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Huperzine A for mild cognitive impairment (Review)

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[Intervention Review]

Huperzine A for mild cognitive impairment

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ABSTRACT

Background

Mild cognitive impairment (MCI) has been proposed as a condition of intermediate symptomatology between the cognitive changes of ageing and fully developed symptoms of dementia. Treatment in the stages of MCI may delay the deterioration of cognitive impairment and delay the progression to dementia. Currently, the treatments for Alzheimer's disease have been focused on increasing acetylcholine levels in the brain. However, these drugs have not been proven to be effective for MCI and have numerous side effects. Huperzine A may have some beneficial effects in MCI.

Objectives

To assess the clinical efficacy and safety of huperzine A for the treatment of patients with MCI.

Search methods

We searched ALOIS: the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 23 May 2011 using the terms: huperzine, ayapin, scoparon. ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases, numerous trial registries and grey literature sources. Additional searches were also performed separately in MEDLINE, EMBASE, PsycINFO, LILACS, clinicalTrials.gov, the ICTRP (WHO portal), CENTRAL (*The Cochrane Library*) and Web of Science with Conference Proceedings.

The following Chinese databases were searched: The Chinese Biomedical Database, VIP Chinese Science and Technique Journals Database, China National Knowledge Infrastructure and The Chinese Clinical Trials Register. In addition, we handsearched 20 Chinese traditional medicine journals from between 1970 and 1989.

Selection criteria

Randomised, parallel-group, placebo-controlled trials comparing huperzine A with placebo in patients with MCI were eligible for inclusion.

Data collection and analysis

Two review authors independently assessed studies for their eligibility for inclusion.

Main results

No eligible trials were identified. In the absence of any suitable randomised placebo-controlled trials in this area, we were unable to perform a meta-analysis.

Authors' conclusions

The currently available evidence is insufficient to assess the potential for huperzine A in the treatment of MCI. Randomised double-blind placebo-controlled trials are needed.

PLAIN LANGUAGE SUMMARY

No evidence from randomised controlled trials for or against the use of huperzine A in the treatment of people with mild cognitive impairment

Mild cognitive impairment (MCI) is a condition in which a person has problems with memory, language or another mental function severe enough to be noticeable to other people and to show up on tests, but not serious enough to interfere with daily life. Research has shown that individuals with MCI have an increased risk of developing Alzheimer's disease (AD) over the following few years, especially when their main problem is memory. Currently available drug treatments for AD are thought to work by inhibiting the enzyme acetylcholinesterase and hence increasing acetylcholine levels in the brain. However, these drugs have not been shown to be effective for MCI and have numerous side effects. Huperzine A is a herbal medicine that is an alkaloid isolated from the Chinese herb *Huperzia serrata*. It has also been found to be an inhibitor of acetylcholinesterase and to possess other properties (such as protecting the brain against glutamate-induced damage, and increasing levels of nerve growth factor), which may have some beneficial effects in MCI. It is used to treat MCI in China, but because no randomised controlled trials of huperzine A versus placebo were found its efficacy and safety could not be analysed in this review. There is a need for randomised placebo-controlled trials of huperzine A for people with MCI.

BACKGROUND

Description of the condition

Mild cognitive impairment (MCI) is a term used to describe a condition of intermediate symptomatology between the cognitive changes of ageing and fully developed symptoms of dementia, such as those seen in Alzheimer's disease (AD) (Mount 2006; Petersen 1999; Petersen 2003). Its relation to the other clinical labels given to the cognitive dysfunctions associated with ageing are not always clear (e.g. benign senescent forgetfulness, age-associated memory impairment, age-associated cognitive decline, mild cognitive decline, mild neurocognitive decline and cognitive impairment no dementia) (Gauthier 2006; Ritchie 2000; Whitehouse 2006; Winblad 2004). MCI was originally classified by Petersen 1999 who proposed the following diagnostic criteria: (1) memory complaint, (2) normal activities of daily living (ADL), (3) normal general cognitive functioning, (4) abnormal memory for age and (5) patient not meeting the criteria for dementia (Petersen 1999). Using this definition in population studies, it was shown that amnestic MCI (aMCI) constituted only a relatively small group of people, and that there were also individuals with mild deficits in one or more other cognitive functions such as language, attention, visuospatial skills and executive functioning (Ganguli 2004; Larrieu 2002; Lopez 2003; Ritchie 2001). Thus, Petersen revised the original criteria and four different MCI subtypes have been proposed: (1) the former aMCI; (2) single non-memory MCI (snmMCI), with isolated impairment of a cognitive domain other than memory; (3) multiple domain amnestic MCI (mdMCI+), characterised by a slight impairment of multiple cognitive domains including memory; (4) multiple domains non-amnestic MCI (mdMCI-), with a slight impairment of multiple cognitive domains but without memory deficits (Petersen 2004). However, there is still a lack of consensus on what types of cognitive tests, how many and what thresholds or cut-off should be used to support or corroborate the diagnosis of MCI (Luis 2003).

