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## Huperzine A preparation for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials

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### Citation

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### Review question(s)

What are the effectiveness and safety of Huperzine A preparations for the treatment of Alzheimer's disease?

### Searches

We will search the following electronic databases from inception until October 2012: PubMed, MEDLINE, EMBASE, Cochrane Dementia and Cognitive Improvement Group, and Cochrane Central Register of Controlled Trials (CENTRAL).

The following Chinese databases will also be searched: China Network Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), Wan Fang Database and Chinese Biomedicine (CBM).

We will also search for ongoing trials from mainstream registries: The metaRegister of Controlled Trials, The US National Institutes of Health Ongoing Trials Register, The Australian New Zealand Clinical Trials Registry, The World Health Organization International Clinical Trials Registry platform, and CentreWatch.

Unpublished postgraduate theses in Chinese databases will also be searched. The reference lists of all relevant papers found electronically will be hand-searched.

Details of the search strategy will be available from the authors on request. No language restriction will be applied.

### Types of study to be included

We will include parallel group, randomized controlled trials to assess the beneficial effects and harms of Huperzine A for treating Alzheimer's disease regardless of blinding or publication types. Cross-over randomized trials will be included, but only outcomes at the first period of treatment will be extracted and analyzed. Quasi-randomized trials will be excluded.

### Condition or domain being studied

Alzheimer's disease, first described by German psychiatrist Alois Alzheimer in 1906, is a progressive neurodegenerative disease characterized by cognitive deterioration together with behavioral disturbances and declining activities of daily living.

### Participants/ population

Inclusion: Patients with Alzheimer's disease regardless of the disease course and severity and diagnosed with any one of the following criteria:

- (1) The International Classification of Disease (ICD) version 9 or 10;
- (2) The Diagnostic and Statistical Manual of Mental Disorder (DSM) III, III-R or IV;
- (3) The National Institute of Neurological and communicative Disorder and Stroke-Alzheimer's Disease and Related Disorder Association (NINCDS/ADRDA).

Exclusion: Patients with dementia of other type.

### Intervention(s), exposure(s)

Huperzine A for patients with Alzheimer's disease, regardless of manufactures, preparation form, dose, and duration.

### Comparator(s)/ control

Placebo, no treatment, conventional intervention.

Co-intervention is allowed if applied in all arms.

## **Context**

No restriction.

## **Outcome(s)**

### **Primary outcomes**

Cognitive function, quality of life (QoL) measured by validated instrument.

### **Secondary outcomes**

Activities of daily living, global clinical assessment, and adverse effects of Huperzine A.

## **Data extraction, (selection and coding)**

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers. Any disagreement will be resolved through discussion with a third reviewer.

A predesigned form will be used to extract data from the included studies for assessment of study quality and data analysis. Extracted information will include: study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; outcome measures and result. Two review authors will extract data independently. Any discrepancies will be identified and resolved through discussion with a third author where necessary.

## **Risk of bias (quality) assessment**

Two review authors will independently assess the risk of bias using Cochrane tool of Risk of bias. The following items will be assessed:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding (performance bias and detection bias)
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias)
- Other bias

For each included study we will give a description supporting our judgment for each item. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

## **Strategy for data synthesis**

We will summarize data using risk ratios (RR) with 95% confidence intervals (CI) for binary outcomes or mean difference (MD) with 95% CI for continuous outcomes. If different measurement scales are used, standardized mean difference (SMD) analyses will be performed. For cross-over trials, only the first intervention will be included. If required data are not reported, we will request data from corresponding author. We will use fixed effects model unless there is evidence of heterogeneity.

Heterogeneity will be assessed using both the Chi-squared test and the I-squared statistic. We will consider an I-squared value greater than 50% to be indicative of substantial heterogeneity. We will conduct sensitivity analyses based on study quality, if necessary. Funnel plots will be generated to detect publication bias if sufficient trials are identified.

If appropriate, we will use cumulative meta-analyses. Results for the meta-analyses and cumulative meta-analyses will be visualized by forest plots. We will also tabulate the findings by a Summary of Finding Table. Specifically, we will construct trial sequential analysis (TSA) to evaluate our meta-analyses, which can reveal insufficient information size and potentially false results in meta-analysis.

## **Analysis of subgroups or subsets**

If the necessary data are available, subgroup analyses will be done for different outcome measures or different Huperzine A durations separately.

## **Dissemination plans**

We will submit our findings to high impact journal to publicize the findings internationally.

## **Contact details for further information**

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01 May 2011

### **Anticipated completion date**

31 December 2012

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### **Conflicts of interest**

None known

### **Language**

English

### **Country**

China

### **Subject index terms status**

Subject indexing assigned by CRD

### **Subject index terms**

Alkaloids; Alzheimer Disease; Humans; Neuroprotective Agents; Sesquiterpenes;

### **Date of registration in PROSPERO**

08 November 2012

### **Date of publication of this revision**

08 November 2012

### **Stage of review at time of this submission**

Preliminary searches

### **Started Completed**

Yes Yes

Piloting of the study selection process

Yes Yes

Formal screening of search results against eligibility criteria

Yes Yes

Data extraction

Yes No

Risk of bias (quality) assessment

Yes No

Data analysis

No No

Prospective meta-analysis

No No

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PROSPERO

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