

The Effectiveness and Safety of Acupuncture for Patients With Alzheimer Disease

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: The use of acupuncture for treating Alzheimer disease (AD) has been increasing in frequency over recent years. As more studies are conducted on the use of acupuncture for treating AD, it is necessary to re-assess the effectiveness and safety of this practice.

The objective of this study was to assess the effectiveness and safety of acupuncture for treating AD.

Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, Embase, PsycINFO, Chinese Biomedicine Literature (CBM), Chinese Medical Current Content (CMCC) and China National Knowledge Infrastructure (CNKI) were searched from their inception to June 2014.

Randomized controlled trials (RCTs) with AD treated by acupuncture or by acupuncture combined with 1 kind of drugs were included.

Two authors extracted data independently. The continuous data were expressed as mean differences (MD) with 95% confidence intervals (CIs). Weighted MD (WMD) was used instead of standardized MD (SMD) when the same scales were used. Adverse reactions related to acupuncture were also investigated.

Ten randomized controlled trials with a total of 585 participants were included in the meta-analysis. The combined results of 6 trials showed that acupuncture was better than drugs at improving scores on the Mini Mental State Examination (MMSE) scale (MD 1.05, 95% CI 0.16–1.93). Evidence from the pooled results of 3 trials showed that acupuncture plus donepezil was more effective than donepezil alone at improving the MMSE scale score (MD 2.37, 95% CI 1.53–3.21). Out of 141 clinical trials, 2 trials reported the incidence of adverse reactions related to acupuncture. Seven out of 3416 patients had adverse reactions

related to acupuncture during or after treatment; the reactions were described as tolerable and not severe.

Acupuncture may be more effective than drugs and may enhance the effect of drugs for treating AD in terms of improving cognitive function. Acupuncture may also be more effective than drugs at improving AD patients' ability to carry out their daily lives. Moreover, acupuncture is safe for treating people with AD.

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Abbreviations: AD = Alzheimer disease, ADAS-cog = Alzheimer's Disease Assessment Scale-Cognition, ADL = ability of daily living, CBM = Chinese Biomedicine Literature, CENTRAL = Central Register of Controlled Trials, CI = confidence intervals, CMCC = Chinese Medical Current Content, CNKI = China National Knowledge Infrastructure, DSM = Diagnostic and Statistical Manual of Mental Disorders, FAQ = functional activities questionnaire, FDA = Food and Drug Administration, HDS = Hasegawa's Dementia Scale, HDS-R = Revised Hasegawa's Dementia Scale, ICD = International Classification of Diseases, ITT = intention-to-treat, MCID = mean minimum clinically important difference, MD = mean differences, MMSE = Mini Mental State Examination, MoCA = Montreal cognitive assessment, MRI = magnetic resonance imaging, NIA-AA = Aging and the Alzheimer's Association workgroup, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, OCDAD = Operational Criteria for the Diagnosis of Alzheimer's Disease, RCTs = Randomized controlled trials, SMD = standardized mean differences, WMD = weighted mean differences.

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Jing Zhou and Zhishun Liu contributed to the conception of the study. The manuscript of the review was drafted by Jing Zhou, and was revised by Weina Peng. The search strategy was developed by all authors and run by Wang Li and Jing Zhou, who also independently screened the potential studies, extracted data from included studies, assessed the risk of bias, and finished the data synthesis. Zhishun Liu and Min Xu arbitrated disagreements and ensured that no errors occurred during the study. All authors approved the publication of the review.

Ethical approval was not needed as the data used in this systematic review was not individual patient data and there were no privacy issues to address. The results will be disseminated by publication of the manuscript in a peer reviewed journal, or presentation at a relevant conference.

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INTRODUCTION

Alzheimer disease (AD) is a degenerative cerebral disorder with insidious onset.¹ Cognitive impairment and neuropathological features are the characteristics of AD.² Decline in cognitive functions leads to loss of independent function of patients that has an wide impact on families and healthcare systems.³ The biggest factor of AD is aging and the population over the age of 85 years have higher frequencies of incidence.⁴ Moreover, female gender are also as a risk factor for AD.⁵ At present, no medical treatment can stop or reverse the progression of AD.⁶ FDA (Food and Drug Administration)-approved drugs only have modest symptomatic effects⁷ and have been related to many adverse reactions.⁸ In recent years, acupuncture has been used for treating AD and reported to have effectiveness to improve the cognitive function.^{9,10} The objective of this systematic review is to assess the effectiveness and safety of acupuncture for the treatment of AD.