The prevalence of MCI is high. Population-based studies in older adults (age > 60 or > 65 years) performed in North America and Europe have reported a prevalence of MCI ranging from 11%

to 17% (Di Carlo 2000; Ganguli 2004; Graham 1997; Lopez 2003; Ritchie 2001). The prevalence of the aMCI subtype has been estimated to be between 3% and 5% (Lopez 2003; Manly 2005).

People with MCI are at increased risk of dementia, but it is not itself a disease entity. The actual risk of incident dementia or AD varies according to the source of the sample (Petersen 2011). It should be noted that in some studies up to 40% of MCI cases have been reported to convert to a normal cognitive condition within two to three years (Kryscio 2006; Larrieu 2002; Solfrizzi 2004; Visser 2005). There is increasing evidence that AD pathophysiological processes are present in some individuals who have normal cognition or only minimal impairment. Thus AD is now regarded as a clinical continuum with individuals progressing from pre-clinical AD through MCI due to AD to AD dementia. A workgroup established by the US National Institute on Aging and the Alzheimer's Association have published criteria for identifying MCI due to AD with four levels of certainty, depending on the presence and nature of biomarker findings (Albert 2011). Obviously, the hope is for effective secondary prevention: that treatment in the MCI stage may delay progression to AD dementia.

Currently, most of the available treatments for AD function by inhibiting the enzyme acetylcholinesterase (AChE), thereby increasing acetylcholine levels in the brain. The US Food and Drug Administration (FDA) has so far approved four drugs with this mechanism that help some of the symptoms of AD - tacrine (Gracon 1996), donepezil (Birks 2006b), rivastigmine (Birks 2000) and galantamine (Loy 2006) - and a fifth drug, memantine, with a different mechanism of action (antagonism of the N-methyl-D-aspartate (NMDA) glutamate receptor) (McShane 2006). However, these drugs have not been shown to be effective for MCI and have significant side effects. One systematic review including two studies with 782 participants demonstrated that donepezil is not beneficial for MCI. Also many subjects suffered side effects unnecessarily (Birks 2006a). Another Cochrane review assessing the effect of galantamine in patients with MCI, utilising data from two trials suggested marginal clinical benefit, but a yet unexplained excess in death rate (Loy 2006). This reality drives research into other modalities of treatment in an attempt to improve the outcome of MCI, including Chinese herbal medicines.

Description of the intervention

Huperzine A (HUP-er-zeen) is a potent chemical derived from a particular type of club moss (*Huperzia serrata* [Thumb] Trev.) (Kozikowski 1999) and was isolated initially in China as a monomeric substance, a new Lycopodium alkaloid (Hup, [(5R, 9R, 11E)-5-amino-11-ethylidene-5, 6, 9, 10-tetrahydro-7-methyl-5, 9-methano-cycloocteno[b] pyridine-2(1H)-one]). Huperzine A has been used in China for centuries for the treatment of swelling, fever and blood disorders (Zhang 2008). In the West, it is used as an herbal supplement and is not approved for pharmaceutical use. It is currently being investigated in clinical trials as a possible treatment for diseases characterised by neurodegeneration, particularly AD (Bai 2000; Zangara 2003).

How the intervention might work

Huperzine A is a competitive, reversible and well-tolerated inhibitor of AChE, which is more potent than donepezil, rivastigmine and galantamine in vivo (Liang 2004; Liang 2007; Wang 2006). Several animal studies have shown that huperzine A can reverse or attenuate cognitive deficits in various animal models (Wang 2006).

