Huperzine A for Alzheimer's disease

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Synopsis

There is currently insufficient evidence of the effects of Huperzine A for Alzheimer's disease (AD).

Huperzine A is derived from Chinese club moss Huperzia serrata, and is described as having several properties which may be beneficial for AD. This review looked for randomized trials comparing Huperzine A with control in patients with AD. Six trials were identified but most trials were of low methodological quality. Although Huperzine A seemed to have some beneficial effects on improvement of general cognitive function, global clinical status, behavioral disturbance and functional performance for patients with AD, the small trials with limited numbers of patients and the low methodological quality resulted in cautious assessment of the results. More large, high-quality randomized trials are needed.

Abstract

Background

Alzheimer's disease (AD) has become a major public health problem around the world due to its increasing prevalence, long duration, caregiver burden, and high financial cost of care. The degeneration of acetylcholine-containing neurons in the basal forebrain has been implicated in the symptoms of AD. Cholinesterase inhibitors may block the degradation of acetylcholine, thus increasing the efficacy of the remaining cholinergic neurons. Huperzine A is a linearly competitive, reversible inhibitor of acetyl cholinesterase that is said to have both central and peripheral activity with the ability to protect cells against hydrogen peroxide, beta-amyloid protein (or peptide), glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis. These properties might qualify Huperzine A as a promising agent for treating dementia (including AD).

Objective

To assess the efficacy and safety of Huperzine A for the treatment of patients with AD.

Search strategy

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group was searched on 1 February 2006 using the search term: huperzin*. The CDCIG Specialized register contains records from all major health care databases (MEDLINE, EMBASE, PsycINFO, CINAHL, SIGLE, ISTP, INSIDE, LILACS) as well as from many trials databases and grey literature sources. In addition, the CBM and AMED databases and relevant websites were searched and some journals were hand-searched. Specialists in the field were approached for unpublished material and any publications found were searched for additional references.

Selection criteria

All relevant randomized controlled trials (RCTs) studying the efficacy and safety of Huperzine A for AD.

Data collection and analysis

Data were extracted independently by two reviewers using a self-developed data extraction form and entered into RevMan 4.2.10 software. Meta-analyses were performed when more than one trial provided data on a comparable outcome on sufficiently similar patients. Random effects analyses were performed whenever heterogeneity between results appeared to be present. Standardized differences in mean outcome measures were used due to the use of different scales and periods of treatment.

Main results

Six trials including a total of 454 patients met our inclusion criteria. The methodological quality of most included trials was not high. It was shown that compared to placebo, Huperzine A had beneficial effects on the improvement of general cognitive function measured by MMSE (WMD 2.81; 95% CI 1.87 to 3.76; P < 0.00001) and ADAS-Cog at six weeks (WMD 1.91; 95% CI 1.27 to 2.55) and at 12 weeks (WMD 2.51; 95% CI 1.74 to 3.28), global clinical assessment measured by CDR (WMD -0.80; 95% CI -0.95 to -0.65) and CIBIC-plus (OR 4.32, 95% CI 2.37 to 7.90), behavioral disturbance measured by ADAS-non-Cog at six weeks (WMD -1.33, 95% CI -2.12 to -0.54) and at 12 weeks (WMD -1.52, 95% CI -2.39 to -0.65), and functional performance measured by ADL (WMD = -7.17; 95% CI -9.13 to -5.22; P < 0.00001). However, Huperzine A was not superior to placebo in the improvement of general cognitive function measured by Hasegawa Dementia Scale (HDS) (WMD: 2.78; 95% CI 0.17 to 5.73, P = 0.06) and specific cognitive function measured by Wesler Memory Scale (WMS) (WMD = 6.64; 95% CI -3.22 to 16.50; P = 0.19). No data were available on quality of life and caregiver burden. The adverse events of Huperzine A were mild and there were no significant differences of adverse events between Huperzine A groups and control groups.

Reviewers' conclusions

From the available evidence, Huperzine A seems to have some beneficial effects on improvement of general cognitive function, global clinical status, behavioral disturbance and functional performance, with no obvious serious adverse events for patients with AD. However, only one study was of adequate quality and size. There is therefore inadequate evidence to make any recommendation about its use. Rigorous design, randomized, multi-centre, large-sample trials of Huperzine A for AD are needed to further assess the effects.

