Acupuncture methods for insomnia in the elderly: protocol for a systematic review and network meta-analysis

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Protocol

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Abstract

Background: Insomnia remains one of the most common sleep disorders in the elderly, with high prevalence and substantial consequences for patients' general health. Despite that increasing clinical trials have indicated that acupuncture seems to be effective for insomnia in the elderly, comparative efficacy and safety of different acupuncture methods for elderly individuals with insomnia has been unclear. Therefore, this protocol outlined a plan to evaluate and rank the efficacy and safety of

various acupuncture approaches for insomnia in the elderly.

Methods: A systematic search of 8 bibliographic databases will be conducted from their inception to 31 October 2021, including Cochrane Library, MEDLINE (via PubMed), Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database, and Chinese Biomedical Literature Database (CBM). Randomized controlled trials investigating acupuncture methods for insomnia in the elderly, published in English or Chinese will be included. The primary outcome is sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI). Two reviewers will independently perform study selection, data extraction and risk assessment of bias. The quality of included literatures will be appraised using Cochrane risk-of-bias tool (ROB 2.0). ADDIS (Aggregate Data Drug Information System) V.1.16.8 will be used to conduct Bayesian network meta-analysis. The quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation System (GRADE).

Discussion: In this study, the results will provide credible evidence to assess the efficacy and safety of acupuncture therapies for elderly patients with insomnia, assisting patients, physicians and clinical research investigators to select the most appropriate acupuncture method.

Trial registration: The protocol has been registered at OSF (https://osf.io/3kjpq/) with a registration number DOI 10.17605/OSF.IO/3KJPQ.

Background

Insomnia is a common disease worldwide, which is one of the most common sleep disorders among the elderly(1–3). It has been shown that more than 50% of the elderly worldwide suffer from sleep disorders, of these, 20–40% suffer from insomnia(4). Women have a higher incidence of insomnia than men(5, 6). The main symptom of insomnia is difficulty in falling asleep or sleep maintenance disorder(7). However, long-term insomnia will not only increase the risk of depression and death in the elderly, but also is an independent risk factor for cardiovascular disease and diabetes(8–12). which seriously affects the quality of life of patients and causes greater psychological and economic burden to patients and their families, and insomnia has become a major public health problem(13–15).

Treatment of insomnia can be divided into pharmacological and non-pharmacological interventions(16). Benzodiazepine receptor agonists as pharmacological interventions have the most evidence for treating

insomnia, with serious side effects such as increased risks of falls and hip fractures, over-sedation, and confusion among the elderly(17–21). Therefore, several authors propose that non-pharmacological interventions should be considered as first-line treatment options for insomnia in the elderly(22). Among non-pharmacological interventions, cognitive behavioral therapy (CBT) has been recognized as a first-line treatment for insomnia(23). However,high costs and lack of professionals limit its availability(24). Consequently, Therefore, for the elderly, seeking for an effective, simple, safe treatment of insomnia appears to have great significance.

Acupuncture, as an important part of complementary and alternative therapies, has numerous advantages, such as wide indication, reliable curative effect, convenient operation, economic safety and has been widely accepted and applied worldwide(25). Acupoints on the meridians are stimulated by using disposable sterile acupuncture needles(26). A growing number of randomized controlled trials (RCT) have indicated that acupuncture could improve sleep quality, prolong sleep time, reduce the severity of insomnia among the elderly(27–29). Clinically, multiple acupuncture methods are available for insomnia in the elderly, such as manual acupuncture, electroacupuncture, auricular acupuncture and auricular acupressure. However, due to the diversity of acupuncture approach, determining the most effective acupuncture method is intractable, which makes clinicians confused about how to select the optimal acupuncture method for elderly individuals with insomnia.

Up to now, among appraising multiple competing interventions, network meta-analysis is considered as precisely effective approach, which can provide the rankings of distinctive acupuncture methods(30). Therefore, the objective of this systematic review and network meta-analysis is to generate a clinically useful evidence-based hierarchy for efficacy and safety of various acupuncture approaches for insomnia in the elderly.

Methods

The protocol was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement and the Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis(31, 32). Meanwhile, it has been registered with OSF with registration number DOI 10.17605/OSF.IO/3KJPQ.

