INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Acupoint stimulation-related therapies for the management of insomnia disorder: A systematic review and meta-analysis protocol

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Review question / Objective: **This meta-analysis will not only summarize all the ASRTs reported in clinical trials but also evaluate their effect on objective and subjective indices related to insomnia disorder. We will also perform subgroup analyses to identify possible confounders of the effects of ASRTs including treatment characteristics (e.g., acupoint selection, stimulation method, treatment duration) and patient characteristics (e.g., age, comorbidities, severity, and course of insomnia disorder). In doing so, we will endeavor to answer questions about whether efficacy varies according to the aspect of sleep targeted and whether the effects differ according to different modes of acupoint stimulation, acupoints applied, or specific types of insomnia, thereby providing the evidence to develop specific recommendations on prescribing ASRTs for insomnia disorder.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 December 2021 and was last updated on 31 December 2021 (registration number INPLASY2021120137).

INTRODUCTION

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whether efficacy varies according to the aspect of sleep targeted and whether the effects differ according to different modes of acupoint stimulation, acupoints applied, or specific types of insomnia, thereby providing the evidence to develop specific recommendations on prescribing ASRTs for insomnia disorder.

Rationale: Insomnia is extremely common across the world, impacting the individual, families, and society. Insomnia affects quality of life and is associated with an increased risk of cardiovascular disease, psychological morbidity, diabetes, and Alzheimer's disease, and it may aggravate co-morbidities and suicidality. Many common pharmacotherapies for insomnia are associated with tolerance and dependence, and cognitive behavioral therapy for insomnia, while effective, is often not available and is costly. Any intervention to treat insomnia disorder would have a massive healthcare and societal impact.

Condition being studied: Acupoint stimulation-related therapies (ASRTs), which are based on the traditional Chinese medicine (TCM) theory, have been widely used in the Chinese healthcare system for thousands of years, and they are increasingly being used by people with insomnia disorder. A large number of clinical trials have now shown that various ASRTs have positive effects on multiple sleep outcomes including sleep efficiency, sleep onset latency, the number of awakening events at night, sleep duration, and daytime functioning. However, existing reviews of these data are often limited to a single therapeutic method and/or a certain type of insomnia disorder, thus limiting the generalizability of the conclusions and hampering efforts to develop recommendations for the use of ASRTs for people with insomnia. Here, using the PRISMA-P framework, we present a systematic review and meta-analysis protocol to evaluate all the ASRTs reported in clinical trials and their effect on objective and subjective indices related to insomnia disorder. To our best knowledge, this will be the first systematic review to evaluate the efficacy and safety of all clinically available acupoint stimulation strategies for the treatment of insomnia disorder with or without comorbid physical or neuropsychiatric diseases.

METHODS

Search strategy: Three main subject heading domains will be combined with the AND operator: one to designate the intervention (different forms of ASRT), the second to designate the clinical condition (insomnia disorder), and the third to designate the study type (RCT). In order to retrieve all potentially relevant studies, a combination of medical subject headings (MeSH) and free-text words related to ASRTs, insomnia disorder, and RCTs will be used in the English databases, and the Chinese search strategy will be adjusted for Chinese medical terms and their use in the literature. The search strategy will be developed in collaboration with a health sciences librarian and reviewed by several experts in the fields of psychology, psychiatry, complementary and alternative medicine, and TCM. Keywords and subject terms will be customized for each database any necessary adjustments made prior to running the search. The retrieval will be conducted with no restrictions regarding the year but limited to English and Chinese. If discrepancies occur, consensus will be reached through consultation.

Participant or population: Participants with insomnia disorder explicitly documented by standardized measures such as the Pittsburgh Sleep Quality Index (PSQI) and Athens Insomnia Scale (ASI); objective measures in a sleep laboratory such as actigraphy, electroencephalography, or polysomnography; reports/diaries kept by participants, partners, other informants, or nursing staff; insomnia disorder diagnosed according to at least one of the standardized international or domestic diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Sleep Disorders (ICSD), International Classification of Diseases (ICD), Chinese Classification of Mental Disorders (CCMD),

or other well-recognized classifications or equivalent standardized diagnostic criteria; or with a complaint of insomnia symptoms or insomnia disorder will be included regardless of age, gender, nationality, ethnicity, occupation, education, and the type, cause, severity, and duration of insomnia. Participants with insomnia symptoms or insomnia disorder seen in clinical practice are likely to have co-morbid conditions, so we will also include participants with comorbid physical or neuropsychiatric diseases.