Results

Of the six included trials, most of trials just reported the mean score of general and specific cognitive function, global clinical assessment and functional performance before and after treatment without the change score from baseline being available. However, we calculated the change score according to the mean score before and after treatment. So the above mentioned outcomes in this systematic review were assessed by using the change score.

1. The change of general cognitive functions
   (1) The change of general cognitive function measured by mini-mental state evaluation (MMSE)
   Huperzine A versus placebo only
Four trials (Liu 1995; Xu 1997; Yang 2003; Zhou 2004b) with 220 patients comparing Huperzine A with placebo only evaluated the effect of Huperzine A on the improvement of general cognitive function measured by MMSE after treatment. The dose of Huperzine A was 0.3 to 0.4 mg daily with a treatment period of eight to 36 weeks. There was a beneficial effect of Huperzine A on the improvement of general cognitive function for AD (WMD = 2.81; 95% CI 1.87 to 3.76; P < 0.00001).

Huperzine A + Vitamin E versus placebo + Vitamin E
One trial (Zhang 2002) with 202 patients comparing Huperzine A plus Vitamin E with Vitamin E plus placebo evaluated the effect of Huperzine A on the improvement of ADL after treatment. The administration of Huperzine A was 0.4 mg daily for 12 weeks. There was a significantly beneficial effect of Huperzine A on the improvement of general cognitive function for AD at six weeks (WMD: 1.91; 95% CI 1.27 to 2.55) and at 12 weeks (WMD: 2.51; 95% CI 1.74 to 3.28).

Huperzine A + treatment versus routine treatment.
One trial (Yang 2003) with 220 patients comparing Huperzine A (0.2 mg daily) plus routine treatment with routine treatment evaluated the effect of Huperzine A on the improvement of general cognitive function after 12 weeks treatment. The routine treatment included psychological consultation and daily life direction. There was a significantly beneficial effect of Huperzine A on the improvement of general cognitive function for AD (WMD: 5.38; 95% CI 3.72 to 7.04).

(2) The change of general cognitive function measured by HDS at the end of treatment or follow-up
Huperzine A + placebo only
Two trials (Liu 1995; Xu 1997) with 131 patients comparing Huperzine A (0.4 mg daily) with placebo only evaluated the effect of Huperzine A on the improvement of general cognitive function measured by HDS after eight weeks treatment. There was no statistically significant difference between two groups (WMD: 2.78; 95% CI -0.17 to 5.73, P = 0.06).

Huperzine A + routine treatment versus routine treatment
No trials.
(3) The change of general cognitive function measured by ADAS-Cog at the end of treatment or follow-up
One trial (Zhang 2002) with 202 patients comparing Huperzine A (0.4 mg daily) plus Vitamin E (200 mg daily) with placebo plus Vitamin E (200 mg daily) evaluated the effect of Huperzine A on the improvement of general cognitive function after six and 12 weeks treatment. It was shown that Huperzine A was superior to placebo on the improvement of ADAS-Cog at six weeks (WMD: -3.73; 95% CI -5.21 to -2.25) and 12 weeks (WMD: -5.36; 95% CI -7.08 to -3.64).

2. The change of specific cognitive function measured by the WMS at the end of treatment or follow-up
Huperzine A versus placebo
Two trials (Liu 1995; Xu 1997) with 131 patients comparing Huperzine A versus placebo evaluated the effect of Huperzine A on the improvement of specific cognitive function measured by WMS at the end of treatment. The dose of Huperzine A was 0.4 mg daily with a treatment period of eight weeks. It was demonstrated that there was no significantly statistical difference between the two groups (WMD = 6.64; 95% CI -3.22 to 16.50; P = 0.19).

3. Global clinical assessment at the end of treatment or follow-up
Huperzine A versus placebo only
One trial (Yang 2003) with 65 patients comparing Huperzine A (0.3 mg daily) with placebo only demonstrated that Huperzine A was remarkably beneficial for the improvement of global clinical assessment measured by CDR test scores after 16 weeks treatment (WMD: -0.80; 95% CI -0.95 to -0.65).