Data from pre-clinical studies have also indicated that huperzine A has multiple neuroprotective effects (Zhang 2006):

1. huperzine A can regulate β-amyloid precursor protein (APP) metabolism. (Peng 2006; Yan 2007; Zhang 2004);
2. huperzine A has an antioxidative effect. It has been found to alleviate Aβ-induced neurotoxicity in cell cultures (Xiao 2000; Xiao 2002; Zhang 2002), and in vivo in rats (Wang 2001a);
3. huperzine A has anti-apoptotic effects. It has been shown to alleviate apoptotic changes induced by Aβ (Xiao 2002; Wang 2001a) and by other agents (Wang 2001b; Zhang 2003) significantly;
4. huperzine A has NMDA antagonism. It binds and blocks the NMDA receptor ion channel and has been shown to protect the brain against glutamate-induced damage (Ha 2011);
5. it increases nerve growth factor levels (Terry 2011).

Huperzine A has been widely used for AD therapy in China. It is also used as a 'brain booster' for enhancing memory and mental function in people without AD (Chen 2000; Wang 1999; Xu 1995; Xu 1999). One systematic review of six RCTs in AD, including a total of 454 patients, concluded that huperzine A may have positive effects on general cognitive function, global clinical status, behavioural disturbance and functional performance, with no obvious serious adverse events (Li 2008). Another review of huperzine for AD (Tiffany 2008) concluded that although available trials indicated some benefits from huperzine A, the trials were generally small and of limited quality. More recently, one multicentre RCT assessed the safety, tolerability and efficacy of huperzine A in 210 patients with mild to moderate AD. Patients were randomised to receive placebo or huperzine A (0.2 mg or 0.4 mg twice daily), for at least 16 weeks. Huperzine A at a dose of 0.2 mg twice daily was ineffective, but some secondary analyses in this trial suggested that the higher dose, 0.4 mg twice daily, may improve cognition; further studies to identify the maximal tolerated dose and evaluate long-term treatment effects may warrant consideration (Rafii 2011). Although some of this research is promising, there is insufficient evidence to draw firm conclusions about the efficacy of huperzine A for cognitive disorders.

Why it is important to do this review

Huperzine A may have some beneficial effects in MCI. Many biological properties of huperzine A (anticholinesterase activity, NMDA antagonism, anti-apoptotic effects) make this natural product a suitable candidate to be advanced for MCI treatment. But its effectiveness and safety in MCI are still uncertain. Therefore, we propose to perform a systematic review of the existing evidence to determine whether huperzine A is an effective treatment for patients with MCI.

OBJECTIVES

To assess the clinical efficacy and safety of huperzine A for the treatment of patients with MCI but no diagnosis of dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs with acceptable methodological quality comparing huperzine A with placebo in patients with MCI. Trials were included irrespective of the publication status and language status. Cross-over trials were excluded.

Types of participants

Participants were diagnosed with MCI using a clear MCI definition, which included the key features of the criteria set out by Petersen 1999 and subsequently elaborated (Petersen 2003; Visser 2005), including recently developed criteria for MCI due to AD (Albert 2011). The key criteria were: no dementia, preserved general cognitive function, intact ADL, significant impairment for age and education in either memory (amnestic MCI) or a single non-memory domain (single non-memory MCI) or more than one cognitive domain (multiple-domain MCI). Studies in which participants did not meet these criteria were excluded.

Types of interventions

Huperzine A in any type, dosage and treatment period compared to placebo.

Types of outcome measures

Primary outcomes

1. Changes to cognitive function: general and specific.
2. Changes to global clinical assessment.
3. All-cause mortality.

Secondary outcomes

1. Changes in behaviour disturbance.
2. Changes in ADL.
3. Quality of life (QoL).
4. Carer burden.
5. Mood.
6. Permanent physical disability.
7. Adverse effects.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's open access Specialized Register on 3 March 2012. The search terms used were: huperzine, ayapin, scoparon.

ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS;
2. monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO portal (which covers ClinicalTrials.gov; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
3. Quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL);
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1. There were no language restrictions.
Further searches were also performed in the following sources by the review author team. The following Chinese databases were searched using the terms 'huperzine A', 'Shishanjianjia', 'Haboyin' and 'Shuangyiping':

- CBM (The Chinese Biomedical Database) (1977 to present);
- China National Knowledge Infrastructure (CNKI) (1979 to present);
- The Chinese Clinical Trials Register (ChiCTR);
- VIP Chinese Science and Technique Journals Database (1989 to present).

