamines are known to compromise the integrity of the BBB, and similar issues may apply to LDX. The BBB is a specialized structure composed of tightly connected brain endothelial cells that form a boundary between the CNS and the rest of the body.[55] Once considered static, the BBB is now recognized as a dynamic interface that responds to signals from various sources. Recent data indicate that drugs of abuse, such as stimulants, can impair its functions.[56] Hyperthermia and hypertension induced by high doses of amphetamines are primary causes of transient BBB disruptions, leading to localized neurodegeneration and neuroinflammation in laboratory animals.[57] In addition, alterations in tight junction complexes have been demonstrated to impair the BBB integrity following methamphetamine administration. Methamphetamine exposure has been shown to reduce the expression of tight junction proteins such as zona occluden 1, occludin, and claudin 5 in both *in vivo* and *in vitro* studies.[58-62] Ultimately, neuroinflammation is proposed as a key mechanism underpinning methamphetamine-induced neurotoxicity and may also contribute to BBB damage.[56]

In summary, the breakdown of the BBB by amphetamines raises concerns about similar effects with LDX. Given that the BBB is essential for maintaining brain homeostasis and neuronal viability, further research is required to ascertain whether LDX can also disrupt its integrity.

5. Discussion

The current evidence suggests a potential association between LDX use and neuropsychological pathologies, which can be categorized into two distinct groups: Early-onset side effects and long-term neurotoxic effects. Although early-onset side effects, including insomnia, appetite suppression, headache, and irritability, are observed shortly after LDX use, it is important to differentiate whether these non-specific symptoms are typical of general stimulant side effects or indicative of underlying neurotoxicity.[63] In contrast, the expected long-term neurotoxic effects, such as oxidative stress, neuroinflammation, and excitotoxicity, are believed to develop gradually and accumulate with increasing exposure.[64]

The temporal gap between early-onset side effects and long-term neurotoxicity raises significant questions about their underlying mechanisms. Some early side effects may reflect acute dopaminergic and noradrenergic overstimulation, which could also contribute to neurotoxicity under chronic conditions.[65,66] Although the pharmacokinetic profile of LDX, as a prodrug that produces a consistent release of d-amphetamine, may help reduce the intensity of such overstimulation in the short term, it could lead to cumulative stress on neural systems over time.[67] However, due to the lack of mechanistic studies investigating both acute and chronic effects within the same experimental framework, no definite link can yet be established. Therefore, future studies should explore whether early behavioral symptoms can serve as biomarkers or early indicators of long-term neuronal damage.

Another significant gap in current knowledge is that, although several neurotoxic mechanisms have been proposed in relation to amphetamine-related compounds, no study to date has specifically examined the temporal sequence or hierarchical contribution of these pathways.

Nonetheless, current preclinical and mechanistic data suggest an interconnected and synergistic network rather than separate pathways operating independently. For instance, while neuroinflammation may itself prolong excitotoxic damage and affect the integrity of the BBB, oxidative stress could act as an upstream trigger, amplifying mitochondrial dysfunction and initiating neuroinflammation.[68] These connections suggest a complex neurotoxic environment where several pathways likely cooperate. Future experimental research is needed to clarify the temporal and causal links among these processes, which could inform both the prediction and prevention of LDX-related neurotoxicity.

Another significant aspect that has been inadequately addressed in earlier studies is the dose-dependent nature of LDX-related effects. With limited research on the dose-dependent long-term effects, human trials of LDX have primarily focused on its efficacy and common side effects.[69,70] While the possibility for cumulative effects at higher or prolonged exposures remains unquantified, LDX gradually delivers d-amphetamine through enzymatic conversion, making it plausible that its pharmacokinetic profile mitigates acute neurotoxic effects at recommended doses. Future research should systematically evaluate dose-response interactions utilizing both neurochemical and functional endpoints across different treatment durations to strengthen risk assessments and inform therapeutic decision-making.

Finally, there are limitations of this study that should be noted. First, as very few clinical trials directly assess the long-term neurotoxicity of LDX in human subjects, the present evidence base on LDX-induced neurotoxicity is essentially derived from preclinical studies on amphetamine and methamphetamine. Although these compounds are pharmacologically linked to LDX's active metabolite (d-amphetamine), they may not entirely reflect the drug's pharmacokinetics and tissue-specific effects. Second, this review utilizes results from various experimental contexts, including different dosages, animal models, and modes of administration, which may limit the generalizability of the findings. Lastly, the lack of longitudinal human studies prevents any definitive conclusions regarding the degree of risk or causality. These limitations emphasize the need for future translational and clinical research to more precisely define the safety profile of LDX.

Despite the potential neurotoxic impacts reviewed in this paper, LDX remains a clinically valuable pharmacological option for treating ADHD and BED.[4,71] It provides a long-acting, well-tolerated substitute with a reduced risk of abuse due to its prodrug design.[72] Therefore, the neurotoxic hazards of this drug should be considered not in isolation, but in line with its therapeutic advantages.

6. Conclusion

The neurotoxic potential of LDX is increasingly concerning, primarily due to its structural resemblance to amphetamines, which are known to cause oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, and impairment of the BBB. While direct studies on the long-term effects of LDX are limited, findings from research on other stimulants, such as amphetamines and methamphetamines, indicate that prolonged exposure to LDX may pose significant risks to neuronal health and CNS function.

7. Future directions

Future research must address the significant gaps in our understanding of LDX-induced neurotoxicity. Comprehensive longitudinal studies are essential to assess the long-term effects of LDX on the brain, with particular focus on oxidative stress, mitochondrial integrity, and synaptic plasticity. The studies should evaluate the drug's effects on neuronal survival, cognitive function, and behavioral outcomes in both preclinical and clinical settings.

Furthermore, investigating the mechanisms through which LDX influences the BBB and immune response is critical. Understanding the impact of prolonged LDX usage on neuroimmune interactions and its role in neuroinflammation may help reduce potential CNS injuries in vulnerable populations. Moreover, pharmacogenomic research may elucidate how genetic variants influence patient responses to LDX, thereby informing personalized treatment strategies to mitigate neurotoxic risks.

Striking a balance between the therapeutic benefits of LDX and its long-term safety is crucial. Enhancing our knowledge of the drug's neurobiological effects will enable clinicians to make more informed treatment decisions, ensuring that LDX remains a viable and safe option for patients.

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Author contributions

Conceptualization: Abbas Aliaghaei
Writing – original draft: Maral Hasanzadeh, Amirreza Beirami
Writing – review & editing: Abbas Aliaghaei, Amir-Hossein Bayat

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