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Huperzine A for vascular dementia

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Abstract

Background—Huperzine A, a form of herbal medicine, has been considered as an alternative treatment for vascular dementia (VaD) in China.

Objectives—To assess the efficacy and safety of Huperzine A in patients with vascular dementia.

Search methods—We searched ALOIS: the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 10 February 2011 using the terms: chinese, plants, huperzine, HUP, ayapin, scoparon. ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS), numerous trial registries and grey literature sources. We also searched the following databases in March 2011 using the terms 'Huperzine A', 'Shishanjianjia', 'Haboyin' and 'Shuangyiping': The Chinese Biomedical Database (CBM) (1977 to March 2011); Chinese Science and Technique Journals Database (VIP) (1989 to March 2011); China National Knowledge Infrastructure (CNKI) (1979 to March 2011); Google (March 2011). In addition, we searched relevant reference lists. We also contacted researchers to request additional information where necessary.

Selection criteria—We considered randomized controlled trials comparing Huperzine A with placebo in people with vascular dementia eligible for inclusion.

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CONTRIBUTIONS OF AUTHORS

Zilong Hao drafted the protocol and participated in all steps of the review.

Professor Ming Liu commented on each draft of the protocol and the review and gave general advice.

Zhiqin Liu refined the protocol and performed the planned searches, identified studies, assessed methodological quality, and commented on all drafts of the review.

DongHao Lv refined the protocol and performed the planned searches, and commented on the review.

Zilong Hao and Zhiqin Liu updated the review.

DECLARATIONS OF INTEREST

None known.

Data collection and analysis—Two review authors independently applied the inclusion criteria, assessed trial quality and extracted the data. We resolved any disagreement by discussion.

Main results—We included only one small trial, involving 14 participants with vascular dementia. No significant effect of Huperzine A on cognitive function measured by MMSE (WMD 2.40; 95% CI -4.78 to 9.58) was observed. There was a significant beneficial effect of Huperzine A on performance of activities of daily living (WMD -13.00; 95% CI -23.24 to -2.76) after six months of treatment. No deaths from any cause at the end of treatment were reported. Behaviour, quality of life and caregiver burden were not assessed in the included trial.

Authors' conclusions—There is currently no high quality evidence to support the use of Huperzine A for the treatment of vascular dementia. Further randomized placebo controlled trials are needed to determine whether there is worthwhile benefit.

Medical Subject Headings (MeSH)

Alkaloids; Dementia, Vascular [* drug therapy]; Drugs, Chinese Herbal [* therapeutic use]; Neuroprotective Agents [* therapeutic use]; Sesquiterpenes [* therapeutic use]

MeSH check words

Humans

BACKGROUND

Description of the condition

Vascular dementia (VaD) is dementia associated with cerebrovascular brain injury. It can be viewed as a subset of the larger syndrome of vascular cognitive impairment (Aggarwal 2007). It is the second most common form of dementia after Alzheimer's disease (AD) among the elderly (O'Brien 2003). Subtypes of VaD can be briefed as follows (O'Brien 2006; Demaerschalk 2007).

- Multi-infarct dementia (cortical VaD:predominantly resulting from large cortical infarcts)
- Small-vessel dementia (subcortical VaD, predominantly resulting from subcortical lacunes, white and/or deep grey matter lesions)
- Strategic infarct dementia (resulting from a unilateral or bilateral infarct in strategic area (i.e. thalamus, hippocampus))
- Hypoperfusion dementia (resulting from brain damage from hypoperfusion)
- Hemorrhagic dementia
- AD with CVD (sometimes known as "mixed dementia")
- Hereditary vascular dementia (CADASIL)

A meta-analysis of the European studies on the incidence of dementia showed that vascular dementia constituted 17.6% of all incident dementia (Grossman 2006). A recent study indicates that 10% of patients developed new dementia soon after their first stroke, and more

than a third had dementia after recurrent strokes (Pendlebury 2009). In Europe and North America, AD predominates over VaD in a 2:1 ratio; in contrast, in Japan and China, VaD accounts for almost 50% of all dementia (Roman 2004). The divergent epidemiological trend may be due to different diagnostic criteria and study populations (Kavirajan 2007). With an increasing number of aging people in most parts of the world, including China and India, where more than two billion people live, it is likely that the interactions between dementia, stroke, and cardiovascular disease will become increasingly important. It is expected that with progressive aging of the population and decline in mortality after stroke, VaD will become the most common form of dementia (Gustavo 2005). However, there is no definitive medical or surgical treatment for vascular dementia. The best evidence to date is for benefit from cholinesterase inhibitors, a class of drugs licensed for the treatment of mild to moderate AD. The currently marketed cholinesterase inhibitors are donepezil, galantamine and rivastigmine. Donepezil has been shown in a meta-analysis to improve cognition function, clinical global impression and activities of daily living in people with probable or possible mild to moderate vascular cognitive impairment after six months of treatment. It was well tolerated, and most of the side effects (nausea, diarrhoea, anorexia, and cramp appeared most frequently) were transient and were resolved by stopping the medication. People treated with donepezil suffered no more serious adverse effects than those treated with placebo (Malouf 2004). Galantamine was also shown to be effective for cognition and executive functioning in one trial, but this was not seen in a second trial which included fewer relevant participants. In both of these trials galantamine was associated with higher rates of gastrointestinal side effects than placebo (Craig 2006). Due to insufficient evidence, rivastigmine cannot be recommended for the treatment of vascular cognitive impairment (Craig 2004). Memantine is an antagonist of glutamate NMDA receptors. It has a detectable beneficial effect on cognition in AD, but not in VaD. It is well tolerated (McShane 2006). In short, the results of an overview meta-analysis concluded that only small benefits of uncertain clinical meaningfulness were available from cholinesterase inhibitors or memantine for people with VaD (Kavirajan 2007). The efficacy of other drugs, such as piracetam (Flicker 2001), nimodipine (Birks 2002), and Ginkgo biloba (Weinmann 2010), are more controversial.