In addition, we handsearched 48 Chinese traditional medicine journals from between 1970 and 1989. Among these were:

- Beijin Journal of Traditional Chinese Medicine;
- China Journal of Basic Medicine in Traditional Chinese Medicine;
- China Journal of Chinese Materia Medica;
- Chinese Journal of Integrated Traditional and Western Medicine;
- Chinese Journal of Traditional Medical Science and Technology;
- Chinese Pharmaceutical Abstracts;
- Chinese Traditional and Herbal Drugs;
- Chinese Traditional Patent Medicine Research;
- Chinese Traditional Patent Medicine;
- Clinical Journal of Anhui Traditional Chinese Medicine;
- Forum on Traditional Chinese Medicine;
- Fujian Journal of Traditional Chinese Medicine;
- Gansu Journal of Traditional Chinese Medicine;
- Guangdong Journal of Traditional Chinese Medicine;
- Guangxi Journal of Traditional Chinese Medicine;
- Hebei Integrated Traditional and Western Medicine;
- Hebei Journal of Traditional Chinese Medicine;
- Heilongjang Journal of Traditional Chinese Medicine;
- Henan Journal of Traditional Chinese Medicine and Pharmacy;
- Henan Journal of Traditional Chinese Medicine;
- Hunan Journal of Traditional Chinese Medicine;
- Jiangshu Journal of Traditional Chinese Medicine;
- Jiangxi Journal of Traditional Chinese Medicine;
- Jilin Journal of Traditional Chinese Medicine;
- Journal of Beijing University of Traditional Chinese Medicine;
- Journal of Chengdu University of Traditional Chinese Medicine;
- Journal of Chinese Medicinal Materials;
- Journal of Guangzhou University of Traditional Chinese Medicine;
- Journal of Practical Chinese Traditional Internal Medicine;
- Journal of Practical Traditional Chinese Medicine;
- Journal of Traditional Chinese Medicine;
- Liaoning Journal of Traditional Chinese Medicine;
- Modern Journal of Integrated Chinese Traditional and Western Medicine;
- Modern Traditional Chinese Medicine;
- Neimongol Journal of Traditional Chinese Medicine;
- New Journal of Traditional Chinese Medicine;
- Pharmacology and Clinics of Chinese Materia Medica;
- Research of Traditional Chinese Medicine;
- Shandong Journal of Traditional Chinese Medicine;
- Shanghai Journal of Traditional Chinese Medicine;
- Shanxi Journal of Traditional Chinese Medicine;
- Shenzhen Journal of Integrated Traditional and Western Medicine;
- Sichuan Journal of Traditional Chinese Medicine;
- Tianjin Journal of Traditional Chinese Medicine;
- Traditional Chinese Medicine Research;
- Xinjiang Journal of Traditional Chinese Medicine;
- Yunnan Journal of Traditional Chinese Medicine and Materia Medica;
- Zhejiang Journal of Traditional Chinese Medicine.

Searching other resources

In addition, we handsearched all reference lists of retrieved articles. Where necessary we would have attempted to contact study authors to obtain further data.

Data collection and analysis

Selection of studies

The title, abstract and keywords of every record retrieved were scanned independently by two review authors (YJR, YM) to determine which studies required further assessment. Full-text articles were retrieved when the information given in the titles, abstracts and keywords conformed to the selection criteria outlined previously.
If there was any doubt regarding these criteria from scanning the titles and abstracts, the full-text article was retrieved for clarification. Disagreement was resolved by discussion with a third review author (BD) if necessary. The authors of trials would have been contacted to provide missing data if necessary.

Data extraction and management

We extracted data on the methodology, interventions and participants to determine whether a study met our inclusion criteria. If not, the trial was excluded and further data was not extracted.

Data synthesis

No studies were eligible for inclusion. The methods we would have used to analyse data are described in the review protocol (Yue 2010). These methods will form the basis for future updates of this review should eligible studies become available.

RESULTS

Description of studies

See: Characteristics of excluded studies.
See the "Characteristics of excluded studies" tables.

Results of the search

The search retrieved a total of 656 results. After initial assessment and de-duplication the authors were left with seven to assess further for potential inclusion within the review.

Included studies

After reviewing the seven possibly relevant references, we did not identify any trials of huperzine A versus placebo. Should such trials become available, we will update the review to include them.

