Efficacy and safety of natural acetylcholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease: an updated meta-analysis
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CRD summary
This review assessed the safety and efficacy of huperzine A in Alzheimer's disease. The authors concluded that huperzine A was a well-tolerated drug that could significantly improve cognitive performance and activities in daily living scale in patients with Alzheimer's disease. However, as the results of the pooled analysis may not be reliable, these conclusions should be viewed with caution.

Authors' objectives
To assess the safety and efficacy of the natural acetyl cholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease.

Searching
MEDLINE, the Cochrane Library and the Chinese Biomedical Literature Database (January 1980 to May 2008) were searched (limited to randomised controlled trials, RCTs) for English and Chinese language studies. Search terms were reported. Recent review articles, published reports of clinical trials, and retrieved studies references and bibliographies were manually cross-referenced.

Study selection
Placebo-controlled RCTs of participants with Alzheimer's disease (without a current diagnosis of any other psychiatric or neurological disorder), aged older than 50 years, were eligible for inclusion. Eligible outcome measures were measures of cognitive performance and activities of daily living scale (ADL). The mini-mental state examination (MMSE) was the primary outcome of interest, used to evaluate the effects of huperzine A on cognitive function. Trials with fewer than 20 participants in each arm and trials that evaluated dementia caused by diseases other than Alzheimer's disease were excluded.

The included trials included patients aged between 50 and 90 years that fulfilled diagnosis criteria DSM3-R or DSM4 (Diagnostic and Statistical Manual of mental disorders). The intervention groups received huperzine A tablets orally and doses ranged from 300 to 500 μg per day. The control groups received placebo tablets in three trials but received *Salvia miltiorrhiza* tablets in one study. Vitamin E was given to all patients as routine treatment in one trial. The trial duration ranged from eight to 24 weeks. All of the included trials were performed in China.

Studies were selected by two reviewers and disagreements resolved by discussion.

Assessment of study quality
Methodological quality was assessed by two reviewers using the Jadad scale (which assessed studies in terms of randomisation, blinding, allocation concealment and withdrawals, to give a score out of 5 points). Disagreements were resolved by discussion.

Data extraction
Where possible intention-to-treat data were extracted, otherwise per protocol outcome data were used. The endpoint data for each outcome was used and the mean difference in changes of the mean score calculated. Adverse events were also extracted. Data were extracted independently by two reviewers and disagreements resolved by discussion with a third.

Methods of synthesis
Pooled weighted mean differences (WMDs) and their 95% confidence intervals (CIs) were calculated using a fixed-effects model; a random-effects model was used if significant heterogeneity was present. Statistical heterogeneity was assessed using the Cochran Q statistic and $\tau^2$ test. A bivariate repeated measures meta-regression was also performed.
using restricted maximum likelihood, with duration of treatment as the covariate.

**Results of the review**

Four RCTs were included in the review (n=474 participants). Sample sizes ranged from 65 to 197. All RCTs described the method of randomisation, two were single blind, two double blind. Withdrawals and drop-outs were reported in two RCTs and only one RCT reported ITT data.

Huperzine A was associated with a beneficial effect on mini-mental state examination (MMSE) scores (WMD 3.52, 95% CI 2.23 to 4.80) and activities of daily living scale (ADL) scores (WMD -4.50, 95% CI -7.05 to -1.96) compared with placebo (four RCTs). Both outcomes were associated with significant heterogeneity (MMSE, Q=11.1 and p=0.01; ADL, Q=11.4 and p=0.0098).

The regression analysis showed significantly better efficacy over time for mean change in MMSE in the huperzine A group and a similar but non-significant trend for time effect on mean ADL.

Some mild peripheral cholinergic side effects (such as nausea or vomiting and diarrhoea) were more likely to occur in the huperzine A group than placebo, but this difference was not significant.

**Authors' conclusions**

Huperzine A was a well-tolerated drug that could significantly improve cognitive performance and ADL in patients with Alzheimer's disease.

**CRD commentary**

The review question was supported by inclusion criteria for participants, intervention, outcomes and study design. As searches were restricted to published studies in English and Chinese, publication and language bias could not be ruled out. Study selection, data extraction and validity assessment were performed in duplicate, reducing the possibility of reviewer error and bias. As significant heterogeneity between studies was detected, the results of the meta-analysis may not be reliable and sources of possible heterogeneity were not investigated. The authors also stated that small sample size, treatment duration less than 24 weeks and limited outcome measures were further limitations to this analysis. Also, all of the included trials were conducted in China, which may limit the generalisability of the results to other populations. The results of the pooled analysis may not be reliable, so the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

The authors did not state any implications for practice or research.

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