INPLASY PROTOCOL

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The authors claim no conflicts of interest.

Efficacy and safety of Chinese herbal medicine in the treatment of Alzheimer's disease: a systematic review and IPD meta-analysis

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Review question / Objective: **This review is intended to explore the efficacy and safety of Chinese Herbal Medicine in the treatment of Alzheimer's disease in comparison with conventional treatment, such as donepezil.**
Condition being studied: **Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of amyloid beta in the form of intracellular and extracellular plaques and tangles of nerve fibers, resulting in neurodegeneration and dementia. About 47 million people suffer from dementia over the world, and the number is expected to increase to 131 million by 2050. AD is the sixth leading cause of death in humans and the fifth leading cause of death in people over 65. Effective treatment for this disease is still limited. Although many new drugs have been developed successfully, phase iii clinical trials have failed to prove their efficacy. Chinese herbal medicine (CHM) in the treatment of AD have a wealth of experience. But the quality of its research, real curative effect and security is still lack of comprehensive evaluation.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 May 2020 and was last updated on 28 May 2020 (registration number INPLASY202050102).

INTRODUCTION

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METHODS

Search strategy: We search the following databases from their inception to 1 May 2020: China National Knowledge Infrastructure (CNKI), China Biological Medicine (CBM), Chinese Scientific Journals Database (VIP), Wanfang database, PubMed, EMBASE, and Cochrane Library. We search English and non-English articles for review, and collect additional references from review references and original research articles. We look for published and unpublished trials, contact researchers and pharmaceutical companies.

Participant or population: Cases were diagnosed with Alzheimer disease.

Intervention: Chinese herbal medicine or conventional treatment combined with Chinese herbal medicine.

Comparator: Conventional treatment, including donepezil and memantine.

Study designs to be included: We will include randomized controlled and double-blinded trials to assess the beneficial effects of the treatments.

Eligibility criteria: Inclusion criteria: (1) it was randomized, double-blinded, and placebo-controlled; (2) the design of the trial was either parallel or crossover; (3) if a crossover trial, it had a washout period greater than 1 week. (4) the enrolled patients were those diagnosed or suspected as Alzheimer disease; (5) the trial involved more than 1 month of treatment with Chinese herbal medicine; (6) main outcomes were measured with the most common neuropsychiatric scales used, the noncognitive portion of the Alzheimer Disease Assessment Scale (ADAS-noncog) or Neuropsychiatric Inventory (NPI). Besides, the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), Activities of Daily Living (ADL) scale are also took in consider; (7) functional outcomes were measured on a validated score separated by ADL and IADL domains. Functional measures that combined ADL and IADL domains were excluded. Exclusion criteria: (1) Using non-drug therapy, such as acupuncture, massage, etc.; (2) Intermittent treatment or treatment for less than 1 month; (3) Unclear diagnostic criteria; (4) Incomplete basic information; (5) Repeated publication of studies; (6) The outcome indicators do not include the main outcome indicators observed; (7) More than 20% of the data is lost or not processed.

Information sources: We search the following databases from their inception to 1 May 2020: China National Knowledge Infrastructure (CNKI), China Biological Medicine (CBM), Chinese Scientific Journals Database (VIP), Wanfang database, PubMed, EMBASE, and Cochrane Library. We search English and non-English articles for review, and collect additional references from review references and original research articles. We look for published and unpublished trials, contact original authors and pharmaceutical companies for further information of individual case.

Main outcome(s): Main outcomes were measured with the most common neuropsychiatric scales used, the noncognitive portion of the Alzheimer Disease Assessment Scale (ADAS-noncog) or Neuropsychiatric Inventory (NPI).

Besides, the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), Activities of Daily Living (ADL) scale are also took in consider.

Additional outcome(s): Alzheimer's disease cooperative study-activities of daily living (ADCS-ADL), instrumental activities of daily living (IADL), basic activity of daily living (BADL), progressive deterioration scale (PDS), adverse events.

Data management: Titles and abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer. After determining the number of trials finally included, contact the original authors of these studies and obtain data on individual cases with their support. Extracted information will include: random data, age of participants, pathological characteristics, interventions, durations of treatment and follow-up, and outcome measures. Two review authors will extract data independently, discrepancies will be identified and resolved through discussion (with a third author when necessary).

Quality assessment / Risk of bias analysis: Two review authors will independently assess the risk of bias in included studies by considering the following characteristics: Randomisation sequence generation: was the allocation sequence adequately generated? Treatment allocation concealment: was the allocated treatment adequately concealed from study participants and clinicians and other healthcare or research staff at the enrolment stage? Blinding: were the personnel assessing outcomes and analysing data sufficiently blinded to the intervention allocation throughout the trial? Completeness of outcome data: were participant exclusions, attrition and incomplete outcome data adequately addressed in the published report? Selective outcome reporting: is there evidence of selective outcome reporting and might this have affected the study results? Other sources of bias: was the trial apparently free of any other problems that could produce a high risk of bias? Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author when necessary. Cochrane risk of bias tool was used to evaluate the study quality. If we found evidence of heterogeneity, we reanalyzed the data to explore potential sources. We used funnel plots and the Kendall tau to evaluate potential publication bias.

Strategy of data synthesis: We will perform the statistical analysis on the data for each therapy by applying the SAS statistical software (version 9.2). Dichotomous data will be analyzed by using the odds ratio (OR) with 95% confidence interval (CI). Continuous variables will be analyzed by using the mean difference (MD) with 95% CI. Between-study heterogeneity will be valued using the χ^2 and the I^2 statistic was calculated. The heterogeneity will be expected statistically significant if the P-values were <0.1. Presence or absence of significant heterogeneity decides the option of random effects model or fixed effects model. Using the function metagen of the R-package meta (R version 2.15.3; R Foundation for Statistical Computing) to estimate integrated effect if there is substantial heterogeneity. The research will be weighted by the inverse-variance method. And result will be presented in forest plots.

Subgroup analysis: If the necessary data are available, subgroup analyses will be done for people with durations of treatment. For each outcome, we will use a logistic regression model to estimate the treatment effect of each type of Chinese herbal medicine separately if 10 or more patients were excluded.

Sensibility analysis: We will test for statistical homogeneity with the Mantel-Haenszel test using P<.10 to reject the null hypothesis that trials were homogeneous and could be combined.If we found evidence of heterogeneity, we will reanalyze the data to explore potential sources. We will use funnel plots and the Kendall tau to evaluate potential publication bias. Stratified and unstratified regression models will be fitted depending on the data in the analysis of IPD.

Language: We will not limit language being imposed on the search.

Country(ies) involved: We will not limit the country in which the overview being carried out.

Keywords: Alzheimer`s disease; dementia; Chinese herbal medicine; systematic review; IPD meta-analysis.

Contributions of each author:
Author 1 - Tian He - Author 1 drafted the manuscript.
Author 2 - Zhi Ma - The author provided statistical expertise.
Author 3 - Zheyi Wang - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Yuanfeng Zhang - The author read, provided feedback and approved the final manuscript.
Author 5 - Tao Lu - The author directed the research and revised the manuscript.