Excluded studies

The reasons for exclusion were as follows:

- one trial was excluded because the participants did not have MCI (Xue 2005);
- four trials were excluded because they were not placebo controlled. Comparator interventions were conventional therapy (Cheng 2008; Jiang 2009; Wang 2005) or nimodipine (Ding 2009);
- one trial was excluded after assessing the full text because it was not a randomised controlled trial (RCT) (Ma 1998);
- one trial was excluded because it used a cross-over method (Lin 2008).

Risk of bias in included studies

We did not identify any suitable trials for inclusion.

Effects of interventions

In the absence of any suitable randomised placebo-controlled trials in this area, we were unable to perform any analyses.

DISCUSSION

Summary of main results

We did not identify any trials of huperzine A versus placebo for treating MCI that met all our eligibility criteria.

Overall completeness and applicability of evidence

We did not identify any suitable trials for inclusion.

Quality of the evidence

The majority of trials of huperzine A in MCI were excluded because they were not placebo controlled and hence were at high risk of performance and detection bias.

Potential biases in the review process

In this review, we searched all published and unpublished articles through electronic database and handsearching 20 Chinese traditional medicine journals from between 1970 and 1989. However, despite our exhaustive search, we only found seven possibly relevant references. All of them are published in Chinese. They were all excluded because of the reasons mentioned above (see Excluded studies).

Agreements and disagreements with other studies or reviews

Although we did not find any studies that met our inclusion criteria, we did find some controlled trials that evaluated the effect of huperzine A in MCI. There were significant methodological limitations in these trials. Four studies without placebo controls reported beneficial effects of huperzine A in patients with MCI. Three studies (Cheng 2008; Jiang 2009; Wang 2005) compared huperzine A plus conventional therapy with conventional therapy alone. The conventional therapy included maintaining the previous medication, such as medication to control blood pressure and blood glucose. Another study (Ding 2009) used nimodipine as a control. These study designs make it hard to interpret the results. Studies without placebo controls are at higher risk of detection and performance bias. It is possible that an active control treatment might make patients worse than a placebo, thereby accounting for an apparent treatment effect. Furthermore, trial quality was overall low in these studies. No studies described adequate methods regarding the sequence of randomisation. No studies reported allocation concealment. No studies reported use of a blinding method.

Three trials (Cheng 2008; Ding 2009; Jiang 2009) did not report loss to follow-up. Number of participants in the studies was insufficient, ranging from 10 to 35 patients in a treatment group.
Lin 2008 reported the randomisation procedure, used placebo as a control, was double-blind and had less than 20% loss to follow-up. However, it was excluded from our review for using a cross-over method. Furthermore, the sample size was tiny (20 participants). It reported that huperzine A could improve cognition in patients with MCI.
Some RCTs and reviews evaluated the effects of huperzine A for AD, which showed that although available trials indicate some benefits from huperzine A for people with AD, the trials were generally small and of limited quality. There is insufficient evidence to draw firm conclusions about the efficacy of huperzine A (Chow 2008; Li 2008; Rafii 2011).
At present, there are no licensed or widely accepted drug treatments for MCI. Donepezil is not beneficial for MCI and has adverse effects (Birks 2006a). If beneficial effects of huperzine A on MCI were demonstrated in methodologically rigorous trials, it could lead to a useful treatment for MCI. Rigorously designed, multicentre, randomised, double-blind, placebo-controlled trials are required to evaluate huperzine A for MCI.

Implications for research

Further high-quality, large-scale, randomised trials of huperzine A for MCI are justified to confirm or refute its efficacy. The following features should be addressed in further studies:

1. detailed reporting of the methods of randomisation and allocation concealment;

2. application and clear description of blinding;

3. description of withdrawal and use of intention-to-treat analysis;

4. adverse events critically assessed by standardised reporting and larger sample RCTs;

5. use of internationally accepted scales and endpoint measurements of primary outcome measurements at long-term follow-up should be made;

6. reports of the trials should conform to the recommendations of the CONSORT (CONsolidated Standards of Reporting Trials) statement.