Description of the intervention

Some traditional Chinese herbal medicines have been developed for treating VaD. Huperzine A is one such herbal medicine, which is an alkaloid isolated from the Chinese herb *Huperzia serrata*.

How the intervention might work

Cholinergic deficits are well documented in VaD, independent of any concomitant AD pathology (Erkinjuntti 2004). Cholinergic structures in the brain are vulnerable to ischaemic damage. In humans, there is a loss of cholinergic neurons in 40% of VaD patients examined neuropathologically, with reduced acetylcholine activity detected in the cortex, hippocampus, and striatum (Demaerschalk 2007). As discussed above, there is some evidence that currently licensed cholinesterase inhibitors, which are indicated for the treatment of mild to moderate AD, may also provide modest benefits for those with VaD (Farlow 2006). Huperzine A is a potent, highly specific and reversible inhibitor of

acetylcholinesterase (AChE) of the central nervous system. It has been authorized for treating AD and benign memory deficits since 1994 in China (Han 2006). The drug is available as a nutraceutical in the US (Little 2008). To date, few side effects have been observed in clinical trials conducted in China, and those side effects most frequently observed (mild dizziness, abdominal distension, and nausea) were transient and were either resolved by stopping the medication or improved with symptomatic treatment (Li 2001; Wang 2004; Zhong 2004). Compared with the cholinesterase inhibitors tacrine, donepezil, and rivastigmine, Huperzine A has better penetration through the blood-brain barrier, higher oral bioavailability, and longer duration of AChE inhibitory action (Wang 2006). A recent small RCT performed in China directly compared Donepezil (N = 21) and Huperzine A (N = 21) in people with VaD (Wang 2010). It concluded that both drugs were equally efficacious and well-tolerated. Recent data have shown that Huperzine A may have neuroprotective effects that go beyond the inhibition of AChE. These effects include modification of beta-amyloid peptide processing, reduction of oxidative stress, neuronal protection against apoptosis, and regulation of the expression and secretion of nerve growth factor (NGF) and NGF signalling (Zhang 2006).

Why it is important to do this review

Although Huperzine A has been widely used in clinical practice and used as a standard intervention in clinical trials, its efficacy and safety in people with VaD are still uncertain. We therefore sought to undertake a rigorous systematic review of the existing evidence to determine whether Huperzine A can be recommended for routine use in people with VaD.

OBJECTIVES

To assess the efficacy and safety of Huperzine A in people with VaD.

METHODS

Criteria for considering studies for this review

Types of studies—We included only unconfounded randomized controlled trials comparing Huperzine A with placebo in people with VaD.

Types of participants—Participants of any age or sex, with a diagnosis of VaD according to accepted criteria, were eligible for inclusion. The accepted criteria were as follows: DSM-III or DSM-III-R or DSM-IV (APA 1980; APA 1987; APA 1994); National Institute of Neurological Disorders and Stroke (NINDS-AIREN) and International Classification of Diseases (ICD-9 or –10) (ICD 1989; WHO 1992); or other validated and reliable criteria, such as the Ischemic Scale (Hachinski 1975); research criteria for subcortical vascular dementia (Erkinjuntti 2000); and Mayo Clinic criteria (Knopman 2002).

Types of interventions—We included trials evaluating Huperzine A regardless of length of treatment period and dosage of treatment. The control interventions were placebo. We excluded confounded trials in which the treatment or control group received another active therapy (e.g. Huperzine A plus other agent versus control or Huperzine A versus another agent).

Types of outcome measures—Primary outcome measures

1. Cognitive function
2. Global function
3. All cause mortality

Secondary outcome measures

1. Safety and adverse effects
2. Behaviour
3. Caregiver burden
4. Quality of life

Search methods for identification of studies

Electronic searches

1. We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 10 February 2011. The search terms used were: chinese, plants, huperzine, HUP, ayapin, scoparon.

ALOIS is maintained by the Trials Search Co-ordinator for Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. 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; ISRCTN; 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 which can be searched ALOIS 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 are available in the 'Methods used in reviews' section within the editorial information about the [Dementia and Cognitive Improvement Group](#).

We performed additional searches 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. We have provided the search strategies in Appendix 1.

We have provided information on searches carried out in the previous version(s) of the review in Appendix 2.

The latest search (February 2011) retrieved a total of 367 results. After a first-assess and a de-duplication of these results, the authors were left with seven references to assess further.

2. Chinese databases:

We searched the following Chinese databases using the terms ‘Huperzine A’, ‘Shishanjianjia’, ‘Haboyin’ and ‘Shuangyiping’:

- CBM (The Chinese Biomedical Database) (1977 to March 2011)
- VIP Chinese Science and Technique Journals Database (1989 to March 2011)
- China National Knowledge Infrastructure (CNKI) (1979 to March 2011)
- Google

3. In addition, we searched all reference lists of retrieved articles. For previous versions of the review, we contacted researchers in an effort to identify further information.

Data collection and analysis

Study selection—Two review authors independently scanned the title, abstract and keywords of every record to determine which studies required further assessment. We retrieved the full articles when the information given in the titles, abstracts, and keywords conformed to the selection criteria outlined previously. We resolved any disagreements by discussion, and, when necessary, in consultation with a third author.

Quality assessment—We performed quality assessment by checking whether each included trial met the following internal validity criteria.

1. Method of randomization.
 - A. adequate sequence generation is reported using one of the following approaches: random number tables or computer-generated random numbers.
 - B. does not specify one of the adequate methods outlined in (A) but only mentioned ‘random’.
 - C. other methods of allocation that appeared to be unbiased.
2. Adequate allocation concealment.