METHODS AND ANALYSIS

Inclusion Criteria for Study Selection

Randomized controlled trials (RCTs) with participants diagnosed as having AD by common diagnostic criteria such as The International Classification of Diseases (ICD),¹¹ the Diagnostic and Statistical Manual of Mental Disorders (DSM),¹ the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),² the Diagnosis of Dementia due to Alzheimer disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup (NIA-AA),¹² or the Operational Criteria for the Diagnosis of Alzheimer's Disease (OCDAD)¹³ were included. Studies reporting acupuncture therapy were included, except those using point injection, laser acupuncture, or tap-pricking. Trials comparing different types of acupuncture and acupoints were excluded. Cognitive function, changes in global disease severity, ability of daily living (ADL), clinical global impression, behavior, death, mood, dependency (such as institutionalization), acceptability of treatment as measured by withdrawal from trials, quality of life, costs, and safety were measured by incidence; severity of adverse effects was assessed respectively for each trial.

Search Methods for Identification of Studies

The following databases were searched by 2 reviewers (Z.J. and L.W.) independently: Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, Embase, PsycINFO, Chinese Biomedicine Literature (CBM), Chinese Medical Current Content (CMCC) and China National Knowledge Infrastructure (CNKI). Relevant references cited in selected studies, conference proceedings, and unpublished literatures were also searched as supplementary sources.

The following search strategy was used for PubMed, and this search strategy was also suitable for other electronic databases:

- (1) randomized controlled trial
- (2) controlled clinical trial
- (3) randomized
- (4) randomly
- (5) placebo
- (6) trial
- (7) 1 or 2–6
- (8) dementia
- (9) Alzheimer disease
- (10) cognitive disorders
- (11) cognitive impairment
- (12) dement*
- (13) Alzheimer*
- (14) 8 or 9–13
- (15) acupuncture therapy
- (16) acupuncture
- (17) acupoints
- (18) acupunct*
- (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

Data Extraction and Management

Two authors (Z.J. and L.W.) independently used a data extraction form to extract data on participants, randomization, interventions, outcomes, duration, follow-up, reasons for discontinuation, numbers of treatment-related adverse events, author information, and interesting conflicts. 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 privacy issues to address.

Assessment of Risk of Bias in Included Studies

The risk of bias in each included study was evaluated according to the Cochrane Handbook for Systematic Reviews of Interventions on the basis of the following 6 domains: sequence generation, allocation concealment, blinding, incomplete data assessment, selective outcome reporting, and other sources of bias. Any disagreement was resolved by discussion with Liu ZS.

Measures of Treatment Effect

For changes in measurement scales, the continuous data were expressed as mean differences (MD) with 95% confidence intervals (CIs). Weighted MD (WMD) was used instead of standardized MD (SMD) when the same scales were used.

Dealing With Missing Data

We attempted to contact the authors to collect additional information for included studies with missing data. If we failed to obtain sufficient data, the trials with missing data were omitted from the data synthesis. An intention-to-treat (ITT) analysis was performed when possible, followed up with a sensitivity analysis to find out whether the results were inconsistent.

Assessment of Heterogeneity

To estimate the level of heterogeneity across the studies, we searched for overlapping CI in forest plots, and used the χ^2 test for statistical heterogeneity and the value of the I^2 statistic ($I^2 > 50\%$ showed the existence of heterogeneity).

Assessment of Reporting Biases

As more than 10 studies were included in the meta-analysis, funnel plots were used to detect potential reporting biases and small-study effects. The Egger method¹⁴ was used to investigate asymmetry.

Data Synthesis

RevMan 5.2.1 software¹⁵ was used to combine MDs for continuous outcomes with 95% CIs. We used the fixed-effect model if there was no evidence of heterogeneity; otherwise, we applied a random-effects model and arrived at a conclusion with more caution. Due to the different tolerance of participants and techniques of the acupuncturists, heterogeneity was likely to exist when performing meta-analysis of adverse reaction data. Hence adverse reactions were summarized qualitatively.

Subgroup Analysis and Sensitivity Analysis

Subgroup analyses were intended to be performed based on the different types of acupuncture when there were more than 3

trials using the same kind acupuncture. A sensitivity analysis was conducted to verify the robustness of study conclusions, assessing the impact of methodological quality, study design, sample size, missing data, and analysis methods on the result of this review.¹⁶

RESULTS

Characteristics of Included Trials and Literature Search Findings

The process of identifying trials is shown in Figure 1, and the characteristics of included trials are summarized^{17–25} in Table 1.

A total of 1324 studies were identified, including 77 RCTs. There were 10 RCTs that met all the inclusion criteria, although none of these included trials provided any information about the degree of atrophy of hippocampal volume as measured by magnetic resonance imaging (MRI). All of the included trials were in Chinese, and all were conducted in China. Six^{17–21} of the 10 RCTs compared acupuncture with drugs, and 1 of the 6 RCTs was an unpublished thesis for a master's degree (Ke YM, MD, unpublished data, June 2014). Three^{22–24} of the 10 RCTs compared acupuncture combined with donepezil with donepezil alone, and the remaining RCT²⁵ compared acupuncture with no treatment. Only 3 of these 10 RCTs used electroacupuncture,^{17,19,22} whereas the other 7 used acupuncture without electrical stimulation. The details of drugs used in comparison groups are given in Table 1.

