

Amphetamine and methamphetamine exposure as an under-recognized accelerator of Alzheimer's disease pathology

Adel Ghorani-Azam * 

Department of Forensic Medicine and Toxicology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran

* Correspondence: Adel Ghorani-Azam. emails: Adelbiochem@gmail.com; qurani.a@umsu.ac.ir

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Alzheimer's disease (AD) is a major concern, impacting millions of people around the globe and creating significant clinical and economic challenges. While factors like age and genetics, particularly the APOE-ε4 gene, are key players in risk assessments, there are also modifiable factors—like vascular disease, diabetes, head injuries, and substance use—that greatly affect when and if someone develops clinical AD. Among the substances that could potentially lead to neurodegenerative issues, amphetamine-type stimulants—both prescription medications and illegal methamphetamine—deserve immediate attention. Their widespread use, whether for medical purposes or recreationally, along with their strong psychostimulant effects and increasing evidence of lasting brain damage, calls for a thorough investigation into how stimulant use might raise the risk of AD or speed up its neurological decline.

1. Convergent mechanisms: How amphetamines map onto AD biology

To establish a solid connection between stimulant use and AD, we need to look at the underlying biological mechanisms. Research across cells, animals, and humans shows that repeated exposure to amphetamines and methamphetamines leads to several interconnected processes that are also involved in AD.

1.1 Oxidative stress and mitochondrial dysfunction

Methamphetamine significantly boosts dopamine levels in the brain and its oxidative breakdown, which creates reactive oxygen species (ROS) that can harm proteins, lipids, and nucleic acids. Exposure to methamphetamine leads to mitochondrial fragmentation, disrupted electron transport, and reduced ATP production in neurons—issues that mirror the mitochondrial problems seen early in AD. This oxidative damage also hampers the body's ability to clear out aggregated proteins, which can worsen the buildup of Aβ and tau [1, 2]. Numerous preclinical studies have shown oxidative markers following stimulant use, and clinical research

has found increased oxidative and inflammatory markers in methamphetamine users [3].

1.2 Neuroinflammation and glial activation

Chronic exposure to stimulants like methamphetamine (METH) activates microglia and astrocytes, leading to the release of various cytokines (such as IL-1β and TNF-α), chemokines, and damage-associated molecular signals like HMGB1. Neuroinflammation has emerged as a key player—not just a passive observer—in the development of AD. Research indicates that METH enhances HMGB1 signaling and triggers other pro-inflammatory pathways that not only promote the processing of amyloid but also compromise the integrity of the blood-brain barrier, creating a setting that favors the progression of AD-like symptoms [3, 4].

1.3 Altered APP processing and amyloid accumulation

When it comes to altered amyloid precursor protein (APP) processing and amyloid buildup, experimental studies show that METH exposure boosts APP levels, increases the expression of β-secretase (BACE1), and elevates the production and accumulation of Aβ in both neuronal cultures and animal models. Meta-analyses of preclinical data consistently demonstrate METH's impact on APP/Aβ regulation, with key signaling pathways involving HMGB1 and issues with autophagy and lysosomal function [3, 5]. Interestingly, using drugs to inhibit BACE1 or enhance autophagic clearance has been shown to reduce some of the Aβ accumulation caused by METH, indicating a specific mechanistic effect [6].

1.4 Tau hyperphosphorylation and proteostasis failure

As for tau hyperphosphorylation and the failure of proteostasis, METH exposure also leads to increased tau phosphorylation in both cell and animal models, likely through the activation of kinases, endoplasmic reticulum (ER) stress, and disrupted autophagy. This dysregulation of tau metabolism, combined with amyloid ac-

cumulation and inflammation, creates a classic pathological cycle that contributes to synaptic dysfunction and neuronal loss in AD [6]. Pathways like the ER stress-mediated unfolded protein response (UPR) are activated by METH and have been directly linked to impaired long-term potentiation and memory formation in rodent studies [7].

1.5 Synaptic dysfunction, hippocampal injury, and network vulnerability

Stimulants have a knack for selectively damaging dopaminergic terminals, which in turn disrupts hippocampal neurogenesis and synaptic plasticity. This leads to lasting deficits in long-term potentiation (LTP), learning, and memory. The hippocampus acts as a key player in the early pathology of AD; the overlapping deficits caused by methamphetamine (METH) hint at a biological pathway through which stimulant use might lower the threshold for clinical AD or speed up the onset of symptoms [8]. Neuroimaging studies of chronic METH users reveal signs of cortical thinning, changes in the hippocampus, and patterns that resemble accelerated aging, especially when paired with genetic vulnerabilities like APOE- $\epsilon 4$ [9].