AUTHORS' CONCLUSIONS

Implications for practice

There was no evidence for or against huperzine A as a treatment for MCI.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cheng 2008	It was not placebo controlled. Comparator interventions were conventional therapy
Ding 2009	It was not placebo controlled. Comparator interventions were nimodipine
Jiang 2009	It was not placebo controlled. Comparator interventions were conventional therapy
Lin 2008	It was a cross-over trial
Ma 1998	It was not a randomised controlled trial
Wang 2005	It was not placebo-controlled. Comparator interventions were conventional therapy
Xue 2005	The participants did not have mild cognitive impairment

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Keyword search: chinese OR plants OR huperzine OR HUP OR ayapin OR scoparon	92
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950 to present (Ovid SP)	1. mci.mp. 2. (cognit* adj3 impair*).mp. 3. AAMI.mp. 4. "age-associated memory impairment".mp. 5. ("aMCI" or "MCIa").ti,ab. 6. AACD.mp. 7. "age-associated cognitive decline".mp. 8. (CIND or SMC).mp. 9. (memor* adj3 complain*).mp. 10. ("pre-clinical AD" or "preclinical AD" or "pre-clinical Alzheimer*" or "preclinical Alzheimer*").mp 11. (dement* adj2 prodrom*).mp. 12. "episod* memor*".mp. 13. dement*.mp. 14. Memory Disorders/ or Dementia/ or Cognition Disorders/ 15. or/1-14 16. huperzi*.mp. 17. ayapin*.mp. 18. scoparon*.mp. 19. *Drugs, Chinese Herbal/ 20. *Medicine, East Asian Traditional/ 21. Plants, Medicinal/ 22. or/16-21 23. randomized controlled trial.pt. 24. controlled clinical trial.pt. 25. randomi?ed.ab. 26. placebo.ab. 27. drug therapy.fs.	200

(*Continued*)

	28. randomly.ab. 29. trial.ab. 30. or/23-29 31. (animals not (humans and animals)).sh. 32. 30 not 31 33. 15 and 22 and 32	
3. EMBASE 1980 to 2011 week 20 (Ovid SP)	1. mci.mp. 2. (cognit* adj3 impair*).mp. 3. AAMI.mp. 4. "age-associated memory impairment".mp. 5. ("aMCI" or "MCIa").ti,ab. 6. AACD.mp. 7. "age-associated cognitive decline".mp. 8. (CIND or SMC).mp. 9. (memor* adj3 complain*).mp. 10. ("pre-clinical AD" or "preclinical AD" or "pre-clinical Alzheimer*" or "preclinical Alzheimer*").mp 11. (dement* adj2 prodrom*).mp. 12. "episod* memor*".mp. 13. dement*.mp. 14. *memory disorder/ 15. *dementia/ 16. *cognitive defect/ 17. or/1-16 18. huperzi*.mp. 19. ayapin*.mp. 20. scoparon*.mp. 21. *Chinese medicine/ 22. *Chinese drug/ or *Chinese herb/ 23. huperzine A/ 24. or/18-23 25. 17 and 24 26. randomized controlled trial/ 27. controlled clinical trial/ 28. randomi?ed.ab. 29. placebo.ab. 30. randomly.ab. 31. ("double-blind*" or "double-mask*" or "single-blind*" or "single-mask*").ti,ab 32. trial.ti,ab. 33. or/26-32 34. 25 and 33	111
4. PsycINFO 1806 to May week 3 2011 (Ovid SP)	1. mci.mp. 2. (cognit* adj3 impair*).mp. 3. AAMI.mp.	140

(*Continued*)

	4. "age-associated memory impairment".mp. 5. ("aMCI" or "MCIa").ti,ab. 6. AACD.mp. 7. "age-associated cognitive decline".mp. 8. (CIND or SMC).mp. 9. (memor* adj3 complain*).mp. 10. ("pre-clinical AD" or "preclinical AD" or "pre-clinical Alzheimer*" or "preclinical Alzheimer*").mp 11. (dement* adj2 prodrom*).mp. 12. "episod* memor*".mp. 13. dement*.mp. 14. *memory disorder/ 15. *dementia/ 16. huperzi*.mp. 17. ayapin*.mp. 18. scoparon*.mp. 19. exp *"Medicinal Herbs and Plants"/ 20. or/1-15 21. or/16-19 22. 20 and 21	
5. CINAHL (EBSCOhost)	S1 TX "cognit* impair*" S2 TX "cognit* defect*" S3 (MH "Cognition Disorders+") S4 TX MCI S5 TX ACMI S6 TX ARCD S7 TX SMC S8 TX CIND S9 TX BSF S10 TX AAMI S11 AB MD S12 AB LCD S13 AB QD OR "questionable dementia" S14 TX AACD S15 TX MNCD S16 TX "N-MCI" or "A-MCI" or "M-MCI" S17 TX "preclinical AD" S18 TX "pre-clinical AD" S19 TX "preclinical alzheimer*" or "pre-clinical alzheimer*" S20 TX aMCI OR MCIa S21 TX "CDR 0.5" or "clinical dementia rating scale 0.5" S22 TX "GDS 3" OR "stage 3 GDS" S23 TX "global deterioration scale" AND	1