Criteria for including studies in this review

Types of studies

RCTs reported in English or Chinese without any regional restrictions will be included. In case of a randomized crossover trial, we will include only the first-phase results. Animal experimental studies, quasi-RCTs, case report, expert experience, conference article and duplicated publications will be excluded.

Types of participants

Elderly patients (≥60 years) who have been diagnosed with insomnia, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)(33), the International Classification of Sleep Disorders (ICSD)(34), the Chinese Classification of Mental Disorders (CCMD)(35) or other accepted diagnostic standards will be included, regardless of gender, race, economic status, ethnicity or the severity of insomnia. Patients with drug allergies or other serious medical conditions such as cancer, liver disease, or kidney disease should be excluded.

Types of interventions

Acupuncture will be defined in this review as acupoint-based therapy, irrespective of needling techniques and stimulation method, including manual acupuncture, electro-acupuncture, auricular acupuncture, auricular acupressure, acupressure, acupoint application, moxibustion, catgut embedding, transcutaneous electrical acupoint stimulation, acupoint injection and others. Interventions without stimulating the acupoint will be ruled out.

Types of control groups

Treatments in the control groups will include sham acupuncture, placebo, pharmacotherapy, no treatment, waiting list, lifestyle modifications or usual care. Studies that compared the distinctive types of acupoint-based therapy will be included.

Types of outcome measures

Studies that report one or more of the below-mentioned outcomes will be included. Otherwise, the trial will be excluded.

Primary outcomes

The review will mainly aim to investigate various acupuncture methods in the improvement of the sleep quality. Therefore, the change of the sleep quality will be measured by the Pittsburgh Sleep Quality Index (PSQI).

Secondary outcomes

The secondary outcomes will include: (I) sleep onset latency (in min) and sleep efficiency (%). Sleep efficiency is defined as the total sleep time, divided by the total recording time; (II) Insomnia Severity Index; (III) Quality of Life Scale (SF-36); and (IV) adverse events measured by the Treatment Emergent Symptom Scale (TESS) or the incidence of adverse events.

Search methods for identification of studies

Electronics searches

The following eight electronic databases including Cochrane Library, MEDLINE (via PubMed), Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database, and Chinese Biomedical Literature Database (CBM) will be searched from their inception to October 2021. Gray literature should also be searched. All randomized controlled trials reported in English or Chinese will be included. In addition, qualified research conference abstracts, reference lists of manuscripts and trial registry database (WHO International Clinical Trials Registry Platform and Clinical Trials. gov) will be retrieved to identify additional studies. The search strategy consists of Medical Subject Headings (MeSH) and free-text terms, such as insomnia OR insomnia disorder AND aged OR elderly AND acupuncture OR acupuncture therapy OR manual acupuncture OR electroacupuncture AND randomized. The proposed detailed search strategy for PubMed is presented in *Table 1*.

Table 1 search strategy in PubMed database

No.	Search items
#1	Acupuncture. Mesh.
#2	Acupuncture therapy. ti. ab.
#3	Acupuncture points. ti. ab.
#4	Manual acupuncture. ti. ab.
#5	Electroacupuncture. ti. ab.
#6	Auricular acupuncture. ti. ab.
#7	Auricular acupressure. ab.
#8	Scalp acupuncture. ti. ab.
#9	Body acupuncture. ti. ab.
#10	1 or 2-9
#11	Randomized controlled trial. Mesh.
#12	Controlled clinical trial. ti. ab.
#13	Randomized. ti. ab.
#14	Randomly. ti. ab.
#15	Trial. ti. ab.
#16	11 or 12-15
#17	Aged. Mesh.
#18	Elderly. ti. ab.
#19	Geriatric. ti. ab.
#20	Old aged. ti. ab.
#21	Aging. ti. ab.
#22	17 or 18-21
#23	Insomnia. Mesh.
#24	Sleeplessness. ti. ab.
#25	Insomnia Disorder. ti. ab.
#26	Insomnias. ti. ab.
#27	Sleep Initiation and Maintenance Disorders. ti. ab.
#28	Disorders of Initiating and Maintaining Sleep. ti. ab.
#29	Sleep Initiation Dysfunction. ti. ab.