The 10 RCTs included a total of 585 patients, with sample sizes ranging from 16 to 49. The age of the participants ranged from 46 to 81 years, and all were recruited in China. All of the participants met the diagnostic criteria. Only 2 RCTs^{17,18} mentioned categories of progression of AD. The treatment duration ranged from 4 weeks²² to 24 weeks¹⁹. Baihui (GV20)^{17,10,22} (Ke YM, MD, unpublished data, June 2014) and Zusanli (ST 36)^{19,21,22} (Ke YM, MD, unpublished data, June 2014) were the most commonly used points, with an incidence of 40% amongst these 10 RCTs. Xuehai (SP10),^{21,26} (Ke YM, MD, unpublished data, June 2014) and Sishencong (EX1)^{17,23} (Ke YM, MD, unpublished data, June 2014) were the next most frequently used points, with an incidence of 30% amongst these 10 RCTs. Other points used in the included RCTs were Taixi (KI3), Dazhui (GV14), Danzhong (CV17), Zhongwan (CV12), Qihai (CV6), Waiguan (TE5), Xuanzhong (GB39), Neiguan (PC6), Shenshu (BL23), Yintang (GV29), Sanyinjiao (SP6) and Dazhong (KI4), as well as scalp acupuncture and 2 special experiential acupoints “Xiu Sanzhen” and “Si Shenzhen.”

Risk of Bias in Included RCTs

All of the included RCTs mentioned randomization. Two RCTs randomized by random number tables, and kept the allocation schedule safely concealed using opaque envelopes.^{17,25} Three RCTs randomized by random number tables, but the process of allocation concealment was unclear (Ke YM, MD, unpublished data, June 2014).^{18,24} The details of the randomization and allocation concealment were unclear in the remaining 5 RCTs, even after contacting the authors for advanced information. Moreover, none of the included RCTs blinded the acupuncturists and the participants because of the nature of acupuncture. The statisticians were blinded in only 2 RCTs,^{17,25} and it is unclear whether the statisticians in the remaining 8 RCTs were genuinely blinded. Additionally, 1 RCT

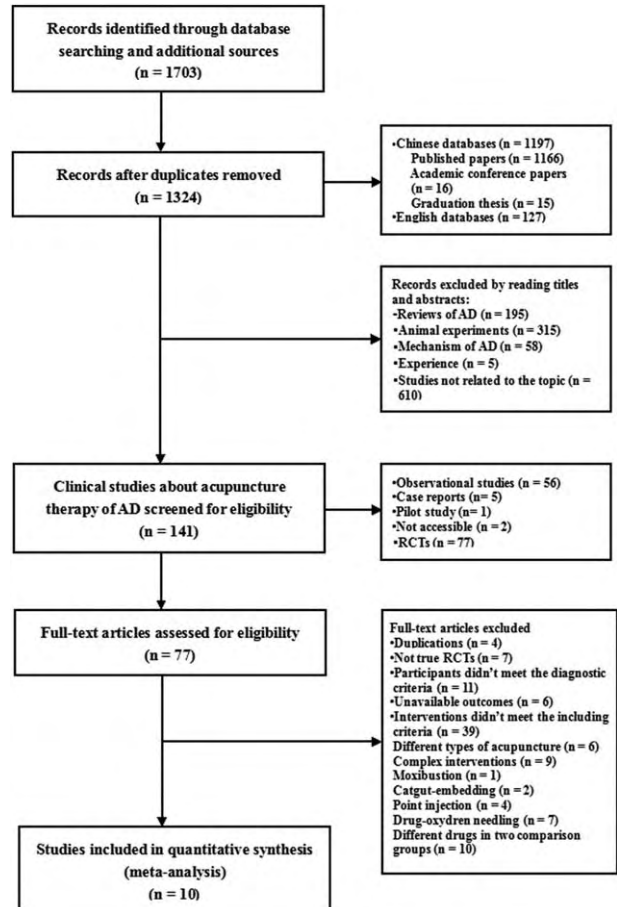


FIGURE 1. Flow chart of trial selection process for this systematic review.

reported 2 drop-outs because of adverse effects related to donepezil such as nausea, loss of appetite, and discomfort in abdomen; however, there was no information about the principle used for dealing with the missing data.²² No information related to missing data in the remaining 9 RCTs was obtained by contacting the authors or screening the full texts.

Effects of Interventions

Ten RCTs were divided into 3 parts to conduct the meta-analysis according to the different types of comparison groups, and the RCTs in these 3 parts had similarities that were then pooled together. Subgroup analysis was not conducted according to different types of acupuncture because of insufficient number of studies.

