Huperzine Studies

Huperzine a as potential treatment of Alzheimer's disease: an assessment on chemistry, pharmacology, and clinical studies.

Abstract
Alzheimer's disease (AD) is the fourth leading cause of death in adults, characterized by hallmark neuritic plaques and neurofibrillary tangles. Current treatments focus only on symptom relief. As a possible new treatment option for AD, huperzine A's chemistry, pharmacology, and clinical effectiveness are assessed. The chemical synthesis of huperzine A has been optimized, while an in vitro technique has provided a renewable plant source. Pharmacological studies showed that the drug inhibits the enzyme acetylcholinesterase reversibly and selectively. Huperzine A also displayed good pharmacokinetics with a rapid absorption and a wide distribution in the body at a low to moderate rate of elimination. Presently, inadequate toxicity data in human have been reported, yet animal studies demonstrated mild to moderate cholinergic side effects at therapeutic doses. Previous clinical trials have shown improvement in memory function using MMSE, MQ, ADAS-COG, and ADL tests. In an unpublished phase II clinical trial, the ADAS-COG and MMSE tests indicated cognitive enhancement at a dose of 0.4 mg, yet no improvement was observed at a dose of 0.2 mg. The MMSE scores indicated cognitive enhancement at 0.4 mg. Promising data suggested that huperzine A is well tolerated at doses up to 0.4 mg for 24 weeks. Therefore, huperzine A seems to be a potential treatment option for AD.

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Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials.
Review article

Abstract
BACKGROUND: Huperzine A is a Chinese herb extract used for Alzheimer's disease. We conducted this review to evaluate the beneficial and harmful effect of Huperzine A for treatment of Alzheimer's disease.

METHODS: We searched for randomized clinical trials (RCTs) of Huperzine A for Alzheimer's disease in PubMed, Cochrane Library, and four major Chinese electronic databases from their inception to June 2013. We performed meta-analyses using RevMan 5.1 software. (Protocol ID: CRD42012003249).

RESULTS: 20 RCTs including 1823 participants were included. The methodological quality of most included trials had a high risk of bias. Compared with placebo, Huperzine A showed a significant beneficial effect on the improvement of cognitive function as measured by Mini-Mental State Examination (MMSE) at 8 weeks, 12 weeks and 16 weeks, and by Hastgawa Dementia Scale (HDS) and Wechsler Memory Scale (WMS) at 8 weeks and 12 weeks. Activities of daily living favored Huperzine A as measured by Activities of Daily Living Scale (ADL) at 6 weeks, 12 weeks and 16 weeks. One trial found Huperzine A improved global clinical assessment as measured by Clinical Dementia Rating Scale (CDR). One trial demonstrated no significant change in cognitive function as measured by Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and activity of daily living as measured by Alzheimer's disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) in Huperzine A group. Trials comparing Huperzine A with no treatment, psychotherapy and conventional medicine demonstrated similar findings. No trial evaluated quality of life. No trial reported severe adverse events of Huperzine A.

CONCLUSIONS: Huperzine A appears to have beneficial effects on improvement of cognitive function, daily living activity, and global clinical assessment in participants with Alzheimer's disease. However, the findings should be interpreted with caution due to the poor methodological quality of the included trials.


Review article

Abstract
The objective of our study was to perform an updated meta-analysis of placebo-controlled RCTs of Huperzine A (Hup A) on patients with Alzheimer's disease (AD) and vascular dementia (VD), in order to provide the basis and reference for clinical rational drug use. The primary outcome measures assessed were minimental state examination (MMSE) and activities of daily living scale (ADL). Eight AD trials with 733 participants and two VD trials with 92 participants that met our inclusion criteria were identified. The results showed that Hup A could significantly improve the MMSE and ADL score of AD and VD patients, and longer durations would result in better efficacy for the patients with AD. It seemed that there was significant improvement of cognitive function measured by memory quotient (MQ) in patients with AD. Most adverse effects in AD were generally of mild to moderate severity and transient. Compared to the patients with AD, Hup A may offer fewer side effects for participants with VD in this study. Therefore, Hup A is a well-tolerated drug that could significantly improve cognitive performance in patients with AD or VD, but we need to use it with caution in the clinical treatment.


Huang XT¹, Qian ZM², He X³, Gong Q³, Wu KC³, Jiang LR⁴, Lu LN³, Zhu ZJ³, Zhang HY⁵, Yung WH³, Ke Y⁶.