#30	Dysfunction, Sleep Initiation. ti. ab.
#31	Dysfunctions, Sleep Initiation. ti.ab.
#32	Sleep Initiation Dysfunctions. ti.ab.
#33	23 or 24-32
#33	#10 and #16 and #22 and #33

Selection of studies

According to the exclusion and inclusion criteria, studies imported into Endnote X9 software after exclusion of duplicated articles will be independently screened by two authors (WD and FZ). Full texts of the relevant study will be reviewed to confirm the final inclusion of studies. For unclear study, the author will be contacted for details to determine whether this literature would be included. Any disagreement on articles will be resolved through discussion or rechecked by a third reviewer (TG) until consensus will be reached. The outline of the study selection procedure will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart *figure 1*.

Data extraction and management

Based on a self-designed data acquisition form, 2 reviewers (RW and XH) will independently extract the following information from eligible studies: (I) general information (country, publication year, first author, study type, number of centers, sample size and study design); (II) patient information (age, gender, ethnicity, diagnosis, insomnia intensity before treatment); (III) intervention and comparator (types of acupuncture, selection of acupuncture points and treatment frequency /session/duration, follow-up period,); (IV) outcomes (data and time points for each measurement, types of outcomes); (V) adverse events; For missing data or clarification for unclear information, an effort will be made to contact the corresponding author to obtain detailed information. In case of ambiguity and divergence, it will be resolved through discussion or the involvement of the third reviewer (CW). Finally, the data will be transferred to RevMan software.

Quality assessment

The quality of the included studies will be evaluated using the Cochrane Risk of Bias tool(36) by two independent reviewers (XC and HZ) according to the below-mentioned six aspects: selection bias (random sequence generation and allocation concealment), performance bias (blinding of investigators and participants), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective reporting bias and other bias. Each trial will be assessed and graded into three levels: “low”, “high”, or “unclear” risk of bias. Any discrepancy will be arbitrated by a third reviewer (TG).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system(37) will be applied to evaluate the strength of the evidence by 2 independent reviewers (WD and FZ). Evidence quality will be judged as“high-quality”, “moderate quality”,“low quality”, or “very low quality” in terms of the risk of bias, inconsistency, indirectness, imprecision and publication bias. If any dispute occurs, the third reviewer (CW) will act as a referee.

Assessment of similarity and consistency

In order to acquire a credible and valid result, the assessment of similarity and consistency will be carried out. Due to the difficulty in determining similarity through statistical analysis, the assessment will be performed based on clinical and methodological characteristics, including study designs (blinding and risk of bias), participant characteristics (age and severity of insomnia) and interventions (duration/types/sessions/intensity of treatment and needling techniques). Z-test will be

conducted to check the consistency, and the p value will be calculated to confirm whether there are inconsistencies during the comparison of direct and indirect evidence. If P value is greater than 0.05, the comparison of direct and indirect evidence will be regarded as consistency; on the contrary, the comparison will be considered as inconsistency.

Statistical analysis

Pairwise meta-analysis

The Pairwise Meta-analysis will be carried out only when there are similarities among the included studies. The software RevMan version 5.4 (Review Manager, The Cochrane Collaboration, 2020) will be applied to conduct Pairwise meta-analysis to compare treatments with direct evidence. The effect sizes will be calculated employing post-treatment values. The Q test and I^2 value will be used to evaluate the heterogeneity among each pairwise comparison. A random effect model will be employed If the I^2 value is more than 50%; instead, a fixed effect model will be adopted. The mean difference (MD) or standardized mean difference (SMD) with their 95% CIs will be used as the effect size, meanwhile, the categorical variables will be expressed as relative risk (RR) or odds ratio (OR) alongside their 95% CIs.

