



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Huperzine A

Evidence Summary

Huperzine A improved some aspects of memory and cognition in patients with vascular dementia and Alzheimer's disease in clinical trials; however, many caveats prevent drawing firm conclusions. Appears safe for short-term use but evidence for long-term safety is lacking.

Neuroprotective Benefit: Multiple short-term (usually <6 month) clinical trials of varying quality and bias suggest possible cognitive benefit. Preclinical studies suggest anti-oxidant, anti-inflammatory, and iron lowering properties.

Aging and related health concerns: Lack of any human studies of huperzine A on aging or mortality. One rat study on induced-hepatocyte replicative senescence suggests anti-oxidant and anti-inflammatory effects.

Safety: Good short-term safety based on dozens of clinical trials lasting up to 6 months reporting few adverse events, but data on chronic use is lacking.

What is it? Huperzine A is a plant alkaloid found in species of *Huperzia*, particularly *Huperzia serrata*. It readily crosses the blood-brain barrier where it inhibits acetylcholinesterase and NMDA receptors.

Neuroprotective Benefit: Multiple short-term (usually <6 month) clinical trials of varying quality and bias suggest possible cognitive benefit. Preclinical studies suggest anti-oxidant, anti-inflammatory, and iron lowering properties.

Types of evidence:

- 4 meta-analyses of 22 unique trials comprising 2033 patients with AD, substantial overlap between analyses
- 2 double-blind RCTs comprising ~90 patients with vascular dementia
- Numerous animal model and *in vitro* cellular studies

22 clinical trials of varying quality have tested oral huperzine A in doses ranging from 0.2 mg to 0.8 mg daily for durations of up to 24 weeks, although most trials lasted 8-12 weeks. These trials were reviewed by 4 separate meta-analyses ([Li et al, 2008](#); [Wang et al, 2009](#); [Yang et al, 2013](#); [Xing et al, 2014](#)). While patients treated with huperzine A tended to show improvements in MMSE, memory tests and activities of daily living, all the analyses agree that it is impossible to aggregate the data to draw broad conclusions because of the heterogeneous study and reporting methodologies, the small subject sizes, the short duration of the trials and the risk for biases (e.g. selection bias, detection bias, attrition bias, and reporting bias). Additionally, an asymmetric funnel plot analysis of published trials suggests publication bias ([Yang et al, 2013](#)).

Two small, double-blind RCTs, comprising ~90 patients, examined huperzine treatment for vascular dementia (reviewed by [Hao et al, 2009](#); [Xu et al, 2012](#)). The smaller trial of 14 patients ([Hao et al, 2009](#)) found no cognitive benefit but significant improvement in activities of daily living after 6 months treatment with 0.15 mg daily huperzine A. The larger trial ([Xu et al, 2012](#)) of 78 patients reported significant cognitive and functional improvements after 12 weeks treatment with 0.1mg daily. Neither trial reported significant adverse effects, and both concluded the treatment was safe within the duration of the trials. No trials have yet tested huperzine A in patients with mild cognitive impairment ([Yue et al, 2012](#)). Longer and larger clinical trials with more rigorous methodology are needed to confirm the trends identified in past underpowered trials.

A large body of preclinical data from cells and animal models provides a biological foundation for the observed human benefits of huperzine A. It was originally identified as an acetylcholinesterase (AChE) inhibitor ([Tang et al, 1989](#)) and may be a 6-8 fold more potent and longer lasting AChE inhibitor than

donepezil or rivastigmine (Liang et al, 2004). However, huperzine A is likely multifunctional in the brain (reviewed by [Zhang et al, 2008](#); [Qian et al, 2014](#)).