Acupuncture Versus Drugs

Mini Mental State Examination (MMSE) Scale

Meta-analysis of 6 RCTs showed heterogeneity ($I^2 = 57%$) (Ke YM, MD, unpublished data, June 2014).^{17–21} A sensitivity analysis was conducted and the heterogeneity may be explained by 1 RCT, (Ke YM, MD, unpublished data, June 2014) which was an unpublished master's thesis with a shorter course of treatment than the other RCTs. The summary MD for all of the RCTs using the random model was 1.05 (95% CI 0.16–1.93),

TABLE 1. Summary of the Included Studies

Reference	Comparisons	Methods	Course, wk	Outcomes
Lin et al ¹⁷	Electroacupuncture, 18	Random number table	12	MMSE, ADL ADAS-cog
	Donepezil, 18	Adequate allocation concealment Outcome assessors blinded		
Liu et al ¹⁸	Acupuncture, 40	Random number table	10	MMSE, HDS
	Almitrine and raubasine, 40	Allocation concealment: unclear Blinding of outcome assessors: unclear		
Luo et al ¹⁹	Electroacupuncture, 49	Process of randomization: unclear	12	MMSE
	Dihydroergotoxine, 48	Allocation concealment: unclear Blinding of outcome assessors: unclear		
Zhao et al ²⁰	Acupuncture, 16	Process of randomization: unclear	8	MMSE, ADL, HDS-R, FAQ
	Nimodipine, 16	Allocation concealment: unclear Blinding of outcome assessors: unclear		
Jia et al ²¹	Acupuncture, 25	Process of randomization: unclear	12	MMSE, ADL
	Piracetam, 26	Allocation concealment: unclear Blinding of outcome assessors: unclear		
Ke YM, MD, unpublished data, June 2014	Acupuncture, 32	Random number table	4	MMSE, ADL
	Donepezil, 32	Allocation concealment: unclear Blinding of outcome assessors: unclear		
Zou and Yang ²²	Electroacupuncture plus donepezil, 20	Process of randomization: unclear	12	MMSE, ADL, MoCA
	Donepezil, 18	Allocation concealment: unclear Blinding of outcome Assessors: unclear		
Jin ²³	Acupuncture plus donepezil, 26	Process of randomization: unclear	4	MMSE, ADL
	Donepezil, 26	Allocation concealment: unclear Blinding of outcome assessors: unclear		
Wang ²⁴	Scalp acupuncture plus donepezil, 27	Random number table	3	MMSE, ADAS-cog
	Donepezil, 28	Allocation concealment: unclear Blinding of outcome assessors: unclear		
Hu et al ²⁵	Acupuncture, 40	Random number table	24	MMSE, ADL
	No treatment, 40	Adequate allocation concealment Outcome assessors blinded		

ADL = ability of daily living; HDS = Hasegawa's Dementia Scale; HDS-R = Revised Hasegawa's Dementia Scale; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognition; FAQ = functional activities questionnaire; MMSE = Mini Mental State Examination; MoCA = Montreal cognitive assessment.

and the MD using the fixed model was 0.54 (95% CI 0.02–1.07). However, the difference between the overall results was very small, and the conclusion remained the same. Therefore, there was a statistically significant difference between acupuncture and drugs in improving the MMSE score (Figures 2 and 3). In addition, the improved MMSE score after treatment compared with the baseline score in 3 of the 5 RCTs was more than 3.72 points (Ke YM, MD, unpublished data, June 2014),^{20,21} which was the mean minimum clinically important difference (MCID) of the MMSE scale.²⁶

Hasegawa's Dementia Scale

One RCT using the Revised Hasegawa's Dementia Scale (HDS-R),²⁰ and another one using the HDS¹⁸ were pooled together. The SMD was 0.09 (95% CI –0.28 to 0.46) using

the fixed model, and there was no statistically significant difference in HDS score increase when comparing acupuncture with Western medicine (Figure 4).

Alzheimer's Disease Assessment Scale-Cognition (ADAS-cog)

The MD was –5.14 (95% CI –8.75 to –1.53) in 1 RCT.¹⁷ There was a statistically significant difference between electroacupuncture and donepezil for reducing the ADAS-cog score (Figure 5).

ADL Scale

Four RCTs were pooled together.^{17,20,21} (Ke YM, MD, unpublished data, June 2014) The MD was –2.80 (95% CI –4.57 to –1.02) using the fixed model, and there was a

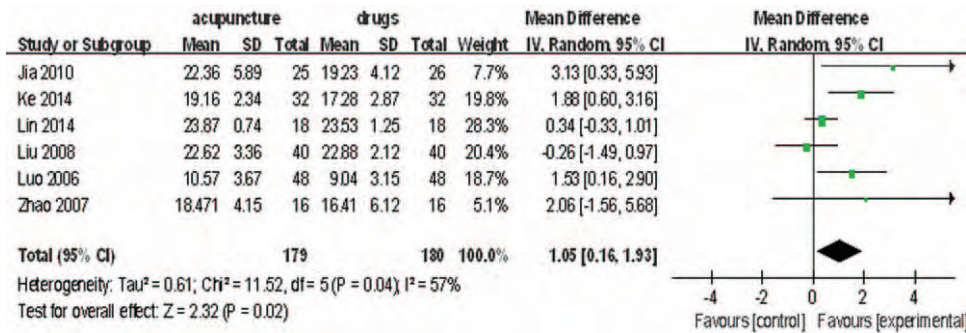


FIGURE 2. Forest plot of the effect of acupuncture versus drugs on the MMSE score using the random model. MMSE = Mini Mental State Examination.

