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Acupuncture for patients with Alzheimer's disease: a systematic review protocol

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ABSTRACT

Introduction: The aim of this protocol is to provide the methods used to assess the effectiveness and safety of acupuncture for the treatment of patients with Alzheimer's disease.

Methods and analysis: We will search the following electronic databases: The Cochrane Library, PubMed, Medline, Embase, PsycINFO, Chinese Biomedical Literature Database, Chinese Medical Current Contents and China National Knowledge Infrastructure without restriction of language and publication status. Other sources such as Chinese acupuncture journals and the reference list of selected studies will also be searched. After screening the studies, a meta-analysis of randomised controlled trials will be conducted, if possible. Results expressed as risk ratios for dichotomous data and standardised or weighted mean differences for continuous data, will be used for data synthesis.

Dissemination: The protocol of this systematic review will be disseminated in a peer-reviewed journal and presented at a relevant conference.

Trial registration number PROSPERO CRD42014009619

Strengths and limitations of this study

- Our systematic review will provide a comprehensive, objective and systematic assessment of the use of acupuncture for the treatment of Alzheimer's disease.
- The results of this systematic review will help clinicians make decisions about treatment, and also provide clues for researchers in this subject area.
- The results of our review may help to expand the treatment options for patients with Alzheimer's disease.
- Because of the heterogeneity arising from various evaluations and reports of adverse reaction outcomes in studies, we will only describe the adverse reactions occurring during the treatment. The small trial sample sizes will also affect the comprehensive estimation of the risk of harm.

INTRODUCTION

Alzheimer's disease (AD) is a progressive brain disorder characterised by neuropathological and neurochemical features.[1][2] The typical pathological characteristics of AD are degeneration of specific nerve cells, presence of neuritic plaques and neurofibrillary tangles.[1] People with AD experience memory loss, cognitive impairment, difficulty communicating and mood changes, all of which will worsen over time.[3] Disability and dependence because of AD place a financial burden on caregivers.[4]

AD is slightly more common in women than in men,[5] and its prevalence doubles every 5 years, with higher frequencies among those aged >85 years.[6] Experts estimated there were about 24.3 million cases of dementia in 2001 among the 14 WHO regions. The number of cases was predicted to reach 81.1 million by 2040, with about 4.6 million new cases appearing every year.[7] The worldwide societal costs of dementia disorders were estimated at US$604 billion in 2010, which comprises about 1% of the aggregated global gross domestic product and has an enormous socioeconomic impact.[8]

There are 10 common diagnosis criteria for AD. The criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) criteria are probably the most widely used.[9] The NINCDS-ADRDA-RC[10] includes distinctive and reliable biomarkers for MRI and positron emission tomography for the diagnosis of AD. The National Institute on Aging and the Alzheimer's Association (NIA-AA) developed research criteria to capture the earliest stages, before full-blown dementia, as well as the full spectrum of the illness.[11] Moreover, there is a Chinese version of

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clinical criteria for AD, the operational criteria for the diagnosis of AD (OCDAD).[12] Because of cultural and regional differences, the understanding and diagnosis of AD becomes more challenging, which can affect the outcomes of clinical studies.

Medical treatment of AD can improve symptoms, but it cannot halt or reverse its progression. Cholinesterase inhibitors are commonly used. Donepezil, rivastigmine and galantamine are approved by the Food and Drug Administration to treat the symptoms of mild to moderate AD. However, raised costs and increased risk of serious adverse events associated with cholinesterase inhibitor treatment have been reported.[13] Further, the effectiveness of memantine was demonstrated for the treatment of moderate to severe AD and its use in combination with donepezil[14] resulted in a significantly slower progression of AD symptoms after long-term treatment.[15] Additionally, nicergoline is used in AD because it increases cerebral blood flow and, consequently, reduces vascular resistance.[16] Nevertheless, no non-pharmacological or pharmacological treatments prevent or cure this disease and the pharmacological interventions have been associated with many adverse events.[17]

Acupuncture originated thousands of years ago and it plays a vital part in traditional Chinese medicine. In recent years, acupuncture has been widely used by researchers in clinical practice for the treatment of AD, with fewer associated adverse events occurring.[18] Some studies in patients with AD who underwent scalp, *Xiu Sanzhen* manipulation and body acupuncture showed improved Mini Mental State Examination (MMSE) scores, activities of daily living and the hierarchic dementia scale.[19 20] According to our pre-search, nearly 20 randomised control trials have been published within the past 5 years and we consider it is necessary to reassess the efficacy and safety of acupuncture for the treatment of AD.