Huperzine A + Vitamin E versus placebo + Vitamin E
One trial (Zhang 2002) with 202 AD patients comparing Huperzine A (0.2 to 0.4mg daily) plus Vitamin E with Vitamin E plus placebo demonstrated that Huperzine A was significantly beneficial for the improvement of global clinical assessment measured by the CIBIC-plus test after 12 weeks of treatment (OR 4.32, 95% CI 2.37 to 7.90).

4. All-cause mortality
No data on all-cause mortality at the end of treatment or follow-up were available from the included trials.

5. The change of behavior disturbance at the end of treatment or follow-up
One trial (Zhang 2002) with 202 AD patients comparing Huperzine A (0.2 to 0.4 mg daily) plus Vitamin E with Vitamin E plus placebo evaluated the effect of Huperzine A on the improvement of behavioral disturbance after six and 12 weeks treatment. It was shown that Huperzine A was superior to placebo on the improvement of ADAS-non-Cog at six weeks (WMD = -1.33, 95% CI -2.12 to -0.54) and 12 weeks (WMD = -1.52, 95% CI -2.39 to -0.65).

6. Functional performance measured by ADL
Huperzine A versus placebo only
Four trials (Liu 1995; Xu 1997; Yang 2003; Zhou 2004b) with 220 patients comparing Huperzine A with placebo only evaluated the effects of Huperzine A on the improvement of functional performance measured by ADL. The dose of Huperzine A was 0.3 to 0.4 mg daily with treatment periods of eight to 36 weeks. It was shown that Huperzine A was superior to placebo for the improvement of ADL (WMD = 1.91; 95% CI -1.29 to 5.25; P = 0.00001).

Huperzine A + Vitamin E versus placebo + Vitamin E
One trial (Zhang 2002) with 202 patients compared Huperzine A (0.4 mg daily) plus Vitamin E (200 mg daily) with placebo plus Vitamin E (200 mg daily) to assess the effects of Huperzine A on the improvement of functional performance after six weeks and 12 weeks treatment. It was shown that Huperzine A was more beneficial than placebo for the improvement of functional performance at six weeks (WMD = -2.36; 95% CI -3.68 to -1.04) and 12 weeks (WMD = -1.92; 95% CI -3.30 to -0.54).

Huperzine A + routine treatment versus routine treatment
One trial (Dong 2002) with 32 patients comparing Huperzine A (0.2 mg daily) plus routine treatment with routine treatment showed that Huperzine A was not beneficial for the improvement of ADL at 12 weeks (WMD = -10.55; 95% CI -23.83 to 2.73).

7. Quality of life
No data on quality of life at the end of treatment and follow-up were available from any of the included trials.

8. Caregiver burden
No data on caregiver burden at the end of treatment or follow-up were available from any of the included trials.

9. Adverse events of Huperzine A
Of the six included trials, five trials (Liu 1995; Xu 1997; Yang 2003; Zhang 2002; Zhou 2004b) described the adverse events in detail, mainly including cholinergic side effects, such as exciting, hyperactivity, nasal obstruction, nausea or vomiting, diarrhea, insomnia, anorexia, dizziness, thirst and constipation. Abnormalities in ECG (e.g. cardiac ischemia or arrhythmia) were reported in one trial (Liu 1995). It was demonstrated that three cholinergic side effects were not statistically significant between groups, with ORs and corresponding 95% CIs of 0.85 (0.29, 2.47), 2.31 (0.58, 9.22) and 1.62 (0.51, 5.17), respectively. One trial with 103 patients comparing Huperzine A with placebo only reported the number of events of exciting, hyperactivity, nasal obstruction, diarrhea and insomnia (Xu 1997). It was shown that these three cholinergic side effects were not statistically significant between groups (P > 0.05). One trial with 28 patients comparing Huperzine A with placebo only reported ECG abnormalities and cholinergic side effects including dry mouth, constipation and insomnia (Zhou 2004b). It was shown that there were no significant differences in ECG abnormalities (OR 0.42, 95% CI 0.19 to 1.91) and the above-mentioned cholinergic side effects between groups (OR 12.43, 95% CI 0.60 to 256.66). One trial with 202 patients comparing Huperzine A plus Vitamin E with placebo plus Vitamin E (Zhang 2002) showed that there was no statistical significance of adverse events (e.g. nausea or vomiting, anorexia, insomnia, bradycardia, headache) between groups (OR 1.02, 95% CI 0.20 to 5.18).