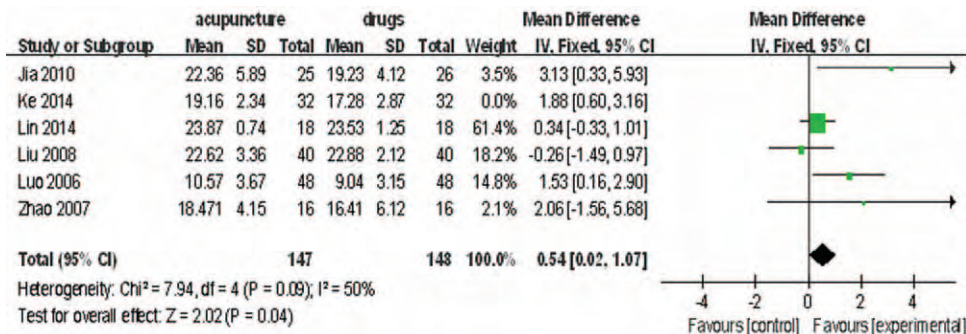


FIGURE 3. Forest plot of the effect of acupuncture versus drugs on the MMSE score using the fixed model. MMSE = Mini Mental State Examination.

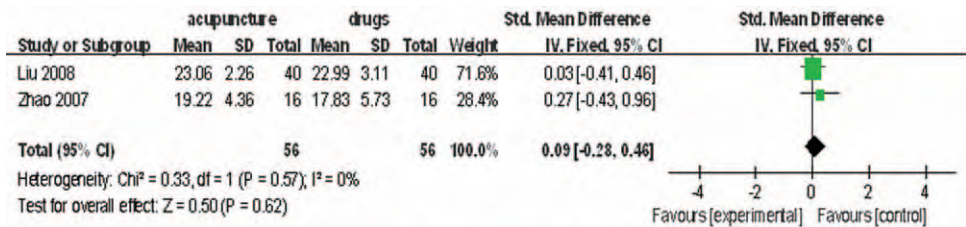


FIGURE 4. Forest plot of the effect of acupuncture versus drugs on the HDS score. HDS = Hasegawa's Dementia Scale.

statistically significant difference between the effects of acupuncture and western medicine (Figure 6).

Functional Activities Questionnaire (FAQ)

The MD was -1.41 (95% CI -4.87 to 2.05) in 1 RCT.²⁰ There was no statistically significant difference between acupuncture and nimodipine in improving the FAQ score (Figure 7).

Acupuncture Plus Donepezil Versus the Same Donepezil Alone

MMSE Scale

Three RCTs were pooled together.²²⁻²⁴ The MD was 2.37 (95% CI 1.53-3.21) using the fixed model, and there was a statistically significant difference between acupuncture plus donepezil and donepezil alone in improving the MMSE score (Figure 8).

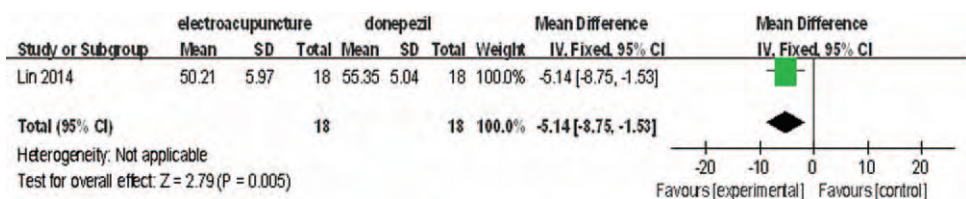


FIGURE 5. Forest plot of the effect of acupuncture versus drug on the ADAS-cog score. ADAS-cog = Alzheimer's Disease Assessment Scale-Cognition.

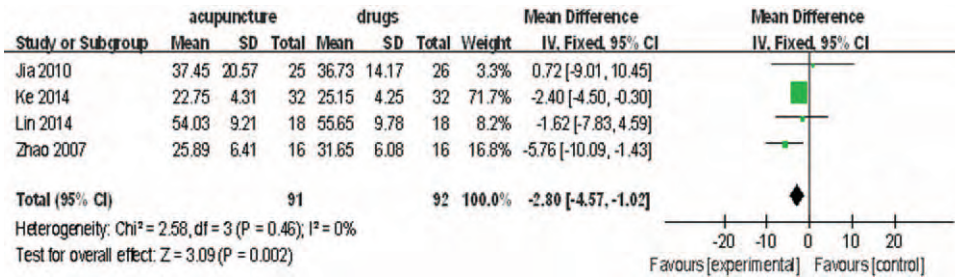


FIGURE 6. Forest plot of the effect of acupuncture versus drugs on the ADL score. ADL = ability of daily living.