- A. adequate measures to conceal allocation such as central controlled randomization; sequentially numbered, opaque, sealed envelopes; or another description that contains convincing elements of concealment.
 - B. unclearly-concealed trials in which the author does not report any allocation concealment approach at all.
 - C. inadequately-concealed allocation that reports an approach that does not fall into one of the categories in (A).
3. Blinding.
- A. blinding of study participants (the recipients and providers of care), blinding of outcome assessors, or both.
 - B. single blinding (blinding of participants).
 - C. non-blinding.
4. Numbers lost to follow-up.
- A. trials where an intention-to-treat analysis is possible and few losses to follow-up are noted.
 - B. trials which report exclusions (as listed in (A) but exclusions were less than 10%).
 - C. no reporting on exclusions or exclusions of more than 10%, or wide differences in exclusions between groups.
5. Intention to treat analysis.

Two authors independently performed quality assessment; we resolved any disagreements by discussion between ourselves, or with a third party when necessary.

Data extraction—Two reviewers extracted data concerning details of participant characteristics, methods, interventions, and outcomes independently using a data extraction form. We resolved any disagreements by discussion. We obtained missing data from the study authors whenever possible. For dichotomous outcomes, we extracted the number of participants experiencing the event and the total number of participants in each arm of the trial. For continuous outcomes, we extracted the mean value and standard deviation for the changes in each arm of the trial along with the total number in each group. Wherever possible, we used outcomes from the intention-to-treat (ITT) population, and if not, then we extracted observed case or per-protocol outcomes.

Data analysis—We expressed results for dichotomous data as risk ratios (RR) with 95% confidence intervals (CI), and results for continuous outcomes as mean difference (MD) or standardized mean difference (SMD). We used a fixed-effect approach unless there was substantial heterogeneity, in which case we used a random-effects approach and we examined the potential causes of heterogeneity. We quantified inconsistency across studies using I^2 . We considered a value greater than 50% to be substantial heterogeneity.

We used subgroup analysis to explore possible sources of heterogeneity: age, sex, type and severity of VaD, dosage levels, route of drug administration (injection or oral) and duration of treatment.

- We excluded studies with inadequate concealment of allocation.
- We excluded studies in which outcome evaluation was not blinded.
- We excluded studies in which loss to follow-up was not reported or was greater than 10%.

We planned to investigate potential publication bias by using a funnel plot.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

For the previous version of this review, the CDCIG search in the Specialized Register in July 2008 found seven possibly relevant references. Two turned out to be irrelevant and we excluded four. We included one trial (Zhou 2004). For details of the included trial, see the Characteristics of included studies table. We identified a further 14 potentially eligible trials in Chinese databases in August 2008, but no trial was eligible for inclusion.

For this updated review, the CDCIG search in the Specialized Register found seven possibly relevant references. Six turned out to be irrelevant and one was a newly identified study which we excluded. We identified a further 11 potentially eligible trials in Chinese databases, but no trial was eligible for inclusion. We excluded 30 trials for the following reasons.

1. We could not obtain detailed information to evaluate one study (Ma 1998), because it had been published only as a conference poster and we were unable to obtain further information from the authors.
2. The participants did not have vascular dementia (Zhang 1991; Aisen 2004; Wang 2005; Ding 2009).
3. The types of participants did not meet the inclusion criteria and Piracetam was used as the comparator (Wang 1999).
4. Allocation was non-random and pyritinol was used as the comparator (Chang 1997).
5. Comparators used were: Aniracetam (Liu 2008), Donepezil (Wang 2010), vitamin C/B1 (Xu 2009; Xu 2009a), nimodipine (Li 2008; Yuan 2010), or Naofukang (Shi 2000; Wang 2000; Wei 2001; Zhang 2001; Wang 2004; Zheng 2006; Ma 2007; Wan 2007; Tang 2008; Zhou 2009).
6. Studies were open-label, i.e. no (placebo) comparator was used (Yin 2001; Shang 2003; Zhong 2004; Song 2008; Yan 2008; Fan 2009; Weng 2010).

Included study

Study design: In Zhou 2004, applying stratified randomization, 25 participants with Alzheimer's disease (AD) and 35 participants with vascular dementia (VaD) were divided into groups: group A (huperzine A), group B (huperzine A + nicergoline), group C (huperzine A + nicergoline + enteric-coated aspirin), group D (huperzine A + nicergoline + enteric-coated aspirin + conjugated estrogen) and group E (placebo). We extracted data from group A (huperzine A) and group E (placebo). We reported data on 14 participants with a diagnosis of VaD: seven belonged to the control group and seven to the huperzine A group.

Participants: The average age of participants in the two groups was 68.3 years and 68.8 years, respectively. There were no significant differences between the two groups in terms of average age, sex, or intelligence score.

Interventions: Participants took Huperzine A orally twice a day at a dose of 0.15 mg for six months.

Outcome measures: Mini-mental state examination (MMSE) and activities of daily living scale (ADL) were performed to detect the cognitive and functional status of the subjects at baseline and after three and six months of treatment. All participants had the outcomes measured.

Risk of bias in included studies

The only randomized controlled unconfounded study had a small number of participants (Zhou 2004). The description of its risk of bias is as follows.

Sequence generation—The study authors used drawing of lots in the sequence generation process; we assessed this as low risk of selection bias.

Allocation concealment—The study authors did not describe their method of concealment; we assessed this as uncertain risk of bias.

Blinding—Participants were not blinded, but outcome assessment was blinded; we assessed this as moderate risk of bias.

Incomplete outcome data—No missing outcome data; we assessed this as low risk of bias. We were not sure of any selective reporting of results and we were unable to investigate potential publication bias by using a funnel plot as only one trial was included.

Effects of interventions

Primary outcome measures

1. Cognitive function: One trial (Zhou 2004) with 14 participants compared Huperzine A with placebo on the improvement of cognitive function measured by the MMSE. The dose of Huperzine A was 0.15 mg daily with a treatment period of six months. There was no significant beneficial effect of Huperzine A (WMD 2.40; 95% CI -4.78 to 9.58).