Discussion
Six trials with a total of 454 patients were included in this review. Because all the included trials were conducted in China and no data from other country were available, the present review is not representative of different racial groups.

The results revealed that, compared with placebo, for patients with AD, Huperzine A significantly improves global cognitive function measured by MMSE and ADAS-Cog, global clinical assessment, and ADAS-non-Cog and functional performance measured by ADL. However, these results need to be interpreted with caution. The results were based on data from a single trial or several trials with a limited number of patients; most of trials were of fair or poor methodological quality with regard to method of randomization, allocation concealment and blinding of assessment except Zhang 2002. However, it should also be mentioned that Zhang 2002 was a confounded study (Huperzine A + Vitamin E versus placebo + Vitamin E). These findings failed to demonstrate that Huperzine A and Vitamin E differentially improve cognitive function. However, it is also possible that the components of the vitamin E may also have a positive impact on cognitive function.

It was not possible to perform a funnel plot to assess the degree of publication bias in this systematic review because of the limited number of trials for each outcome. All the six included trials in this review were conducted in China and published in Chinese. Vickers and colleagues (Vickers 1998) found that some countries, including China, publish unusually high proportions of positive results. Although we have undertaken extensive searches for published material, we could not exclude the possibility that studies with negative findings remain unpublished.

References

References to studies included in this review

Dong 2002 {published data only}


Liu 1995 {published data only}


Xu 1997 {published data only}


Yang 2003 {published data only}


Zhang 2002 {published data only}


Zhou 2004 {published data only}


* indicates the major publication for the study

References to studies excluded from this review

Kuang 2004


Liu 2001


Wang 1999 a


Wang 1999 b


Wang 2002


Wang 2003


Wang 2004


http://www.medicinacomplementar.com.br/convertido/do-0045.htm
Ye 2001

Zhang 1991

Zhou 2004a

Zhu 2005

Ongoing studies
Aisen 2004
Aisen PS. A multi-center, double-blind, placebo-controlled therapeutic trial to determine whether natural Huperzine A improves cognitive function. 2004:-.

Additional references
AD Association 2007a

AD Association 2007b

APA 1980

APA 1987

APA 1994
In: Diagnostic criteria from DSM-IV American Psychiatric Association, 1994:-.

Baumgarten 1994

Birks 2000

Birks 2006
Birks JS, Harvey R. Donepezil for dementia due to Alzheimer’s disease. Cochrane Database of Systematic Reviews 2006:-.

Brookmeyer 1998

Cacabelos 1999

Chen 2000a

Chen 2000b


CSHA 1994

Egger 1997

Emre 2001

Evans 1990

Gracon 1996

He 2002

Higgins 2003

ICD 1989

Larson 2004

Li 1999

Liang 2004

Liang 2007
Liang YQ, Huang XT, Tang XC. Huperzine A reverses cholinergic and monoaminergic dysfunction induced by bilateral nucleus basalis magnocellularis injection of P-amyloid peptide (1-40) in rats. Cellular and Molecular Neurobiology 2007:1573-6830 (online):-.

Liu 1999

Liu 1998

Mckhann 1998
Mckhann G, Drachman D, Folstein M. Clinical diagnosis of Alzheimer’s disease: Report of the NINCDS-ADRDA Work Group under the...

McShane 2006
McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database of Systematic Reviews 2006;-

Qizilbash 2002

Rogers 1991

Rosler 1999

Santaguida 2004
Santaguida PS, Raina P, Booker L, Patterson C, Badalassarre F, Cowan D. Pharmacological Treatment of Dementia. -.

Schulz 1995

Tang 1999

USGAO 1998
Alzheimer's disease: Estimates of prevalence in the US. 1998;-

Vickers 1998

Wang 1985

Wang 2000

Wang 2005

Whitehouse 1981

WHO 1992

Xu 1996

Xu 1999

Zhang 1998

Zhou 2001