ADAS-cog

The MD was -0.90 (95% CI -4.00 to 2.20) for 1 RCT.²⁴ There was no statistically significant difference between acupuncture plus donepezil and donepezil alone in reducing the ADAS-cog score (Figure 9).

Montreal Cognitive Assessment (MoCA)

The MD was 2.00 (95% CI -0.89 to 4.89) for 1 RCT.²² There was no statistically significant difference between acupuncture plus donepezil and donepezil alone in increasing the MoCA score (Figure 10).

ADL Scale

Two RCTs were pooled together.^{22,23} The MD was -2.64 (95% CI -4.95 to -0.32) using the fixed model. There was a statistically significant difference between acupuncture plus donepezil and donepezil alone in reducing the ADL score (Figure 11).

Acupuncture Versus No Treatment

MMSE Scale

The MD of 1 RCT²⁵ was 3.74 (95% CI 1.34-6.14). There was a statistically significant difference between acup-

puncture and no treatment in increasing the MMSE score (Figure 12).

ADL Scale

The MD for 1 RCT²⁵ was -8.82 (95% CI -19.83 to 2.19) using the fixed model. There was no statistically significant difference between acupuncture and no treatment in reducing the ADL score (Figure 13).

Safety

There were 141 clinical studies with a total of 3416 AD patients treated by acupuncture or by acupuncture combined with other therapy. None of these studies reported any severe adverse events related to acupuncture. However, 2 trials ineligible for included in meta-analysis reported the incidence of adverse reactions related to acupuncture.^{28,29} One trial (experimental group treated by acupuncture, n = 15) reported 1 case of hemorrhage of local skin, 1 case of fatigue, 2 cases of feeling faint during acupuncture, and 2 cases of drowsy and sleepy feelings after acupuncture.²⁷ The incidence of adverse reactions in this trial was 40%, and the percentage of patient compliance was 87.3%. The other trial that reported an adverse reaction was an observational study about AD treated by acupuncture (n = 103) that reported 1 case of dizziness and nausea during

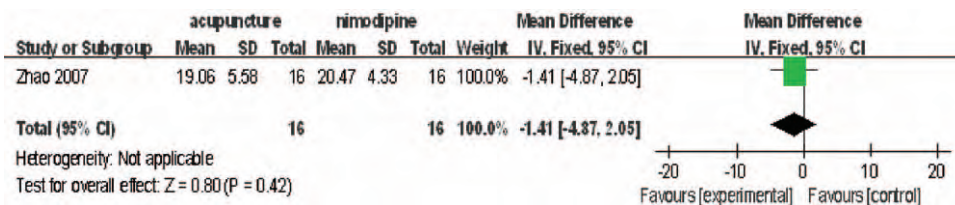


FIGURE 7. Forest plot of the effect of acupuncture versus drugs on the FAQ score. FAQ = functional activities questionnaire.

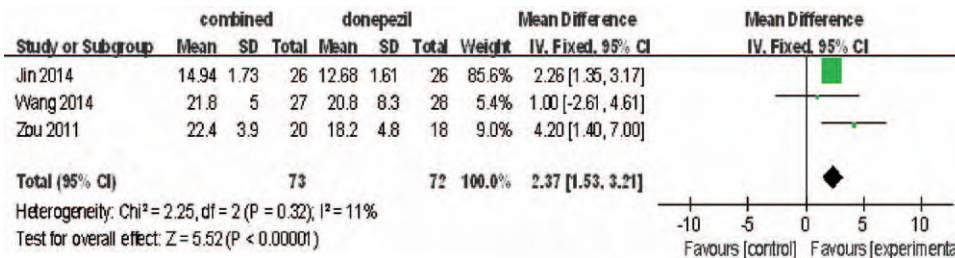


FIGURE 8. Forest plot of the effect of acupuncture plus donepezil versus donepezil alone on the MMSE score. MMSE = Mini Mental State Examination.

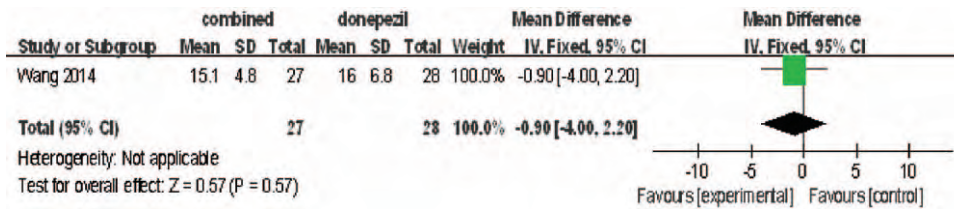


FIGURE 9. Forest plot of the effect of acupuncture plus donepezil versus donepezil alone on the ADAS-cog score. ADAS-cog = Alzheimer’s Disease Assessment Scale-Cognition.