(*Continued*)

	"stage 3" S24 TX "Benign senescent forgetfulness" S25 TX "mild neurocognit* disorder*" S26 TX prodrom* N2 dement* S27 TX "age-related symptom*" S28 TX cognit* N2 deficit* S29 TX cognit* N2 deteriorat* S30 TX cognit* N2 declin* S31 TX cognit* N2 degenerat* S32 TX cognit* N2 complain* S33 TX cognit* N2 disturb* S34 TX cognit* N2 disorder* S35 TX memory N2 episod* or TX memory N2 los* or TX memory N2 impair* or TX memory N2 complain* S36 TX memory N2 disturb* or TX memory N2 disorder* or TX cerebr* N2 impair* or TX cerebr* N2 los* S37 TX cerebr* N2 complain* or TX cerebr* N2 deteriorat* or TX cerebr* N2 disorder* or TX cerebr* N2 disturb* S38 TX mental* N2 declin* or TX mental* N2 los* or TX mental* N2 impair* or TX mental* N2 deteriorat* S39 TX "pre-clinical dementia" or TX "preclinical dementia" S40 or/1-39 S41 TX huperz* S42 TX ayapin S43 TX scoparon* S44 S61 or S62 or S63 S45 S40 AND S44	
6. ISI Web of Knowledge - all databases (includes: Web of Science (1945 to present); BIOSIS Previews (1926 to present); MEDLINE (1950 to present); Journal Citation Reports)	Topic=(mci OR "cognit* impair*" OR AAMI OR CIND OR SMC OR "episod* memory" OR "dement* prodrom*") AND Topic=(huperzi* OR ayapin* OR scoparon*) AND Topic=(trial OR RCT OR random* OR placebo OR "double-blind*" OR "single-blind*") Timespan=All Years. Databases= SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH	14
7. LILACS (BIREME)	huperzine OR ayapin OR scoparon	1
8. CENTRAL (*The Cochrane Library*) (Issue 4 of 4, Oct 2010)	#1 "cognit* impair*" #2 MeSH descriptor Cognition Disorders explode all trees	9

(*Continued*)

	#3 MCI #4 ACMI #5 ARCD #6 SMC #7 CIND #8 BSF #9 AAMI #10 LCD #11 QD OR "questionable dementia" #12 AACD #13 MNCD #14 MCD #15 "N-MCI" or "A-MCI" or "M-MCI" #16 (cognit* or memory or cerebr* or mental*) NEAR/3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*) #17 "preclinical AD" #18 "pre-clinical AD" #19 "preclinical alzheimer*" or "pre-clinical alzheimer*" #20 aMCI OR MCIa #21 "CDR 0.5" OR "clinical dementia rating scale 0.5" #22 "GDS 3" OR "stage 3 GDS" #23 "global deterioration scale" AND "stage 3" #24 "Benign senescent forgetfulness" #25 "mild neurocognit* disorder*" #26 (prodrom* NEAR/2 dement*) #27 episodic* NEAR/2 memory #28 "preclinical dementia" OR "pre-clinical dementia" #29 episodic NEAR/2 memory #30 "pre-clinical dementia" OR "preclinical dementia" #31 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30) #32 huperzi* OR ayapin* OR scoparon* #33 (#31 AND #32)	
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Keyword search: huperzine OR ayapin OR scoparon OR scoparone	7

(*Continued*)

10. ICTRP search portal (apps.who.int/trialsearch) (includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register)	Keyword search: huperzine OR ayapin OR scoparon	7
TOTAL before de-duplication		582
TOTAL after de-duplication and first assessment		4

Appendix 2. Assessment of risk of bias

Criteria for a judgment of 'yes' for the sources of bias

1. Was the allocation sequence randomly generated?

Yes, low risk of bias

A random (unpredictable) assignment sequence.

Examples of adequate methods of sequence generation are computer-generated random sequence, pre-ordered sealed envelopes, telephone call to a central office, coin toss (for studies with two groups), rolling a dice (for studies with two or more groups), drawing of balls of different colours.