2. Global function: There was a significant beneficial effect of Huperzine A on the improvement of ADL for VaD (WMD -13.00; 95% CI -23.24 to -2.76) after six months of treatment.

3. All cause mortality: The included trial did not report any deaths from any cause.

Secondary outcome measures

1. Safety and adverse effects: The included trial reported no severe adverse effects. Most frequently observed adverse effects were gastrointestinal upset or constipation with no significant difference between treatment group and control group.

2. Behaviour: The included trial provided no data on behaviour.

3. Caregiver burden: The included trial gave no data on caregiver burden.

4. Quality of life: The trial did not undertake any assessments of quality of life. We could find neither beneficial nor harmful effects of Huperzine A based on the limited data available. If further trials become suitable for enrolment, we will update the review to include them. We are not aware of any ongoing trials.

There was only one trial, so we could not assess heterogeneity and perform the preplanned sensitivity and subgroup analyses.

DISCUSSION

Summary of main results

We included only one trial with 14 participants in this review. No data from any countries other than China were available. In this trial there was no significant improvement of cognitive function measured by MMSE after Huperzine A treatment compared with placebo, whereas there was a significant beneficial effect of Huperzine A on the improvement of ADL. The trial reported no deaths from any cause at the end of treatment. It reported no severe adverse effects. We must emphasize that the results were based on a subset of just 14 participants from one trial. The very small sample size means that the confidence interval for the treatment effect estimate is wide and includes both clinically significant benefits and clinically significant harms.

Overall completeness and applicability of evidence

At present, there are no definitive treatments for VaD. There is some evidence to support the use of donepezil (Malouf 2004; Román 2010). Although Huperzine A has mainly been used for the treatment of cognitive impairment (such as in AD and VaD), it has also been used for the treatment of myasthenia gravis in China for many years. Few side effects have been observed in clinical trials and the side effects most frequently observed (mild dizziness, abdominal distension, nausea) were transient and were either resolved by stopping the medication or improved with symptomatic treatment. Consequently, if beneficial effects of Huperzine A on cognitive function could be demonstrated in methodologically rigorous trials, it could lead to a useful and low-cost treatment for VaD and be used outside China.

Therefore, further high-quality, large, randomized placebo-controlled trials are needed to determine whether there is worthwhile benefit.

Quality of the evidence

The methodological quality of potentially eligible trials was generally “poor”. The limitations of most trials were as follows: in the majority, we could not be sure that treatment allocation was truly randomized and information about the concealment of randomization was not available (this could lead to selection bias); some trials used “positive drugs” (i.e. Naofukang, Vitamin) as control, but the efficacy of these drugs was uncertain. Trials of Huperzine A versus care as usual (i.e. no placebo) would be very unlikely to be blind with respect to treatment allocation (this could lead to detection bias); it was unclear whether most trials had used a blinded method to assess outcome; some trials did not report adverse events and we also could not be sure whether the losses to follow-up were reported and whether an ITT approach was adopted.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no high quality evidence to support the use of Huperzine A for the treatment of vascular dementia.

Implications for research

Huperzine A, which is a potent, highly specific and reversible inhibitor for acetylcholinesterase of the central nervous system, deserves further research. Further high-quality, large-scale, randomized trials of Huperzine A for vascular dementia are justified to confirm or refute its efficacy. The following features should be addressed in further studies: adequate concealment of allocation; placebo control; blinding of outcome assessors; use of internationally accepted scales and endpoint measurements of primary outcome measurements at long-term follow-up; critical assessment of adverse events, because the evaluation of side effects is as important as the efficacy; and description of withdrawal and use of ITT analysis. Finally, reports of the trials should conform to the recommendations of the CONSORT statement.

Acknowledgments

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We thank the Cochrane Dementia and Cognitive Improvement Group for their help with writing the updated review.

If anyone knows of trials that we have omitted we would be grateful if they could contact Dr Ming Liu.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Zhou 2004

Methods	Method of randomization: Drawing of lots. The method of concealment was not described Blinding: single-blind (outcome assessment) Loss to follow-up: none ITT analysis: not stated Duration: six months	
Participants	Country: China Number of participants: 14 (male?) Average age: treatment: 68.3 ± 10.6 years, placebo: 68.8 ± 9.7 years Diagnosis: according to DSM-IV The average age, sex, and intelligence score between two groups: no significant difference Other dementia excluded by MRI or CT scan, brain injury,severe physical or psychotic disorders, alcohol or drug abuse, severe heart or renal or liver or pulmonary failure, tumour and peptic ulcer also were excluded	
Interventions	Huperzine A versus placebo Huperzine A: 0.15 mg twice a day for six months placebo	
Outcomes	Cognitive function: MMSE All cause death	
Notes	ITT: intention-to-treat analysis MMSE: Mini-mental state evaluation	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing of lots was used in the sequence generation process
Allocation concealment (selection bias)	Unclear risk	The method of concealment was not described in the article
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, and we were not sure of any selective reporting of results
Other bias	Low risk	

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aisen 2004	The participants did not have vascular dementia
Chang 1997	Participants were allocated according to the sequence of admission. The comparison was inappropriate: Huperzine A versus pyritinol
Ding 2009	The participants did not have vascular dementia

