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Conflicts of interest:
None declared.

The Clinical Efficacy and Safety of Sixteen CPMs in Combination with Benzodiazepines/Non-Benzodiazepines for Chronic Adult Insomnia: A Multiple-Treatments Meta-Analysis

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Review question / Objective: **Chronic adult insomnia has become a common disease, affecting the health and quality of life of modern people, and is considered a universal sub-health condition. Chinese patent medicines (CPMs) combined with benzodiazepines/non-benzodiazepines (BZDs/N-BZDs) are often used in routine clinical practice; however, the available evidence on the relative effectiveness and safety of these joint interventions is still uncertain. Thus, a multiple-treatments meta-analysis (MTMA) was conducted with the aim of assessing the comparative efficacy and safety of sixteen CPMs combined with BZDs/N-BZDs regimens for treating chronic adult insomnia.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 March 2023 and was last updated on 06 March 2023 (registration number INPLASY202330020).

INTRODUCTION

Review question / Objective: **Chronic adult insomnia has become a common disease, affecting the health and quality of life of modern people, and is considered a universal sub-health condition. Chinese patent medicines (CPMs) combined with benzodiazepines/non-benzodiazepines (BZDs/N-BZDs) are often used in routine clinical practice; however, the available evidence on the relative effectiveness and safety of these joint interventions is still uncertain. Thus, a multiple-treatments meta-analysis (MTMA) was conducted with the aim of assessing the comparative**

efficacy and safety of sixteen CPMs combined with BZDs/N-BZDs regimens for treating chronic adult insomnia.

Condition being studied: Chronic insomnia, also known as "chronic insomnia disorder", is a common sleep disorder that affects an estimated 10%-30% of the adult population worldwide. The International Classification of Sleep Disorders, third edition (ICSD-3) and the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-5) describe chronic insomnia as difficulty in starting or maintaining sleep or waking up prematurely and having related daytime consequences despite sufficient sleep opportunities and sleep environment. Sleep difficulties must occur at least three times a week and last for at least three months . Chronic insomnia in adults is increasingly recognized as a major public health problem and is associated with a range of negative consequences, including decreased quality of life, increased medical care costs, reduced work efficiency, etc.
The primary treatments for chronic adult insomnia are cognitive and behavioral therapies and pharmacological therapies . Psychological and behavioral therapy, especially cognitive behavioral therapy (CBT-I) for insomnia, has been recommended as the first-line therapy for adult chronic insomnia by the American Academy of Sleep Medicine and the American College of Physicians . However, most patients with chronic insomnia cannot benefit from CBT-I treatment due to the lack of sleep therapists or other trained providers, cost constraints, lack of insurance coverage, and patient compliance issues . Therefore, drug therapy is still a popular choice for treating sleep disorders. Benzodiazepines and non-benzodiazepines are generally considered the first-line treatment for chronic insomnia in adults . However, long-term use of benzodiazepines has serious side effects, limiting its clinical use . For this reason, many physicians and patients actively seek effective drugs or alternative therapies to reduce adverse reactions and improve the sleep quality of patients.

In Asia and China, Chinese patent medicines (CPMs) have been used for centuries as a form of complementary and alternative medicine. In recent years, CPMs have become increasingly popular as an alternative to traditional Western pharmaceuticals for the treatment of chronic adult insomnia. Studies have reported the efficacy and safety of various CPMs combined with benzodiazepines (BZDs) and non-benzodiazepines (N-BZDs) in treating chronic adult insomnia. Nevertheless, the most effective combination of CPMs and BZDs/N-BZDs remains unclear in treating chronic adult insomnia, which may be difficult for clinicians in the medical therapy. Multiple-treatments meta-analysis (MTMA) is a statistical technique that allows for the integration of data from direct and indirect evidence to compare different treatments . Therefore, in this work, we adopted MTMA to identify the most effective combination of CPMs and BZDs/N-BZDs for the treatment of chronic adult insomnia, to provide additional understanding for future clinical practice.