METHODS AND ANALYSIS
Inclusion criteria for study selection
Types of studies
Randomised controlled trials without any restrictions of language and publication type are eligible for inclusion.

Types of participants
Studies evaluating people diagnosed with AD will be included regardless of their age, sex, ethnicity, education or economic status and whether or not they were living in their own homes or in a residential care facility or hospital, according to following criteria:
1. International Classification of Diseases (ICD) version-10[2]
2. DSM-IV[5]
3. NINCDS-ADRDA criteria[1]
4. NINCDS-ADRDA-RC[10]
5. NIA-AA workgroup criteria[11]
6. OCDAD.[12]

If studies also include participants with other forms of dementia, then they will only be included if the patients with AD are reported separately. If the diagnostic criteria are not been clearly stated, trial authors will be contacted for clarifications. We will also include those studies that have applied different versions of the diagnostic criteria listed above because different organisations have often issued revised or updated versions.

Types of interventions
Studies reporting any type of acupuncture treatment will be included (body acupuncture, scalp acupuncture, auricular acupuncture, electroacupuncture, fire needling, elongated needle, intradermal needling). Point injection, laser acupuncture, tap-pricking will be excluded. We will exclude trials mainly comparing different acupuncture points of acupuncture or comparing different types of acupuncture.

Comparison interventions, including placebo control, sham acupuncture, no treatment, waiting list control, Western medicine, usual care and other conventional treatments, will also be included. Additionally, studies evaluating acupuncture combined with another treatment compared with that other treatment alone will also be included.

Types of outcome assessments
1. Cognitive function
2. Changes in global disease severity
3. Activities of daily living
4. Clinical global impression
5. Behaviour
6. Death
7. Mood
8. Safety as measured by incidence and severity of adverse effects
9. Dependency (such as institutionalisation)
10. Acceptability of treatment as measured by withdrawal from trials
11. Quality of life
12. Costs.

As for the outcome assessments, studies which applied scales such as MMSE, CDR (clinical dementia rating), CIBIC-plus (clinicians' interview-based impression of change-plus), NPI (neuropsychiatric inventory), etc, related to the types of outcome assessment domains listed above will be included.

Search methods for identification of studies
Electronic searches
We will search the following electronic databases without restriction of language and publication status from inception to 2014: Cochrane Central Register of Controlled Trials (The Cochrane Library), PubMed, Medline, Embase (Excerpta Medica Database), PsycINFO, Chinese Biomedical Literature Database, Chinese Medical Current Contents and China National Knowledge Infrastructure.

We will use the following search terms: AD, Alzheimer, dementia, acupuncture, body acupuncture, scalp acupuncture, auricular acupuncture, electroacupuncture, fire needling, elongated needle and intradermal needling. A Chinese translation of the same search terms will be used to search in the Chinese databases. The search strategy for PubMed is shown in table 1.

Other sources

The following journals published in Chinese will be searched: *Chinese Acupuncture and Moxibustion* (1981–2014), *Journal of Clinical Acupuncture and Moxibustion* (1985–2014), *Journal of Traditional Chinese Medicine* (1960–2014), *New Journal of Traditional Chinese Medicine* (1969–2014), *Shanghai Journal of Acupuncture and Moxibustion* (1982–2014) and *Research of Acupuncture and Moxibustion* (1976–2014). Relevant references cited in the studies selected will also be searched as supplementary sources. Conference proceedings and unpublished literature will also be included.

Data collection and analysis

Selection of studies

Two authors (JZ and WL) will review and screen the titles and abstracts to identify eligible trials according to the inclusion criteria; the full text will be read if necessary. Excluded studies will be listed in a table with the reasons for their exclusion. Any discrepancies will be resolved by discussion with ZL.