Intervention: Interventions will be restricted to ASRTs. To clarify the efficacy and safety of ASRTs for the treatment of insomnia disorder, trials evaluating all acupoint stimulation strategies (acupoints used according to TCM nomenclature) to treat or manage insomnia disorder/symptoms will be included, including but not restricted to acupressure, magnetic acupressure, manual acupuncture, electroacupuncture, laser acupuncture, auricular acupoint therapy, scalp acupuncture, warm acupuncture, acupoint injection, intradermal acupuncture, acupoint catgut embedding, transcutaneous electrical acupoint stimulation, moxibustion, cupping therapy, massage, or their combinations regardless of stimulation method, acupoint selection, setting, provider, frequency, number of sessions, session duration, or total period of intervention.

Comparator: Control interventions will be no treatment, waiting lists, standard care/ usual care, placebo or sham intervention, or other active treatment (e.g., conventional medications, psychotherapy, exercise therapy, or CBT). The following comparisons will be considered: (1) ASRT alone versus no treatment or waiting lists; (2) ASRT alone versus placebo or sham intervention alone; (3) ASRT alone versus other active treatment alone; (4) ASRT plus other active treatment versus other active treatment alone; and (5) ASRT plus other active treatment versus placebo or sham intervention plus other active treatment.We will exclude trials comparing only different methods of ASRT, different groups of acupoints, or different treatment doses with the same intervention.

Study designs to be included: As randomized controlled trials (RCTs) represent the highest level of evidence for unbiased information, only full-text articles of peer-reviewed and published RCTs, including all relevant parallel-group RCTs including the first phase of crossover trials and cluster-randomized trials, will be considered eligible for this review.

Eligibility criteria: Eligibility criteria will be established according to the review objectives and the participants, intervention, comparison, outcome, and study design (PICOS) approach.

Information sources: Studies will be identified through a literature search from inception to the search date in the following English and Chinese electronic databases: 1) PubMed; 2) Embase; 3) Cochrane Library; 4) Web of Science; 5) Chinese National Knowledge Infrastructure (CNKI); and 6) Wanfang Database. Additionally, the reference lists of the included studies and relevant systematic reviews will be manually searched to identify any other eligible publications missed by electronic searching. We will not include grey literature due to high risk of bias without being peer-reviewed. If discrepancies occur, consensus will be reached through consultation. The search will be repeated prior to the publication of the review in an aim to include any potential eligible study that might have been published after the initial search.

Main outcome(s): Frequency of improvement in sleep quality (proportion of participants who had significant improvements in insomnia disorder or satisfaction with sleep quality), measured as a dichotomous outcome of improvement based on parameters such as prolonged total sleep duration, improved sleep efficiency or sleep quality, or symptom relief. Since improvement in sleep quality is subjective, for the purposes of this review it can be variably defined, with or without the use of a sleep score or other sleep

parameter (e.g., sleep onset latency, total sleep duration, total wake time, wake after sleep onset).

Additional outcome(s): (1) Sleep parameters, as measured by a sleep diary or other objective measurements such as actigraphy, electroencephalography, or polysomnography; (i) sleep onset latency; (ii) total sleep duration; (iii) total awake time; (iv) wake after sleep onset (WASO); (v) nocturnal and early morning wakening (defined by the trialist); and (vi) sleep efficiency (ratio of time asleep to time in bed). (2) Scales or indices of sleep quality, as measured by standardized scales related to sleep, such as Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Athens Insomnia Scale (ASI), or the Leeds Sleep Evaluation Questionnaire (LSEQ). (3) Daytime dysfunction, as measured by performance tasks tests or self-reported using a standardized measure such as the Stanford Sleepiness Scale and Epworth Sleepiness Scale. (4) Health-related quality of life (HRQoL), as measured as a continuous variable using any validated global assessment of functioning scales such as the World Health Organization Quality of Life, Short Form-36 (SF-36), or other well-recognized HRQoL scales. (5) Adverse events (AEs); incidence of AEs reported in the studies or measured using validated scales such as Treatment Emergent Symptom Scale (TESS) or Side Effects Rating Scale (SERS).