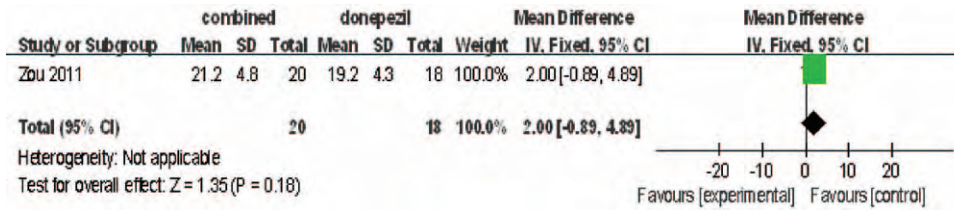


FIGURE 10. Forest plot of the effect of acupuncture plus donepezil versus donepezil alone on the MoCA score. MoCA = Montreal cognitive assessment.

the treatment, giving an incidence of 0.97%.²⁸ None of the remaining clinical trials reported any adverse reactions related to acupuncture.

DISCUSSION

AD is a chronic and progressive disease.²⁹ There is currently no effective cure for this serious disorder,³⁰ and adverse events have been reported to be correlated with pharmacological interventions.³¹ Acupuncture has shown effectiveness in improving cognitive function, and is progressively being used in more clinical practices.¹⁰ Ten RCTs were included in this meta-analysis, with a total of 585 participants that had their outcome measured using the MMSE scale.

One RCT concluded that acupuncture was better than no treatment in improving the MMSE score.²⁵ However, meta-analysis was not possible for only a single RCT. Moreover, this single-centre trial was not designed to assess the patients at follow-up, and the sample size was too small to provide powerful evidence. Therefore, evidence on the effectiveness of acupuncture in improving the cognitive function of AD patients was not powerful enough.

The combined results of 6 RCTs showed that acupuncture was superior to drugs in improving the MMSE score, and acupuncture plus donepezil was better than donepezil alone in improving the MMSE score (Ke YM, MD, unpublished data, June 2014).¹⁷⁻²¹ However, there was too little information in

these 10 RCTs regarding the processes of randomization and allocation concealment, which may have led to a high risk of selection bias. Additionally, only two^{17,25} out of the 10 RCTs blinded the statisticians, which may have led to considerable risk of bias. Inadequate information about missing data may also have potential attrition bias. One RCT was an unpublished thesis for a master’s degree (Ke YM, MD, unpublished data, June 2014) and all of the included RCTs were conducted in China and published in Chinese, which may have led to publication bias. Moreover, none of the RCTs were designed to assess patients’ condition by follow-up for a period of time after treatment. So overall there was an inadequate number of high quality RCTs to provide powerful evidence.

Nevertheless, amongst the included 10 RCTs, a group of 5 RCTs^{17,21-24} (Ke YM, MD, unpublished data, June 2014) used donepezil and 1 trial used nimodipine;²⁰ these 2 drugs are both strongly recommended by the British Association for Psychopharmacology for treating dementia.³² Although the drugs used in the remaining RCTs (amitriptyline and rubasine,¹⁸ hydroergotoxine,¹⁹ and piracetam²¹) have not been proven in evidence-based studies, they have been shown to improve cognitive function.³⁰ Furthermore, memory impairment is the core symptom of AD,³² and memory is 1 part of cognitive function. The MMSE scale is the most commonly used measurement for assessing cognitive function,³³ and the improved score compared with baseline was 3.72, which is the mean MCID.²⁶ The MMSE score of 5 RCTs out of the included 10 RCTs compared with the baseline score

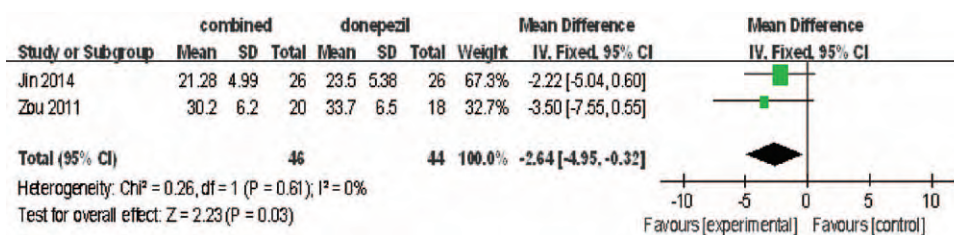


FIGURE 11. Forest plot of the effect of acupuncture plus donepezil versus donepezil alone on the ADL score. ADL = ability of daily living.

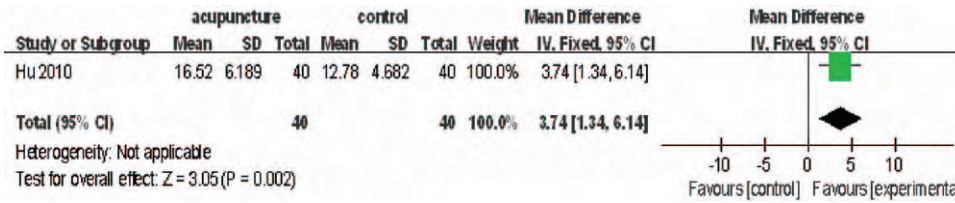


FIGURE 12. Forest plot of the effect of acupuncture versus no treatment on the MMSE score. MMSE = Mini Mental State Examination.

was improved by more than 3.72 points,^{20–23} (Ke YM, MD, unpublished data, June 2014) which means the treatment of AD with acupuncture was clinically meaningful with respect to improving cognitive function.³⁴ In general, the results of the meta-analysis were meaningful for clinical practice, and indicate that acupuncture may be better than drugs and may enhance the effect of donepezil in terms of improving the cognitive function of AD patients.