Study	Reason for exclusion
Fan 2009	The comparison was inappropriate: Huperzine A plus nimodipine versus nimodipine
Li 2008	The comparison was inappropriate: Huperzine A versus nimodipine
Liu 2008	The comparison was inappropriate: Huperzine A versus Aniracetam
Ma 1998	We cannot obtain detail information to carry out evaluation
Ma 2007	The comparison was inappropriate: Huperzine A plus Ginkgo leaf versus Naofukang (positive control)
Shang 2003	The comparison was inappropriate: Huperzine A plus cognitive training versus cognitive training
Shi 2000	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Song 2008	The comparison was inappropriate: Huperzine A versus no placebo
Tang 2008	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Wan 2007	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Wang 1999	The types of participants did not meet the inclusion criteria and used Piracetam as comparator
Wang 2000	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Wang 2004	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Wang 2005	The participants did not have vascular dementia
Wang 2010	The comparison was inappropriate: Huperzine A versus Donepezil (positive control)
Wei 2001	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Weng 2010	The comparison was inappropriate: Huperzine A plus Xinnao Shutong Capsule versus Xinnao Shutong Capsule
Xu 2009	The comparison was inappropriate: Huperzine A versus Vitamin C
Xu 2009a	The comparison was inappropriate: Huperzine A versus Vitamin B1
Yan 2008	The comparison was inappropriate: Huperzine A versus no placebo
Yin 2001	The comparison was inappropriate: Huperzine A versus no placebo
Yuan 2010	The comparison was inappropriate: Huperzine A versus nimodipine
Zhang 1991	The participants did not have vascular dementia
Zhang 2001	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Zheng 2006	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)
Zhong 2004	The comparison was inappropriate: Huperzine A versus no placebo
Zhou 2009	The comparison was inappropriate: Huperzine A versus Naofukang (positive control)

DATA AND ANALYSES

Comparison 1 Huperzine A versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The change of cognitive function measured by MMSE at the end of treatment	1	14	Mean Difference (IV, Fixed, 95% CI)	2.40 [-4.78, 9.58]
2 The change of ADL at the end of treatment	1	14	Mean Difference (IV, Random, 95% CI)	-13.0 [-23.24, -2.76]
3 Death from all causes at the end of treatment	1	14	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1
Comparison 1 Huperzine A versus placebo, Outcome 1
The change of cognitive function measured by MMSE
at the end of treatment

Review: Huperzine A for vascular dementia

Comparison: 1 Huperzine A versus placebo

Outcome: 1 The change of cognitive function measured by MMSE at the end of treatment

Analysis 1.2
Comparison 1 Huperzine A versus placebo, Outcome 2
The change of ADL at the end of treatment

Review: Huperzine A for vascular dementia

Comparison: 1 Huperzine A versus placebo

Outcome: 2 The change of ADL at the end of treatment

Analysis 1.3
Comparison 1 Huperzine A versus placebo, Outcome 3
Death from all causes at the end of treatment

Review: Huperzine A for vascular dementia

Comparison: 1 Huperzine A versus placebo

Outcome: 3 Death from all causes at the end of treatment

Appendix 1. Update search: February 2011

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Keyword search: chinese OR plants OR huperzine ORHUP ORayapin OR scoparon	92
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	<ol style="list-style-type: none"> 1 exp Dementia/ 2 Delirium/ 3 Wernicke Encephalopathy/ 4 Delirium, Dementia, Amnestic, Cognitive Disorders/ 5 dement*.mp. 6 alzheimer*.mp. 7 (lewy* adj2 bod*).mp. 8 deliri*.mp. 9 (chronic adj2 cerebrovascular).mp. 10 ("organic brain disease" or "organic brain syndrome").mp 11 ("normal pressure hydrocephalus" and "shunt*").mp. 12 "benign senescent forgetfulness".mp. 13 (cerebr* adj2 deteriorat*).mp. 14 (cerebral* adj2 insufficient*).mp. 15 (pick* adj2 disease).mp. 16 (creutzfeldt or jcd or cjd).mp. 17 huntington*.mp. 18 binswanger*.mp. 19 korsako*.mp. 20 or/1-19 21 "cognit* impair*".mp. 	53

Source	Search strategy	Hits retrieved
	22 exp *Cognition Disorders/	
	23 MCI.ti,ab.	
	24 ACMI.ti,ab.	
	25 ARCD.ti,ab.	
	26 SMC.ti,ab.	
	27 CIND.ti,ab.	
	28 BSF.ti,ab.	
	29 AAMI.ti,ab.	
	30 MD.ti,ab.	
	31 LCD.ti,ab.	
	32 QD.ti,ab.	
	33 AACD.ti,ab.	
	34 MNCD.ti,ab.	
	35 MCD.ti,ab.	
	36 ("N-MCI" or "A-MCI" or "M-MCI").ti,ab.	
	37 ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or de-teriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab	
	38 "preclinical AD".mp.	
	39 "pre-clinical AD".mp.	
	40 ("preclinical alzheimer*" or "pre-clinical alzheimer*").mp	
	41 (aMCI or MCIa).ti,ab.	
	42 ("CDR 0.5" or "clinical dementia rating scale 0.5").ti,ab	
	43 ("GDS 3" or "stage 3 GDS").ti,ab.	
	44 ("global deterioration scale" and "stage 3").mp.	
	45 "Benign senescent forgetfulness".ti,ab.	
	46 "mild neurocognit* disorder*".ti,ab.	
	47 (prodrom* adj2 dement*).ti,ab.	
	48 (episodic* adj2 memory).mp.	
	49 ("preclinical dementia" or "pre-clinical dementia"), mp.	
	50 ("vascular cognitive impairment" or VCI).ti,ab.	
	51 or/21-50	
	52 20 or 51	
	53 huperzi*.ti,ab.	
	54 ayapin.ti,ab.	
	55 scoparon*.d,ab.	
	56 or/53-55	
	57 52 and 56	
	58 randomized controlled trial.pt.	