Network meta-analysis

The network meta-analysis will be conducted using Aggregate Data Drug Information System (ADDIS) V.1.16.8 software (Drugis, Groningen, NL)(38, 39). A random effects model will be applied to perform a Bayesian network meta-analysis to integrate the direct and indirect evidence with the Markov Chain Monte Carlo method. Four chains will be applied as parameters for simulation. There are 50,000 simulation iterations in each chain, and the researcher will discard the first 20,000 simulations to remove the effect of the initial value. Visual inspection of the trace plots will be used to appraise model convergence and taking the Gelman-Rubin statistic into consideration. In the meantime, the network diagram will be generated using STATA V.15.0 software (Stata Corp, College Station, TX, USA) and compare each outcome. In light of each specific outcome, the effects of different acupuncture

approaches will be sequenced to display the most effective surface under the cumulative ranking curve and mean ranks with their 95% CI.

Assessment of heterogeneity

The Q test and I^2 statistics will be applied to calculate statistical heterogeneity among studies. In the light of the Cochrane Handbook(40), The I^2 value is rated as the following four levels: little or no heterogeneity (0%–40%), moderate heterogeneity (30%–60%), substantial heterogeneity (50%–90%) and considerable heterogeneity (75%–100%). To explore potential sources of heterogeneity from the clinical and methodological perspective, subgroup or sensitivity analysis will be performed.

Meta-regression, subgroup analysis and sensitivity analysis

A random effect network meta-regression model will used to perform a network meta-regression to explore sources of heterogeneity. In case of obtaining sufficient evidence, subgroup analysis will be conducted based on the severity of insomnia, the various comparators and various types of acupuncture approaches. To assess the robustness of the results, sensitivity analysis will be performed by means of eliminating not only effects of trials with small sample size, but also the studies rated as high risk of bias based on accounting of methodological quality. Only in this way can we ensure the accuracy and depth of inferences from the results.

Assessment of publication bias

When more than 10 studies are included, the software RevMan version 5.4 will be used to generate funnel plots to observe potential reporting bias. In case of the asymmetrical funnel plot, the causes of asymmetry will be analyzed by means of Egger's regression test.

Ethics and informed consents

No ethics approval is required since this systematic review and network meta-analysis do not collect confidential personal data and do not perform interventions in treating patients. Besides, the findings will be disseminated through a peer-reviewed journal.

Discussion

It is reported that various acupuncture methods have been proved to be effective for insomnia in the elderly. However, due to high variability in selecting these acupuncture approaches for clinicians, the Bayesian network meta-analysis will be applied to compare not only the efficacy of available acupuncture therapies, but also rank the probability of acupuncture methods regarding each domain of insomnia in the elderly. To the best of our knowledge, the protocol will be the first systemic review (SR) and NMA to examine acupuncture methods for c elderly individuals with insomnia. We sincerely hope that the findings could assist patients, physicians and clinical research investigators to making more informed treatment decisions. Admittedly, it is worth noting that there may be some limitations existing in this

review. On the one hand, only Chinese and English studies were retrieved because of language barrier, which may result in bias. On the other hand, our proposed methodology will only place emphasis on acupuncture approaches, whereas less attention will be paid to the analysis of specific details regarding acupuncture application or acupuncture points selection. The results will be disseminated through peer-reviewed journals or conference reports. The protocol will be updated quickly when supplements are required.

Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

RCT: Randomized controlled trial

MD: Mean difference

CI: Confidence interval.

SMD: Standardized mean difference

RR: Relative risk

OR: Odds ratio

Declarations

Authors' Contributions

D-WT and FZ will identify eligible studies after reading titles and abstracts and read the full texts to perform further selection. Several studies from different opinions will be determined by the G-TT. Data will be extracted from the original reports by RW and H-XM. The assessment of the risk of bias will be carried out by C-XL and Z-HC. Any discrepancies will be resolved by discussion with a third CW. D-WT and FZ will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. D-WT conceived the review protocol and drafted the manuscript. CW will monitor each procedure of the review. All authors have read and approved the publication of the protocol.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

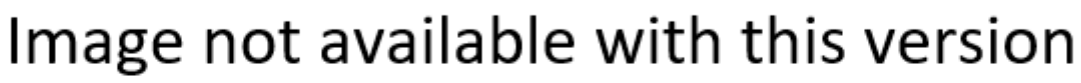

Figure 1

The PRISMA flow diagram of the study selection process.

Supplementary Files

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- PRISMAP2015Checklist.docx