Data management: An electronic standardized data extraction form will be prepared in Microsoft Excel before data extraction according to the inclusion criteria. Calibration will also be performed prior to starting data extraction and management to ensure high consistency and accuracy of extractions between reviewers. For studies fulfilling the eligibility criteria, four reviewers will independently extract the data from the selected studies, which will include the study details (article title, first author, publication year, publication source, publication language, country, setting), study design (eligibility criteria, recruitment method, randomization method, allocation concealment method, blinding method, time points, follow-up period), notes (financial source, competing interests), participant characteristics (number of arms, sample size, proportion of gender, mean age, diagnostic criteria, baseline insomnia disorder condition, with or without physical or neuropsychiatric diseases), intervention and comparison characteristics (type, acupoint selection, provider, frequency, number of sessions, session duration, total period in the intervention; type of comparison, details of comparison), outcome data (methods of outcome assessment, primary outcomes, secondary outcomes, dates of treatment withdrawal, reasons for treatment withdrawal, the improved Jadad scale score, the Cochrane Collaboration's RoB), and conclusions (key findings of the study).

Quality assessment / Risk of bias analysis: The methodological quality of each eligible study will be assessed by two independent reviewers according to the Cochrane Collaboration's RoB version 2.0 tool, which is the revised Cochrane Collaboration's RoB tool for randomized trials. The version is structured into five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain includes several signaling questions which elicit information relevant to an assessment of RoB. Based on the answers of all signaling questions in one domain, the domain can be rated as low risk of bias, some concerns, or high risk of bias. Finally, the overall risk of bias judgement can be graded as low risk of bias, some concerns, or high risk of bias considering the risk of bias judgement in five domains. While the Cochrane RoB assessment tool represents a qualitative tool, the improved Jadad scale will be used as a quantitative method to assess the methodological quality of the included studies. The improved Jadad scale rates studies according to (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel or outcome assessment, and (4) reporting of

the number of dropouts and reasons for withdrawal. Each trial will be scored on a scale from 0 to 7, with 0–3 indicating low quality, 4–5 moderate quality, and 6–7 high quality, respectively. Any discrepancy in the assessment of methodological quality of included studies between reviewers will be arbitrated by discussion to reach a consensus.

Strategy of data synthesis: Eligible studies and results will be qualitatively summarized. If more than three studies evaluate similar treatments and outcomes, a meta-analysis will be conducted. Meta-analysis of RCTs with available data will be performed using RevMan v5.4 software to estimate the treatment effect. For meta-analyses, we will include studies that score equal to or greater than 4 on the improved Jadad scale (0-7), since these studies can be regarded as having sufficient similarity in clinical characteristics and high methodological quality. We will adopt the Mantel-Haenszel random-effects model for all meta-analysis due to the broad spectrum of intervention components in the included studies. The pooled estimates of the standard mean difference (SMD) with 95% confidence intervals (CIs) will be calculated for continuous outcomes, while for dichotomous outcomes, data will be analyzed using the risk ratio (RR) with 95% CIs. Throughout the analyses, two-sided tests will be used and a P-value.

Subgroup analysis: Where sufficient data are available in the included RCTs, we will carry out subgroup analyses and multiple meta-regressions for efficacy and safety outcomes to investigate possible sources of heterogeneity including in the following characteristics: publication year, publication language, setting, sample size, gender, age, nationality, ethnicity, occupation, education, diagnostic criteria, type, cause, severity or duration of insomnia disorder, with or without co-morbidity, acupoint selection, format, frequency, number of sessions, session duration, total period of intervention, type of comparison, time-point of outcomes, duration of follow-up, and the methodological quality of the selected RCTs.

Sensitivity analysis: Sensitivity analyses will be performed for efficacy and safety outcomes to explore the robustness and reliability of the review conclusions where feasible. Meta-analysis will be repeated by excluding each related study with small sample sizes, a high risk of bias, selected statistical model, and incomplete results one at a time and re-evaluating the effect size. If the results are inconsistent, they will be discussed and caution will be taken when drawing conclusions.

Language: English and Chinese.

Country(ies) involved: China.

Keywords: Acupoint stimulation related therapies, efficacy, insomnia disorder, meta-analysis, nursing, randomized controlled trial, safety, systematic review, protocol.

Dissemination plans: The results will have implications for clinical practice and further research, so the findings will be disseminated as a peer-reviewed publication and/or conference presentation.

Contributions of each author:

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