Abstract

Huperzine A (HupA), a natural inhibitor of acetylcholinesterase derived from a plant, is a licensed anti-Alzheimer's disease (AD) drug in China and a nutraceutical in the United States. In addition to acting as an acetylcholinesterase inhibitor, HupA possesses neuroprotective properties. However, the relevant mechanism is unknown. Here, we showed that the neuroprotective effect of HupA was derived from a novel action on brain iron regulation. HupA treatment reduced insoluble and soluble beta amyloid levels, ameliorated amyloid plaques formation, and hyperphosphorylated tau in the cortex and hippocampus of APPswe/PS1dE9 transgenic AD mice. Also, HupA decreased beta amyloid oligomers and amyloid precursor protein levels, and increased A Disintegrin And Metalloprotease Domain 10 (ADAM10) expression in these treated AD mice. However, these beneficial effects of HupA were largely abolished by feeding the animals with a high iron diet. In parallel, we found that HupA decreased iron content in the brain and demonstrated that HupA also has a role to reduce the expression of transferrin-receptor 1 as well as the transferrin-bound iron uptake in cultured neurons. The findings implied that reducing iron in the brain is a novel mechanism of HupA in the treatment of Alzheimer's disease.
Treatment with Huperzine A improves cognition in vascular dementia patients.
Xu ZQ¹, Liang XM, Juan-Wu, Zhang YF, Zhu CX, Jiang XJ.

Abstract
In the present study, we tested the efficacy and safety of Huperzine A in treatment of mild to moderate vascular dementia (VaD). This was a randomized, double-blinded, placebo-controlled study with 78 patients with mild to moderate VaD. The participants were randomized to receive either vitamin C (100-mg bid) as placebo (n = 39) or Huperzine A (0.1-mg bid) (n = 39) for 12 consecutive weeks. The mini-mental state examination (MMSE), clinical dementia rating (CDR), and activities of daily living (ADL) scores were used for the assessment of cognition. The assessments were made prior to treatment, and 4, 8, and 12 weeks of the treatment. The adverse effects of the treatment were also recorded. After 12 weeks of treatment, the MMSE, CDR, and ADL scores significantly improved in the Huperzine A group (P < 0.01 for all comparisons), whereas the placebo group did not show any such improvement (P > 0.05 for all comparisons). No serious adverse events were recorded during the treatment.

CONCLUSION:
Huperzine A can significantly improve the cognitive function in patients with mild to moderate vascular dementia. Further, the medicament is safe.

Comparison of the efficacy of four cholinesterase inhibitors in combination with memantine for the treatment of Alzheimer's disease.
Shao ZQ¹.

Abstract
BACKGROUND:
Combined use of memantine and acetylcholinesterase inhibitors (AChEIs) has shown improved outcomes in patients with Alzheimer's disease (AD). However, it is not clear which AChEI is the optimal for the combined treatment with memantine.

METHODS:
A total of 110 AD patients were randomized to receive memantine and one of the following add-on drugs: placebo, donepezil, rivastigmine, galantamine, and huperzine A for 24 weeks (n=22). At baseline, 12 weeks, and 24 weeks, the patients were evaluated using mini-mental state examination (MMSE) and Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scales. Adverse events were recorded to analyze the safety profile.
RESULTS:
The MMSE scores were significantly increased and the ADL scores were significantly decreased at 12 weeks and 24 weeks in all five groups compared with baseline (all P<0.01). At 24 weeks, patients treated with memantine+huperzine A showed better MMSE and ADL scores than those treated with memantine+placebo.

CONCLUSIONS:
Huperzine A may be an optimal choice for the combined therapy with memantine in treating AD.


Huperzine A: Is it an Effective Disease-Modifying Drug for Alzheimer's Disease?

Qian ZM1, Ke Y2.

Abstract
Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which there is no cure. Huperzine A (HupA) is a natural inhibitor of acetylcholinesterase (AChE) derived from the Chinese folk medicine Huperzia serrata (Qian Ceng Ta). It is a licensed anti-AD drug in China and is available as a nutraceutical in the US. A growing body of evidence has demonstrated that HupA has multifaceted pharmacological effects. In addition to the symptomatic, cognitive-enhancing effect via inhibition of AChE, a number of recent studies have reported that this drug has "non-cholinergic" effects on AD. Most important among these is the protective effect of HupA on neurons against amyloid beta-induced oxidative injury and mitochondrial dysfunction as well as via the up-regulation of nerve growth factor and antagonizing N-methyl-d-aspartate receptors. The most recent discovery that HupA may reduce brain iron accumulation lends further support to the argument that HupA could serve as a potential disease-modifying agent for AD and also other neurodegenerative disorders by significantly slowing down the course of neuronal death.