METHODS

Search strategy: In this MTMA, we searched CINAHL, Embase, Chinese Biological Medicine Literature, China National Knowledge Infrastructure (CNKI), Technology Journal Database (VIP), Wanfang, PubMed, and Cochrane Library from their inception to February 1, 2023, with no language restrictions. At the same time, we supplemented the literature, studies, and ongoing RCTs with manual searches outside of electronic databases. We contacted pharmaceutical companies that produce and sell proprietary Chinese medicines for insomnia and asked for additional unpublished information on pre-marketing and post-marketing studies. We also contacted the research authors by email to supplement the incomplete report of the original paper or provide data for unpublished research, but most of them did not respond.

Participant or population: We included randomized controlled trials (RCTs)

comparing CPMs in combination with BZDs/N-BZDs with BZDs/N-BZDs monotherapy for the treatment of adults (≥18 years old and of both sexes, no restrictions on race, region, or nationality) with a primary diagnosis of chronic insomnia according to standard operationalized diagnostic criteria (ICSD-3,DSM-5, and ICD-10) (Vieta et al., 2016; Devries et al., 2021; Skodol et al., 2012; Outland et al.,2015). We included all treatment of insomnia CPMs approved by the regulatory agencies in China.

Intervention: CPMs in combination with BZDs/N-BZDs.

Comparator: BZDs/N-BZDs monotherapy.

Study designs to be included: We included randomized controlled trials (RCTs).

Eligibility criteria: Finally, we excluded Chinese herbal medicine and other traditional Chinese medicine non-drug treatments (emotional therapy, static breathing control, acupuncture, and moxibustion); repeated publications; and research with incomplete or incorrect data, research without one of the above outcome indicators, and cognitive behavioral therapy (CBT-I).

Information sources: In this MTMA, we searched CINAHL, Embase, Chinese Biological Medicine Literature, China National Knowledge Infrastructure (CNKI), Technology Journal Database (VIP), Wanfang, PubMed, and Cochrane Library from their inception to February 1, 2023, with no language restrictions.

Main outcome(s): Our primary outcomes were the total effective rate (determined as Cure+markedly effective+effective) and sleep quality (measured using the Pittsburgh Sleep Quality Index (PSQI)). Security outcome indicators included the incidence of somnolence, dry mouth, and dizziness. We recorded the results of all analyses as close to 4 weeks as possible. If there is no 4-week information, we use data between 2 and 8 weeks (giving priority to the time point closest to 4 weeks; if equidistant, we take the longer result). When data are referred to in multiple reports, the earliest published report is given priority.

Quality assessment / Risk of bias analysis: we evaluated the bias risk of these studies according to the Cochrane Intervention System Review Manual.

Strategy of data synthesis: EndNote was utilized to manage the retrieved trials. For the published research (i.e. duplicates), we only selected the report with the richest and most complete data. This study employed network meta-analysis to estimate the summary odds ratio (ORs) of dichotomous results and the standardized mean difference (SMD, Cohen's d) of continuous results. In a multiple-treatments meta-analysis, binomial likelihood was used for binary results, and normal likelihood of continuous results was used for continuous results. Then, a random-effects multiple-treatments meta-analysis model was used to comprehensively study the effect size. All MTMA were performed using R4.3.5 software for statistical data processing and investigation, while Bayesian inference was implemented with a Markov chain Monte Carlo model. To sort the processing of each result, we used R4.3.5 and Stata MP17 software to draw the cumulative probability sorting curve (SUCRA) and mean ranks. Additionally, clustering analysis was adopted for synthesizing and comparing interventions with two outcome indicators, aiming to acquire the best selection of two results (Watt et al.,2022; Watt et al., 2019). Moreover, we employed a comparison-adjusted funnel plot to assess the potential publication bias. Furthermore, we evaluated the bias risk of these studies according to the Cochrane Intervention System Review Manual.

Subgroup analysis: No.

Sensitivity analysis: No.

Language restriction: No.

Country(ies) involved: China.

Keywords: a multiple-treatments meta-analysis , Benodiazepines/non-benzodiazepines, Chinese patent medicines, Chronic adult Insomnia, Combined therapy, Chinese herbal medicine.

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