2. Clinical and epidemiological evidence

While the mechanistic data is quite solid, human evidence is still in the early stages and varies widely. Studies at the population level, along with cohort and case studies, provide converging but not yet conclusive support. Large-scale analyses of administrative data and cohort studies have found links between amphetamine-related disorders and an increased risk of dementia, including cases of earlier onset dementia. One population-level study indicated a higher incidence of dementia among individuals with a history of amphetamine-related disorders compared to matched controls, even after accounting for other factors [9, 10]. MRI studies complement these findings by showing patterns of brain atrophy and cognitive deficits in chronic METH users, while small longitudinal cohorts connect ongoing METH use to deteriorating cognitive trajectories over months to years. Notably, some studies point out that there may be synergistic effects with APOE- $\epsilon 4$ status, suggesting that stimulant exposure could interact with genetic vulnerabilities for AD, exacerbating brain atrophy and cognitive decline [11].

3. Biomarkers and molecular signatures in humans

Recent studies on biomarkers have found that METH users show higher levels of certain markers in their blood and cerebrospinal fluid (CSF) that are linked to AD pathology. Specifically, there are notable increases in plasma and CSF A β fragments and phosphorylated tau proteins in samples from METH-dependent individuals compared to those without such dependence. While these findings are limited by factors like small sample sizes, the cross-sectional nature of the studies, and the presence of other health issues (like polydrug

use, infections, and vascular risks), they do provide compelling molecular evidence that exposure to stimulants is tied to AD-related protein changes in humans [12].

4. Neuropsychiatric and cognitive phenotype

Clinical studies involving both former and current METH users reveal significant challenges in areas like executive function, episodic memory, processing speed, and social cognition—skills that overlap with early signs of AD. What's particularly concerning is that some of these cognitive impairments continue even after a person has stopped using METH, suggesting that there may be irreversible neurodegenerative changes in at least some individuals. Although rare and potentially influenced by publication bias, there are case reports and small series documenting instances of young-onset dementia following long-term amphetamine abuse [11, 13].

5. Clinical and public health implications

When it comes to the clinical and public health implications of stimulant exposure, especially if it speeds up AD pathology in those who are vulnerable, the stakes are high. Doctors prescribing amphetamines need to carefully consider the long-term risks, particularly for older adults or individuals with genetic predispositions like the APOE- $\epsilon 4$ allele. Harm-reduction strategies and treatment programs for stimulant use disorder should include cognitive screenings and, when possible, follow-ups with biomarkers or imaging to catch any early signs of neurodegeneration. It's also crucial for clinicians to talk to their patients about the potential long-term cognitive risks associated with chronic stimulant misuse and to think about monitoring their neurocognitive function over time.

As for research priorities, moving from just a theory to actionable insights requires focusing on five key areas:

5.1 Longitudinal studies with biomarker endpoints

We need well-defined groups of current and former stimulant users, monitored over time with regular cognitive tests, MRIs, and fluid biomarkers (like plasma/CSF A β , p-tau species, and neurofilament light) to understand how exposure relates to AD biomarker changes.

5.2 Studies on dose-response, exposure patterns, and age interactions

Both animal and human research should explore whether low, intermittent, or prescribed stimulant use poses different risks compared to chronic high-dose illicit use, whether exposure during adolescence is riskier than in adulthood, and how genetics (like APOE) influence these outcomes.

5.3 Understanding mechanisms and therapeutic windows

Research should aim to find out if the amyloid and tau changes caused by stimulants can be reversed (for instance, through enhanced clearance, anti-inflammatories, or mitochondrial protectants), which could guide potential treatments.

5.4 Differentiating between stimulant classes and formulations

It is not helpful to lump all psychostimulants together; future studies need to distinguish between amphetamine salts, methylphenidate, and methamphetamine, while also considering how they are administered, their formulations, and any co-medications involved.

5.5 Intervention trials

If we have solid translational evidence pointing to modifiable pathways like neuroinflammation, autophagy, and oxidative stress, then running pilot trials with targeted therapies on abstinent users who are at high risk could be a great way to explore strategies for slowing down the progression toward dementia.

6. Conclusion

There's a growing body of evidence from molecular studies, animal research, imaging, and new biomarker findings that shows amphetamine-type stimulants lead to neuropathological changes that significantly overlap with the biology of AD. These include oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, issues with APP processing and A β buildup, tau hyperphosphorylation, and damage to the hippocampus and synapses. While we still need to establish direct causality at the population level, the biological plausibility and early signals in humans are compelling enough to suggest a shift in perspective: we should view stimulant exposure as a potential modifiable factor that could accelerate AD pathology, particularly in individuals who are genetically predisposed.

Given how widespread both prescription amphetamines and illicit methamphetamine use are, it would be unwise to overlook this potential pathway. We should prioritize research investments in long-term biomarker studies, human model systems that explore mechanisms, and intervention trials focused on reducing stimulant-induced neurodegeneration. From a clinical standpoint, a sensible approach would involve educating patients, practicing careful prescribing, monitoring cognitive health in long-term users, and providing integrated addiction services—all while ensuring we avoid stigmatization and emphasize prevention.

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Author Contributions

The author did all the research work for this study.

Competing Interests

No conflicts of interest exist.

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