Source	Search strategy	Hits retrieved
	59 controlled clinical trial.pt.	
	60 random*.ab.	
	61 placebo.ab.	
	62 drug therapy.fs.	
	63 trial.ab.	
	64 groups.ab.	
	65 or/58-64	
	66 (animals not (humans and animals)), sh.	
	67 65 not 66	
	68 57 and 67	
3. EMBASE 1980-2011 week 5 (Ovid SP)	1 exp dementia/ 2 Lewy body/ 3 delirium/ 4 Wernicke encephalopathy/ 5 cognitive defect/ 6 dement*.mp. 7 alzheimer*.mp. 8 (lewy* adj2 bod*).mp. 9 deliri*.mp. 10 (chronic adj2 cerebrovascular).mp. 11 ("organic brain disease" or "organic brain syndrome").mp 12 "supranuclear palsy".mp. 13 ("normal pressure hydrocephalus" and "shunt*").mp. 14 "benign senescent forgetfulness".mp. 15 (cerebr* adj2 deteriorat*).mp. 16 (cerebral* adj2 insufficient*).mp. 17 (pick* adj2 disease).mp. 18 (creutzfeldt or jcd or cjd).mp. 19 huntington*.mp. 20 binswanger*.mp. 21 korsako*.mp. 22 CADASIL.mp. 23 or/1-22 24 "cognit* impair*".mp. 25 exp cognitive defect/ 26 exp mild cognitive impairment/ 27 MCI.ti.ab. 28 ACMI.ti.ab. 29 ARCD.ti.ab. 30 SMC.ti.ab.	55

Source	Search strategy	Hits retrieved
	31 CIND.ti,ab.	
	32 BSF.ti,ab.	
	33 AAMI.ti,ab.	
	34 MD.ti,ab.	
	35 LCD.ti,ab.	
	36 QD.ti,ab.	
	37 AACD.ti,ab.	
	38 MNCD.ti,ab.	
	39 MCD.ti,ab.	
	40 ("N-MCI" or "A-MCI" or "M-MCI") .ti,ab.	
	41 ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or de-teriorat* or degenerat* or complain* or disturb* or disorder*)) .ti,ab	
	42 "preclinical AD".mp.	
	43 "pre-clinical AD".mp.	
	44 ("preclinical alzheimer*" or "pre-clinical alzheimer*").mp	
	45 (aMCI or MCIa).ti,ab.	
	46 ("CDR 0.5" or "clinical dementia rating scale 0.5").ti,ab	
	47 ("GDS 3" or "stage 3 GDS").ti,ab.	
	48 ("global deterioration scale" and "stage 3").mp.	
	49 "Benign senescent forgetfulness".ti,ab.	
	50 "mild neurocognit* disorder*".ti,ab.	
	51 (prodrom* adj2 dement*).ti,ab.	
	52 "age-related symptom*".mp.	
	53 (episodic adj2 memory).mp.	
	54 ("pre-clinical dementia" or "preclinical dementia"), mp.	
	55 or/24-54	
	56 23 or 55	
	57 huperz*.d,ab.	
	58 HUPERZINE A/	
	59 ayapin.ti,ab.	
	60 scoparon.d,ab.	
	61 or/57-60	
	62 56 and 61	
	63 random*.ti,ab.	
	64 randomized controlled trial/	
	65 controlled clinical trial/	
	66 trial.ab.	
	67 placebo.ab.	

Source	Search strategy	Hits retrieved
	68 "control group*".ab.	
	69 ("double-blind*" or "single-blind*" or "triple-blind*") .ti,ab	
	70 or/63-69	
	71 62 and 70	
4. PSYCINFO 1806-February week 1 2011 (Ovid SP)	1 exp Dementia/ 2 exp Delirium/ 3 exp Fluntingtons Disease/ 4 exp Kluver Bucy Syndrome/ 5 exp Wernickes Syndrome/ 6 exp Cognitive Impairment/ 7 dement*.mp. 8 alzheimer*.mp. 9 (lewy* adj2 bod*).mp. 10 deliri*.mp. 11 (chronic adj2 cerebrovascular).mp. 12 ("organic brain disease" or "organic brain syndrome").mp 13 "supranuclear palsy".mp. 14 ("normal pressure hydrocephalus" and "shunt* ").mp. 15 "benign senescent forgetfulness".mp. 16 (cerebr* adj2 deteriorat*).mp. 17 (cerebral* adj2 insufficient*).mp. 18 (pick* adj2 disease).mp. 19 (creutzfeldt or jcd or cjd).mp. 20 huntington*.mp. 21 binswanger*.mp. 22 korsako*.mp. 23 ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp 24 or/1-23 25 "cognit* impair*".mp. 26 exp Cognitive Impairment/ 27 MCI.ti,ab. 28 ACMI.ti,ab. 29 ARCD.d,ab. 30 SMC.ti,ab. 31 CIND.d,ab. 32 BSF.d,ab. 33 AAMI.ti,ab. 34 MD.d,ab. 35 LCD.d,ab.	25

Source	Search strategy	Hits retrieved
	36 QD.ti.ab.	
	37 AACD.ti.ab.	
	38 MNCD.ti.ab.	
	39 MCD.d.ab.	
	40 ("N-MCI" or "A-MCI" or "M-MCI") .ti.ab.	
	41 ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or de-teriorat* or degenerat* or complain* or disturb* or disorder*)).ti.ab	
	42 "preclinical AD".mp.	
	43 "pre-clinical AD".mp.	
	44 ("preclinical alzheimer*" or "pre-clinical alzheimer*").mp	
	45 (aMCI or MCIa).ti.ab.	
	46 ("CDR 0.5" or "clinical dementia rating scale 0.5").ti.ab	
	47 ("GDS 3" or "stage 3 GDS").ti.ab.	
	48 ("global deterioration scale" and "stage 3").mp.	
	49 "Benign senescent forgetfulness".ti.ab.	
	50 "mild neurocognit* disorder*".ti.ab.	
	51 (prodrom* adj2 dement*).ti.ab.	
	52 "age-related symptom*".mp.	
	53 (episodic adj2 memory).mp.	
	54 ("pre-clinical dementia" or "preclinical dementia"), mp.	
	55 or/25-54	
	56 24 or 55	
	57 huperz*.ti.ab.	
	58 ayapin.ti.ab.	
	59 scoparon.d.ab.	
	60 or/57-59	
	61 56 and 60	
5. CINAHL (EBSCOhost)	S1 (MH "Dementia+")	12
	S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders")	
	S3 (MH "Wernickes Encephalopathy")	
	S4 TX dement*	
	S5 TX alzheimer*	
	S6 TX lewy* N2 bod*	
	S7 TX deliri*	
	S8 TX chronic N2 cerebrovascular	
	S9 TX "organic brain disease" or "organic brain syndrome"	