The symptoms of AD are also reflected in other ways besides impairment of cognitive function.²⁹ One RCT showed that acupuncture did not reduce the ADL score,²⁵ but meta-analysis is impossible for only 1 RCT; therefore the evidence on the effectiveness of acupuncture in improving the ability of AD patients to carry out daily life was insufficient. The combined results from 4 RCTs found that acupuncture was superior to drugs (donepezil,¹⁷ [Ke YM, MD, unpublished data, June 2014] nimodipine,²⁰ and piracetam²¹) in reducing the ADL score; however, due to the lack of high quality studies, the power of the evidence is limited. Therefore we can only conclude that acupuncture may be more effective than drugs for improving the ability of AD patients to carry out daily living. Furthermore, assessment of improvement in the condition of AD patients as measured by other scales such as MoCA, HDS, ADAS-cog, and FAQ was limited by small sample sizes and an inadequate number of RCTs. This also meant that the evidence was insufficient to show the effectiveness of acupuncture to enhance the effect of drugs for treating AD.

It is difficult to conduct a meta-analysis due to the variety of symptoms and the low number of adverse reactions reported, so a description of adverse reactions was conducted. One hundred forty-one clinical studies with a total of 3416 AD patients treated by acupuncture or by acupuncture combined with another therapy were screened to assess the safety of acupuncture for treating AD. Adverse reactions related to acupuncture occurred in only 7 cases, in which the reactions were described as tolerable and not severe; none of the other studies mentioned any adverse reactions related to acupuncture. Therefore acupuncture is safe for treating patients with AD.

There are some limitations of our systematic review. We attempted to minimize publication bias by searching the databases of conference literatures and theses, and hand-searching the journals that were not included in the electronic databases;

however, there were difficulties in obtaining all of the unpublished data, and only Chinese and English databases were searched. Reporting biases could not be detected by funnel plot due to lack of adequate RCTs. Moreover, all of the included RCTs only made the clinical diagnosis, but did not report the atrophy volume of the hippocampus of patients. In addition, none of the included RCTs assessed the condition of patients by follow-up after treatment. Finally, the included RCTs were all conducted in China, so more studies are needed to make the conclusions more applicable to other areas.

There are 2 other existing systematic reviews of acupuncture treatment of AD patients; 1 reviewed 3 trials and was published in 2009,³⁵ and the other reviewed 8 trials and was published in 2012.³⁶ These 2 reviews only included studies that compared acupuncture with drugs, and the effectiveness of acupuncture for enhancing the effect of drugs was not explored. The 2 previous reviews found no difference between acupuncture and drugs for improving the MMSE score or reducing the ADL score. Furthermore, the safety aspect of acupuncture was not mentioned in these 2 reviews. Our systematic review included more trials as it had different inclusion criteria for interventions.

CONCLUSIONS

In conclusion, the results of the meta-analysis indicate that acupuncture may be more effective than drugs, and may also enhance the effect of donepezil in improving the cognitive function of patients with AD. Acupuncture might also be more effective than drugs in improving the ability of daily living of patients with AD. Moreover, acupuncture is safe for treating patients with AD. For future research, the process of randomization and allocation concealment must be rigorously controlled and described, and more detailed methodologies need to be reported. There also needs to be more information provided in future studies about the diagnosis of AD, supported by the degree of atrophy of hippocampal volume as measured by MRI. A detailed description should be given of the data integrity and the methods used to deal with missing data. Well-designed trials with larger sample sizes are needed to provide reliable evidence on the effectiveness of acupuncture for treating AD.

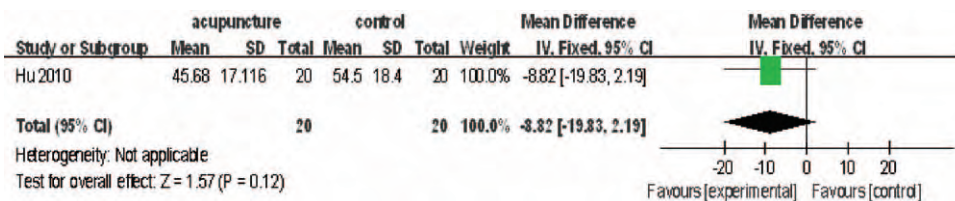


FIGURE 13. Forest plot of the effect of acupuncture versus no treatment on the ADL score. ADL = ability of daily living.

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