No, high risk of bias

- Quasi-randomised approach: examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study and hospital registration number.
- Non-random approaches: allocation by judgement of the clinician, by preference of the participant, based on the results of a laboratory test or a series of tests, by availability of the intervention.

Unclear

Insufficient information about the sequence generation process to permit judgement.

2. Was the treatment allocation adequately concealed?

Yes, low risk of bias

Assignment must be generated independently by a person not responsible for determining the eligibility of the participants. This person has no information about the people included in the trial and has no influence on the assignment sequence or on the decision about whether the person is eligible to enter the trial. Examples of adequate methods of allocation concealment are: central allocation, including telephone, web-based, and pharmacy controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

No, high risk of bias

Examples of inadequate methods of allocation concealment are: alternate medical record numbers, unsealed envelopes; date of birth; case record number; alternation or rotation; an open list of random numbers any information in the study that indicated that investigators or participants could influence the intervention group.

Unclear

Randomisation stated but no information on method of allocation used is available.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Was the participant blinded to the intervention?

Yes, low risk of bias

The treatment and control groups are indistinguishable for the participants or if the participant was described as blinded and the method of blinding was described.

No, high risk of bias

Blinding of study participants attempted, but it is likely that the blinding could have been broken; participants were not blinded, and the non-blinding of others is likely to introduce bias.

Unclear

Was the care provider blinded to the intervention?

Yes, low risk of bias

The treatment and control groups are indistinguishable for the care/treatment providers or if the care provider was described as blinded and the method of blinding was described.

No, high risk of bias

Blinding of care/treatment providers attempted, but likely that the blinding could have been broken; care/treatment providers were not blinded, and the non-blinding of others is likely to introduce bias.

Unclear

Was the outcome assessor blinded to the intervention?

Yes, low risk of bias

Adequacy of blinding should be assessed for the primary outcomes. The outcome assessor was described as blinded and the method of blinding was described.

No, high risk of bias

No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.

Unclear

4. Were incomplete outcome data adequately addressed?

Was the drop-out rate described and acceptable?

The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given.

Yes, low risk of bias

If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias (note: these percentages are arbitrary, not supported by literature).

No missing outcome data

Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Missing data have been imputed using appropriate methods.

No, high risk of bias

Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.

Unclear

Were all randomised participants analysed in the group to which they were allocated? (intention-to-treat (ITT) analysis)

Yes, low risk of bias

Specifically reported by authors that ITT was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that all randomised participants are reported/analysed in the group they were allocated to for the most important time point of outcome measurement (minus missing values) irrespective of non-compliance and co-interventions.

No, high risk of bias

Lack of ITT confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether ITT reported or not.
'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Unclear

Described as ITT analysis, but unable to confirm on study assessment, or not reported and unable to confirm by study assessment.

HISTORY

Protocol first published: Issue 11, 2010

Review first published: Issue 12, 2012

CONTRIBUTIONS OF AUTHORS

Jirong Yue conceived the review question and co-ordinated the review development, completed the first draft and edited the review.

Bi Rong Dong secured funding and advised on the review, co-ordinated the review development and performed part of writing and editing of the review, approved the final version of the review prior to submission and was guarantor.

Xiufang Lin developed and edited the review and made an intellectual contribution to the review.

Ming Yang conceived the review question, edited the review and made an intellectual contribution to the review.

Hong Mei Wu advised and performed part of the writing and editing of the review and made an intellectual contribution to the review.

Taixiang Wu provided methodological expertise.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Center, China.

External sources

- Cochrane Dementia and Cognitive Improvement Review Group, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As there were no studies for inclusion we were unable to perform any data analysis. We have therefore omitted the methods that were not actually implemented in our review. The methods we would have used to analyse data are described in the review protocol (Yue 2010), see list below. These methods will form the basis for future updates of this review should eligible studies become available.

- Data extraction and management.
- Assessment of risk of bias in included studies.
- Measures of treatment effect.
- Unit of analysis issues.
- Dealing with missing data.
- Assessment of heterogeneity.
- Assessment of reporting biases.
- Data synthesis.

- Subgroup analysis and investigation of heterogeneity.
- Sensitivity analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Alkaloids [*therapeutic use]; Cholinesterase Inhibitors [therapeutic use]; Cognitive Dysfunction [*drug therapy]; Neuroprotective Agents [*therapeutic use]; Sesquiterpenes [*therapeutic use]

MeSH check words

Humans