Several studies suggest huperzine A protects neurons from glutamate toxicity, which is part of the disease pathology of Alzheimer's disease (AD) and other neurological diseases ([Ved et al, 1997](#); [Gordon et al, 2001](#)). Studies in rats and isolated neurons suggest huperzine A treatment can increase cerebral blood flow as well as increase production of the neuroprotective trophic factor NGF ([Wang et al, 2000](#); [Tang et al, 2005a](#); [Tang et al, 2005b](#)). In rodents, huperzine A increased endogenous antioxidants like glutathione ([Pohanka et al, 2012](#)) or improved mitochondrial function and neuroprotection from beta-amyloid toxicity ([Gao et al, 2009](#); [Yang et al, 2012](#)). Brain iron accumulation is a feature of Alzheimer's and other neurodegenerative diseases, as well as being causative of iron-dependent neurodegeneration. Several studies using rodent AD models suggest huperzine A treatment decreases brain iron levels as well as improving the brain's capacity to deal with excess iron ([Pohanka et al, 2011](#); [Huang et al, 2014](#)). Huperzine A also lowers neuroinflammation in a mouse model of multiple sclerosis ([Wang et al, 2012a](#)), although its impact on neuroinflammation in AD remains unclear.

Lastly, several studies in rodent models of AD suggest huperzine A may positively benefit several disease pathways. Treatment impacts amyloid production pathways, by decreasing toxic beta-amyloid production while boosting non-toxic amyloid processing ([Wang et al, 2011](#); [Wang et al, 2012b](#)). Huperzine A also improves learning and memory in AD transgenic mice ([Ratia et al, 2013](#)). These studies suggest that huperzine A could potentially be neuroprotective in humans and have utility as a treatment, perhaps even disease-modifying treatment, for Alzheimer's disease.

APOE4 interactions: There is no data available to suggest huperzine A might be differently effective in *APOE4* carriers versus non-carriers.

Aging, mortality and related health concerns: Lack of any human studies of huperzine A on aging or mortality. One rat study on induced-hepatocyte replicative senescence suggests anti-oxidant and anti-inflammatory effects.

Types of evidence:

- 1 preclinical rat study

There is no evidence from any human studies to suggest that huperzine A slows aging or reduces mortality risk. However, one study in young rats suggests it may impact several age-related pathways. Injection of the sugar D-galactose induces replicative senescence of liver cells as well as increasing



reactive oxygen species and inflammatory responses. Co-administration of huperzine A blocked these effects, including the induction of hepatocyte senescence ([Ruan et al, 2013](#)). While these results hint at potential broader effects of huperzine A on age-related processes, follow-up studies are needed to examine its role in overall longevity.

Safety: Good short-term safety based on dozens of clinical trials lasting up to 6 months reporting few adverse events, but data on chronic use is lacking.

Types of evidence:

- 24 small, short-term clinical trials of AD and vascular dementia patients

Huperzine A appears safe for short-term use, with dozens of clinical trials lasting up to 6 months reporting very few, if any, adverse effects. Reported adverse effects included headache, dizziness and blurred vision as well as some gastrointestinal disturbances, but these were rare. Huperzine A should be avoided when taking other AChE inhibitors like donepezil and rivastigmine.

[Drugs.com](#) lists no known interactions with prescription medications. However, [WebMD](#) states that huperzine A can lower heart rate. No scientific literature was found to support this warning in humans, but a study in pigs using other AChE inhibitors suggests they can interfere with cardiac neurons that control heart rate ([Darvesh et al, 2004](#)). WebMD also warns that huperzine A may aggravate symptoms of epilepsy, but a sizable body of literature actually argues against that and even suggests huperzine A may be an effective treatment for some types of epilepsy (reviewed by [Bialer et al, 2015](#)). Longer human studies are required to fully evaluate safety for chronic use.

Dosing and Sources: Huperzine A is orally bioavailable. Most clinical trials reported doses of huperzine A between 0.2 mg and 0.8 mg per day, with the most well-tolerated dose being 0.4 mg per day ([Yang et al, 2013](#)).

Future research: Large, well-designed clinical trials are needed to confirm huperzine A's potential as a treatment for AD and vascular dementia and to establish safety for chronic use, but none are currently ongoing. One trial is currently recruiting to test huperzine A as a treatment for moderate to severe TBI and is expected to report results in late 2016 ([NCT01676311](#)).

PubMed Search terms:

Huperzine A + following terms with and without filters for “clinical trial”, “meta-analysis”, and “review”



- Alzheimer's disease
- Neurodegeneration
- Dementia
- Cognition
- Cognitive decline
- Aging
- Longevity
- Lifespan
- Telomere
- Telomerase
- Diabetes
- Lipids
- Cholesterol
- Hypertension
- Blood Pressure
- Toxicology
- Safety

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit [Cognitive Vitality's Rating page](#).