Source	Search strategy	Hits retrieved
	S10 TX "normal pressure hydrocephalus" and "shunt*"	
	S11 TX "benign senescent forgetfulness"	
	S12 TX cerebr* N2 deteriorat*	
	S13 TX cerebral* N2 insufficient*	
	S14 TX pick* N2 disease	
	S15 TX creutzfeldt or jcd or cjd	
	S16 TX huntington*	
	S17 TX binswanger*	
	S18 TX korsako*	
	S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18	
	S20 TX "cognit* impair*"	
	S21 TX "cognit* defect*"	
	S22 (MH "Cognition Disorders+")	
	S23 TX MCI	
	S24 TXACMI	
	S25 TX ARCD	
	S26 TX SMC	
	S27 TX CIND	
	S28 TX BSF	
	S29 TXAAMI	
	S30 AB MD	
	S31 AB LCD	
	S32 AB QD OR "questionable dementia"	
	S33 TXAACD	
	S34 TX MNCD	
	S35 TX "N-MCI" or "A-MCI" or "MMCI"	
	S36 TX "preclinical AD"	
	S37 TX "pre-clinical AD"	
	S38 TX "preclinical alzheimer*" or "preclinical alzheimer*"	
	S39 TX aMCI ORMC1a	
	S40 TX "CDR 0.5" or "clinical dementia rating scale 0.5"	
	S41 TX "GDS 3" OR "stage 3 GDS"	
	S42 TX "global deterioration scale" AND "stage 3"	
	S43 TX "Benign senescent forgetfulness"	
	S44 TX "mild neurocognit* disorder*"	
	S45 TX prodrom* N2 dement*	
	S46 TX "age-related symptom*"	
	S47 TX cognit* N2 deficit*	

Source	Search strategy	Hits retrieved
	S48 TX cognit* N2 deteriorat*	
	S49 TX cognit* N2 declin*	
	S50 TX cognit* N2 degenerat*	
	S51 TX cognit* N2 complain*	
	S52 TX cognit* N2 disturb*	
	S53 TX cognit* N2 disorder*	
	S54 TX memory N2 episod* or TX memory N2 los* or TX memory N2 impair* or TX memory N2 complain*	
	S55 TX memoryN2 disturb* orTX memoryN2 disorder* orTXcerebr* N2 impair* or TX cerebr* N2 los*	
	S56 TX cerebr* N2 complain* or TX cerebr* N2 deteriorat* or TX cerebr* N2 disorder* or TX cerebr* N2 disturb*	
	S57 TX mental* N2 declin* or TX mental* N2 los* or TX mental* N2 impair* or TX mental* N2 deteriorat*	
	S58 TX "pre-clinical dementia" or TX "preclinical dementia"	
	S59 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58	
	S60 S19 or S59	
	S61 TX huperz*	
	S62 TX ayapin	
	S63 TX scoparon*	
	S64 S61 or S62 or S63	
	S65 S60 or S64	
6. ISI Web of Knowledge - all databases [includes: Web of Science (1945-present) ; BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports]	#1 Topic=(huperzi* OR ayapin OR scoparon*)	82
	#2 Topic=(dement* OR alzheimer* OR VaD OR MCI OR cognit*)	
	#3 Topic=(random* OR trial OR placebo OR "double-blind*" OR "single-blind*")	
	#4 #3 AND #2 AND #1	
7. LILACS (BIREME)	huperzine OR ayapin OR scoparon	1
8. CENTRAL (The Cochrane Library) (Issue 4 of 4, Oct 2010)	#1 MeSH descriptor Dementia explode all trees	31
	#2 MeSH descriptor Delirium, this term only	
	#3 MeSH descriptor Wernicke Encephalopathy, this term only	

Source	Search strategy	Hits retrieved
	#4 MeSH descriptor Delirium, Dementia, Amnestic, Cognitive Disorders, this term only	
	#5 dement*	
	#6 alzheimer*	
	#7 "lewy* bod*"	
	#8 deliri*	
	#9 "chronic cerebrovascular"	
	#10 "organic brain disease" or "organic brain syndrome"	
	#11 "normal pressure hydrocephalus" and "shunt*"	
	#12 "benign senescent forgetfulness"	
	#13 "cerebr* deteriorat*"	
	#14 "cerebral* insufficient*"	
	#15 "pick* disease"	
	#16 creutzfeldt or jcd or cjd	
	#17 huntington*	
	#18 binswanger*	
	#19 korsako*	
	#20 (#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)	
	#21 (huperzi*)	
	#22 ayapin	
	#23 #21 OR #22	
	#24 #20 AND #23	
	#25 #20 OR #24	
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Keyword search: huperzine OR ayapin OR scoparon	7
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrials.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		367
TOTAL after de-dupe and first-assess		7

