INPLASY PROTOCOL

To cite: Xu et al. Efficacy and Safety of Chinese Herbal Medicines Combined with Chemical Drugs for Alzheimer's Disease: A Systematic Review and Meta-Analysis. Inplasy protocol 202280007. doi: 10.37766/inplasy2022.8.0007

Received: 02 August 2022

Published: 02 August 2022

Corresponding author:
Zhe Zhang

zhe_zhang@hotmail.com

Author Affiliation:
Shandong University of Traditional Chinese Medicine.

Support: **TCM Bur. of Shandong Province.**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None declared.

Efficacy and Safety of Chinese Herbal Medicines Combined with Chemical Drugs for Alzheimer's Disease: A Systematic Review and Meta-Analysis

Xu, Li[1]; Chen, WJ[2]; Tian, CJ[3]; Zhang, Y[4]; Ma, Y[5]; Li, TH[6]; Zhang, Z[7]; Liu, HJ[8].

Review question / Objective: **It is a common practice to apply Chinese herbal medicine with chemical drugs like donepezil to treat Alzheimer's disease in China. Therefore, the aim of this meta-analysis of randomized controlled trials is to evaluate whether this combination is more effective and safer than chemical drugs applied alone.**

Information sources: **Literatures will be searched in China National Knowledge Infrastructure (CNKI) (http://www.cnki.net/), Wanfang Database (http://www.wanfangdata.com.cn), and the Chinese Scientific Journals Full-Text Database (VIP) (http://www.cqvip.com/) in Chinese, in the Japan Science and Technology Information Aggregator, Electronic (J-STAGE) in Japanese and English, and in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://apps.webofknowledge.com) in English.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 August 2022 and was last updated on 02 August 2022 (registration number INPLASY202280007).

INTRODUCTION

Review question / Objective: **It is a common practice to apply Chinese herbal medicine with chemical drugs like donepezil to treat Alzheimer's disease in China. Therefore, the aim of this meta-analysis of randomized controlled trials is to evaluate whether this combination is more effective and safer than chemical drugs applied alone.**

Condition being studied: **Alzheimer's disease (AD) is a progressive disease with symptoms that gradually worsen over a number of years. Although there is no cure**

for AD at present, five prescription drugs (donepezil, galantamine, rivastigmine, tacrine, and memantine) have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD, in addition to aducanumab, which has been recently approved by US FDA with controversies on June 7, 2021. Donepezil, galantamine, rivastigmine and tacrine are cholinesterase inhibitors; memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that exhibits low-to-moderate affinity. Cholinesterase inhibitors are associated with several adverse effects and so is memantine. In China and neighboring countries, AD has been treated with Chinese herb medicines (CHMs) for thousands of years. Over recent years, a number of randomized clinical trials have been carried out to evaluate the efficacy and safety of cholinesterase inhibitors and NMDA receptor antagonist in combination with CHMs with promising results. In the present study, we will systematically review previous publications relating to the combination of CHMs with cholinesterase inhibitors and NMDA receptor antagonists and perform a meta-analysis to evaluate the efficacy and safety of these combinations.

METHODS

Search strategy: RCTs that investigated the combination of CHMs and donepezil, galantamine, rivastigmine, tacrine, or memantine will by searched in the China National Knowledge Infrastructure (CNKI) (http://www.cnki.net/), Wanfang Database (http://www.wanfangdata.com.cn), and the Chinese Scientific Journals Full-Text Database (VIP) (http://www.cqvip.com/) in Chinese, in the Japan Science and Technology Information Aggregator, Electronic (J-STAGE) in Japanese and English, and in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://apps.webofknowledge.com) in English. All searches will be from database inception to January 2022. Our searches (in Chinese, Japanese, and English) involved the following terms: Alzheimer's disease, AD, dementia, amyloid beta (Aβ), Chinese herbal medicine, traditional Chinese medicine, Kampo, oriental medicine, traditional Japanese medicine, randomized controlled trial, RCT, integrated Chinese herbal medicine, integrated traditional Chinese and western medicine, donepezil, galantine, rivastigmine, tacrine, and memantine.

Participant or population: Patients with AD were diagnosed using established diagnosis standards, such as Diagnostic and Statistical Manual of Mental Disorders (DSM-III or DSM-IV), International Working Group (IWG)-2 criteria, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCD-ADRDA) criteria, and Chinese Classification of Mental Disorders (CCMD-3). There will be no limitation with regard to age or gender.

Intervention: The experimental group was treated with donepezil, galantamine, rivastigmine, tacrine or memantine combined with Chinese herbal medicines.

Comparator: The control group was only treated with donepezil, galantamine, rivastigmine, tacrine, or memantine, alone or in combination.

Study designs to be included: Randomized controlled trials (RCTs) will be included.

Eligibility criteria: Exclusion criteria: (1) AD patients had been treated with drugs other than donepezil, galantamine, rivastigmine, tacrine, memantine, and CHMs; or those that combined CHMs with acupuncture or other non-pharmacological therapies. (2) Duplicated publications.

Information sources: Literatures will be searched in China National Knowledge Infrastructure (CNKI) (http://www.cnki.net/), Wanfang Database (http://www.wanfangdata.com.cn), and the Chinese Scientific Journals Full-Text Database (VIP) (http://www.cqvip.com/) in Chinese, in the Japan Science and Technology Information Aggregator, Electronic (J-STAGE) in Japanese and English, and in PubMed (https://

www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://apps.webofknowledge.com) in English.

Main outcome(s): MMSE score.

Additional outcome(s): ADAS-Cog score and safety evaluation.

Data management: The weighted mean difference (WMD) will be used for MMSE score, and 95% confidence intervals (CIs) will be calculated. $P < 0.05$ is considered statistically significant. The weighted mean difference (WMD) will be used for ADAS-Cog score, risk ratio (RR) will be used for safety evaluation, and 95% confidence interval (CI) will be calculated. $P < 0.05$ is considered to be statistically significant.

Quality assessment / Risk of bias analysis: The Cochrane Collaboration's risk of bias assessment tool will be used to assess the methodological quality of each RCT included in the present study. This tool will be applied independently by two researchers. Item quality will be graded as low, high, or unclear risk.

Strategy of data synthesis: Data analysis will be performed using RevMan version 5.3 software. Homogeneity testing, involving $P \geq 0.1$ and $I^2 \leq 50\%$, is typically used to identify homogeneous trials that can be analyzed with a fixed-effect model. When $P < 0.1$ and $I^2 > 50\%$, trials are considered to be heterogeneous, and a random-effects model is traditionally used. However, in our analyses, the comparators and intervention methods are different; therefore, the random-effects model is more favorable.

Subgroup analysis: Subgroup analyses will be carried out to determine the sources of heterogeneity.

Sensitivity analysis: Set the sensitivity analysis conditions manually, identify the analyzed studies to be included/excluded in every condition manually, and tick/untick the box to see the changes in the forest plot and note them manually.

Language restriction: Literatures will be searche in Chinese, English and Japanese.

Country(ies) involved: China.

Keywords: Alzheimer's disease; Chinese herbal medicine; donepezil; rivastigmine; memantine; meta-analysis; randomized controlled trials.

Contributions of each author:
Author 1 - Li Xu.
Author 2 - Wenjun Chen.
Author 3 - Caijun Tian.
Author 4 - Yan Zhang.
Author 5 - Yan Ma.
Author 6 - Tianhao Li.
Author 7 - Zhe Zhang.
Author 8 - Hongjie Liu.