Data extraction and management

Two authors (JZ and WL) will extract data on participants, randomisation, interventions, outcomes, duration, follow-up and reasons for discontinuations, number of treatment-related adverse events, author information and interesting conflicts, independently using a data extraction form and then we will enter the data into Review Manager software (RevMan V.5.2.1). Different opinions will be discussed and missing data will be obtained by contacting trial authors for more information.

According to the different tolerance of participants and techniques of the acupuncturists, heterogeneity may exist in performing a meta-analysis of adverse reaction data. Adverse reactions will be summarised qualitatively according to the following three aspects: (1) number of fainting or other symptoms during acupuncture; (2) number of haematomas during treatment and (3) number of local infections.

Assessment of risk of bias in included studies

The Cochrane Collaboration Risk of Bias Tool[21] will be used to assess the methodological quality by the two authors (WL and JZ). The risk of bias in included studies will be evaluated according to the six domains: sequence generation, allocation concealment, blinding, incomplete data assessment, selective outcome reporting, other sources of bias. Other sources of bias may be caused by the different characteristics and representativeness of participants and by selective outcome reports due to conflict of interest. Additionally, based on these domains, the included studies will be classified into three categories: low risk, high risk and unclear. If there are insufficient or unclear items affecting the judgement of risk of bias, the study authors will be contacted for more details. Any disagreement will be resolved by discussion with ZL.

In acupuncture, blinding of acupuncturists is impossible, but for the studies using sham or placebo acupuncture as a control treatment, the assessment of blinding in both participants and outcome assessors can be conducted. For those studies in which blinding of participants is difficult—for example, those comparing acupuncture with another type of treatment, we will only assess blinding of the outcome assessors.

Measures of treatment effect

For dichotomous data, risk ratio with corresponding 95% CIs will be used while continuous data will be expressed as mean differences with 95% CIs. Weighted mean differences will be used for data measured on the same scales and for which the same units are used; otherwise, standardised mean differences will be used.

Table 1	Search strategy used in PubMed database
No	**Search items**
1	Randomised controlled trial
2	Controlled clinical trial
3	Randomised
4	Randomly
5	Placebo
6	Trial
7	1 or 2–6
8	Dementia
9	Alzheimer's disease
10	Cognitive disorders
11	Cognitive impairment
12	dement*
13	Alzheimer*
14	8 or 9–13
15	Acupuncture therapy
16	Acupuncture
17	Acupoints
18	Acupuncture*
19	Body acupuncture
20	Scalp acupuncture
21	Auricular acupuncture
22	Electroacupuncture
23	Fire needling
24	Elongated needle
25	Intradermal needling
26	15 or 16–25
27	7 and 14 and 26

*Any words containing this searching item will be searched.
This search strategy will be suitable for other electronic databases.

Dealing with missing data

We will attempt to collect additional information by contacting authors of included studies with missing data. If we fail to obtained sufficient data, the trials with missing data will be omitted from the data synthesis. An intention-to-treat analysis will be performed, if possible (the analysis should include the data of all the participants in the groups to which they were originally randomly assigned), and a sensitivity analysis will be used to determine whether the results are inconsistent.

Assessment of heterogeneity

We will search for overlapping CIs in forest plots and use a χ^2 test for statistical heterogeneity and the I^2 statistic ($I^2 > 50\%$ shows the existence of heterogeneity) to estimate the level of heterogeneity across the studies.

Assessment of reporting biases

We will use funnel plots to detect potential reporting biases and small-study effects. The Egger method[22] will be used to explain the asymmetry if more than 10 studies are included in the meta-analysis.

Data synthesis

If it is possible to carry out a meta-analysis, RevMan V.5.2.1 software will be used to combine the relative risks for dichotomous outcomes and mean differences for continuous outcomes both with 95% CIs. We will use the fixed-effect model if there is no evidence of heterogeneity; otherwise, we will apply a random-effects model and reach a conclusion more cautiously. If significant heterogeneity between studies is found, we will search for the possible causes from both clinical and methodological perspectives and provide an explanation or conduct subgroup analysis. Finally, if there is substantial heterogeneity between studies, we will conduct a descriptive analysis.