Appendix 2. Update search: July 2008

Source searched	Search strategy
CDCIG SR	huperzine OR ayapin OR scoparon*
Medline (Ovid SP)	<ol style="list-style-type: none"> 1 (huperzi* OR ayapin OR scoparon*).mp. 2 dement*.mp. 3 (lewy* and bod*).mp. 4 subcortical lacunes.mp. 5 white matter lesions.mp. 6 CADASIL.mp. 7 Dementia, Vascular/ or Dementia, Multi-Infarct/ or Dementia/ 8 ("organic brain disease" or "organic brain syndrome").mp. 9 "supra nuclear palsy".mp. 10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 11 1 and 10 12 randomized controlled trial.pt. 13 controlled clinical trial.pt. 14 randimi?ed.ab. 15 placebo.ab. 16 randomly.ab. 17 trial.ab. 18 groups.ab. 19 12 or 13 or 14 or 15 or 16 or 17 or 18 20 humans.sh. 21 19 and 20 22 11 and 21
Embase (Ovid SP)	<ol style="list-style-type: none"> 1 (huperzi* OR ayapin OR scoparon*).mp. 2 dement*.mp. 3 (lewy* and bod*).mp. 4 subcortical lacunes.mp. 5 white matter lesions.mp. 6 CADASIL.mp. 7 Dementia, Vascular/ or Dementia, Multi-Infarct/ or Dementia/ 8 ("organic brain disease" or "organic brain syndrome").mp. 9 "supra nuclear palsy".mp. 10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 11 1 and 10 12 "randomi?ed controlled trial*".mp. 13 "randomized controlled trial"/ 14 randomly.ab. 15 placebo.ab. 16 clinical trial.mp. 17 12 or 13 or 14 or 15 or 16

Source searched	Search strategy
	18 11 and 17
Cinahl (Ovid SP)	<p>1 (huperzi* OR ayapin OR scoparon*).mp.</p> <p>2 dement*.mp.</p> <p>3 (cerebrovascular disease or (chronic and cerebrovascular) or (cerebr* and (insuffi-cien* or deteriorat*))).mp</p> <p>4 (lewy* and bod*).mp.</p> <p>5 subcortical lacunes.mp.</p> <p>6 white matter lesions.mp.</p> <p>7 CADASIL.mp.</p> <p>8 Dementia, Vascular/ or Dementia, Multi-Infarct/ or Dementia/</p> <p>9 (“organic brain disease” or “organic brain syndrome”).mp. [mp=title, abstract, heading word, table of contents, key concepts]</p> <p>10 “supra nuclear palsy”.mp.</p> <p>11 2 or 4 or 5 or 6 or 7 or 8 or 9 or 10</p> <p>12 1 and 11</p> <p>13 “randomi?ed controlled trial*”.mp.</p> <p>14 “randomized controlled trial”/</p> <p>15 randomly.ab.</p> <p>16 placebo.ab.</p> <p>17 clinical trial.mp.</p> <p>18 13 or 14 or 15 or 16 or 17</p> <p>19 12 and 18</p>
PsycInfo (Ovid SP)	<p>1 (huperzi* OR ayapin OR scoparon*).mp.</p> <p>2 dement*.mp.</p> <p>3 (cerebrovascular disease or (chronic and cerebrovascular) or (cerebr* and (insufficien* or deteriorat*))).mp</p> <p>4 (lewy* and bod*).mp.</p> <p>5 subcortical lacunes.mp.</p> <p>6 white matter lesions.mp.</p> <p>7 CADASIL.mp.</p> <p>8 Dementia, Vascular/ or Dementia, Multi-Infarct/ or Dementia/</p> <p>9 (“organic brain disease” or “organic brain syndrome”).mp. [mp=title, abstract, heading word, table of contents, key concepts]</p> <p>10 “supra nuclear palsy”.mp.</p> <p>11 2 or 4 or 5 or 6 or 7 or 8 or 9 or 10</p> <p>12 1 and 11</p> <p>13 “randomi?ed controlled trial*”.mp.</p> <p>14 “randomized controlled trial”/</p> <p>15 randomly.ab.</p> <p>16 placebo.ab.</p> <p>17 clinical trial.mp.</p> <p>18 13 or 14 or 15 or 16 or 17</p>

Source searched	Search strategy
	19 12 and 18
Lilacs	Huperzin\$
The Cochrane Library	#1 huperz* [in Clinical Trials] #2 dement* [in Clinical Trials] #3 (#1 AND #2) #4 "accession" number near pubmed #5 "accession number" near2 embase #6 (#4 OR#5) #7 (#3 AND NOT #6)
ISI Conference Proceedings	#1 huperzi* OR ayapin OR scoparon* #2 dement* #3 random* #4 (#1 AND #2 AND #3)
Current Controlled Trials mRCT	huperz% AND dement%
ISRCTN Register	huperzine OR ayapin OR scoparon%
ClinicalTrials.gov	huperzine
IFPMA	huperzine
Netherlands Trial Register	huperzine
UMIN Japan Trial Register	huperzine
Dissertation Abstracts Online	huperzine AND dementia
Database of African Theses and Dissertations	huperzine
Theses Canada	huperzine [any keyword]
Australasian Digital Theses Program	huperzine

WHAT'S NEW

Last assessed as up-to-date: 23 May 2011.

Date	Event	Description
11 February 2011	New search has been performed	An update search was performed for this review on 10 February 2011. Twelve further trials were identified, but no trial was eligible for inclusion in this review.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 2, 2009

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

There is currently no high quality evidence to support the use of Huperzine A for the treatment of vascular dementia

Vascular dementia (VaD) refers to cognitive impairment associated with cerebrovascular brain injury. It influences quality of life seriously. However, there is no definitive medical or surgical treatment for vascular dementia. Huperzine A is an alkaloid isolated from the Chinese herb *Huperzia serrata*. It has been authorized for treating Alzheimer's disease (AD) and benign memory deficits since 1994 in China. The drug is available as a nutraceutical in the US. Although Huperzine A has been widely used in clinical practice and used as a standard intervention in clinical trials, its efficacy and safety in people with VaD are still uncertain. This review, involving 14 participants, indicates there is currently no high quality evidence to support the use of Huperzine A for the treatment of vascular dementia. Results from well-conducted randomized controlled trials are needed to assess accurately the benefits and harms of Huperzine A in people with VaD.