Subgroup analysis

A subgroup analysis will be performed based on the type of acupuncture intervention (body acupuncture, scalp acupuncture, auricular acupuncture, electroacupuncture, fire needling, elongated needle, intradermal needling,) because this is the main factor causing heterogeneity. Additionally, the duration of treatment and combination of treatment (acupuncture alone or acupuncture with another treatment) will also be considered. Furthermore, sample sites will be classified based on the place of participants' residence (such as own homes, a residential care facility or hospitals), and the different progression of AD will also be considered and classified into three categories: mild, moderate and severe.

Sensitivity analysis

We will conduct a sensitivity analysis to verify the robustness of the study conclusions, assessing the impact of methodological quality, study design, sample size and

the effect of missing data as well as the analysis methods on the result of this review.[23] We will also use sensitivity analyses to investigate suspected funnel plot asymmetry.

Ethics and dissemination

Ethical approval will not be needed because the data used in this systematic review will not be individual patient data and there will be no concerns about privacy. The results will be disseminated by its publication of the manuscript in a peer-reviewed journal or presented at a relevant conference.

DISCUSSION

A systematic review of acupuncture for AD published in 2009 analysed three randomised control trials. In the previous review, type of participants, outcome assessment and other details of the methodology were not clearly and specifically described. The serious methodological flaws did not allow the authors to draw convincing conclusions. Furthermore, the researchers did not calculate the proportion of treatment-related adverse events.[24] Thus, a comprehensive and objective systematic
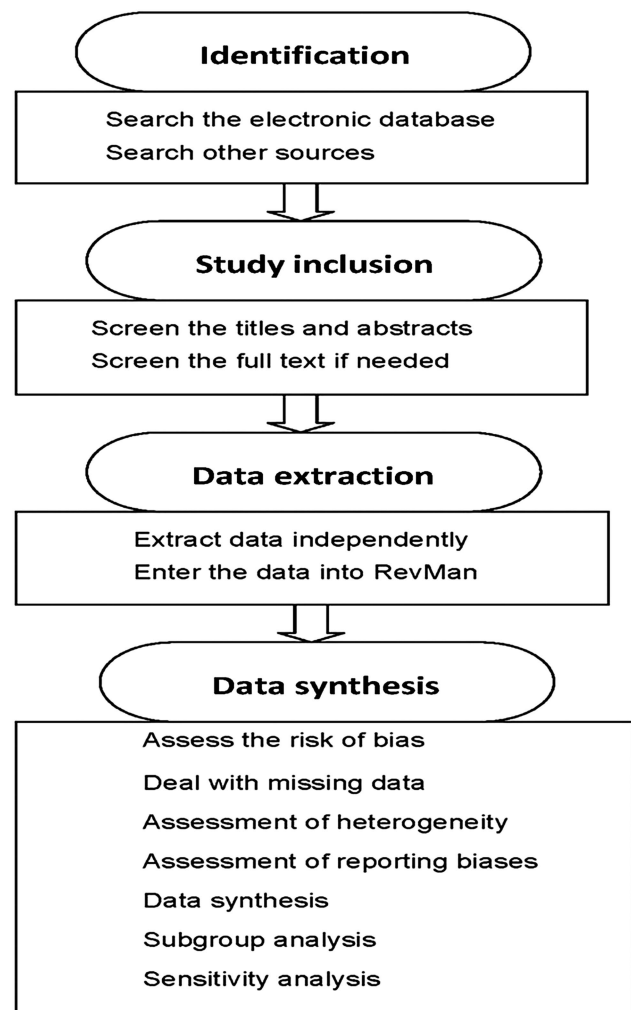

Figure 1 Process of the systematic review.

review is needed. The process of performing this systematic review, shown in figure 1, will be separated into four parts: identification, study inclusion, data extraction and data synthesis. Collection of data is continuing for our study. We consider that this review will assist clinicians during the decision-making process when treating patients with AD and will also provide clues for researchers in this subject area. At the same time, patients with AD may benefit from additional treatment alternatives.

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