INPLASY PROTOCOL

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Support: **NSFC.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Pharmacological and non-pharmacological treatments for insomnia: protocol for a systematic review and network meta-analysis

Wang, C[1]; Deng, C[2]; Han, Q[3]; Zhu, D[4]; Li, Z[5]; Li, J[6].

Review question / Objective: **Although non-pharmacological therapies (ie., cognitive behavioral therapy) are recommended as first-line treatments for insomnia, they don't widely implement in practice owing to costly or time-consuming. As a result, pharmacotherapy remains to be commonly prescribed for patients with the sleep disorder. Pharmacotherapy for insomnia consists of different types of drugs. Few studies focused on comprehensively evaluating all available drugs for insomnia. Our review aims to compare efficacy and safety of pharmacological and non-pharmacological treatments by synthesizing direct evidence and indirect evidence to help clinicians and patients make informed decisions for insomnia.**
Condition being studied: **Insomnia is defined as difficulty falling asleep, difficulty maintaining sleep, or waking up too early , which might occur despite adequate opportunities for sleep, and is associated with cardiovascular diseases, hypertension, depression, daytime cognitive impairment, and mortality. It caused substantial economic and societal burdens.Therefore, our network meta-analysis will be conducted to compare all available drugs in patients with primary insomnia using data from randomized, controlled trials.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 June 2021 and was last updated on 10 June 2021 (registration number INPLASY202160031).

INTRODUCTION

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disorder. Pharmacotherapy for insomnia consists of different types of drugs. Few studies focused on comprehensively evaluating all available drugs for insomnia. Our review aims to compare efficacy and safety of pharmacological and non-pharmacological treatments by synthesizing direct evidence and indirect evidence to help clinicians and patients make informed decisions for insomnia.

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METHODS

Participant or population: Adults aged over 18 or older will be included.They were diagnosed through any standardised diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R, DSM-IV, DSM-IV TR), the International Classification of Diseases (ICD-10) or the International Classification of Sleep Disorders (ICSD-2/3). We will exclude patients with insomnia due to psychiatric or physical comorbidity. We also exclude health subjects. The age of elderly patients is measured at least 65 years old, or the mean age should be over 70 years old. There will be no limits in terms of gender or ethnicity.

Intervention: All available pharmacological interventions using to treat insomnia will be included. Drug dose should be approved by FDA. Herbal preparations (e.g. Valerian, chamomile, hops, kava-kava, passionflower, or traditional chinese medicines), homeopathy, nutrients or non-pharmacological interventions will be excluded. We also will exclude drugs that were withdrawn from the market or drugs that have been discontinued researching or developing. non-pharmacological therapies includes lifestyle and dietary interventions, psychotherapy interventions, complementary and alternative interventions.

Comparator: Any active drugs and/or Placebo.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: We will include randomized controlled trials comparing active agents with other active drugs and/or placebo as monotherapy or non-pharmacological therapies in the treatment of primary insomnia. Cluster-randomized trials, controlled trials and quasi-randomized trials will be excluded.Any discrepancies were settled by discussion.

Information sources: We will comprehensively search three electronic databases including PubMed, Ovid EMBASE, the Cochrane Central Register of Controlled Trials, to identify eligible trials without the restriction of language or publication date.

Main outcome(s): Quality of sleep or satisfaction with sleep as assessed by any validated self rated scale e.g. the Pittsburgh Sleep Quality Index or the Insomnia Severity Index. 2.Daytime functioning as measured by any validated self-rating scale, for example the 36-item short-form, the Stanford Sleepiness Scale or the Epworth Sleepiness Scale.3.risk of falls or fractures.

Additional outcome(s): The following outcomes will be secondary outcomes, as appropriate:1.subjective sleep onset latency (sSOL); 2.sujective total sleep time (sTST);3.subjective Wake time after sleep onset (sWASO); 4. discontinuation due to adverse events.

Quality assessment / Risk of bias analysis: The quality of the trials included was assessed in accordance with the Cochrane

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Collaboration's risk of bias tool as described in the Cochrane Collaboration Handbook. Two investigators independently determined risks bias to be low, unclear, or high based on the presence or absence of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and "other source of bias" (other bias). Subsequently, we divided study quality into three rates from low risk to high risk on the basis of the method described by the article (Cipriani et al., 2018). Discrepancies were resolved via discussion.

Strategy of data synthesis: We will perform pairwise meta-analyses for primary and secondary outcomes using Stata 14.3 software.We will estimate summary RRs for dichotomous outcomes and MDs or SMDs for continuous outcomes. A random-effects model was used to derive pooled estimates across studies, because it takes between-study differences into account. Between-study heterogeneity was quantitatively assessed using the I^2 statistic, with I^2 of >50% indicating high heterogeneity and <50% indicating low heterogeneity. We will then perform the network meta-analysis (NMA) for primary outcomes using the GeMTC package of R and JAGS (Just Another Gibbs Sampler) software in combination on basis of Bayesian theory.We will calculate each model with n. adapt = 5000 and n. iter = 20000. Convergence of models will be examined by visual inspection of three chains and after considering the Brooks–Gelman–Rubin diagnostic. We also will use that model to draw forrest plots and examine consistency, heterogeneity and node-splitting tests. Loop inconsistency will be assessed in every closed triangular or quadratic loop via the "loopspecific" approach, wherein a 95% CI excluding zero suggests that the loop is inconsistent. The "design-by-treatment" interaction model will be used to assess global consistency in networks. The surface under the cumulative ranking curve (SUCRA) and the mean ranks will be calculated to rank the treatments for each outcome. The comparison-adjusted funnel plots will be generated to investigate whether there will be study-small effects in the intervention network.The Loop inconsistency, the global consistency, the SUCRA and The comparison-adjusted funnel plots will be generated using Stata 14.3 software. We will grade the evidence of the network meta-analysis for primary outcomes based on the recommendations of CINeMA. CINeMA considers six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence.

Subgroup analysis: The following several subgroup analyses will be performed, if possible: i. elderly patients versus younger patients; ii. sponsoring of pharmaceutical industry; iii.single-center study versus multicenter study; iv. outpatients versus inpatients.

Sensitivity analysis: We will plan the following sensitivity analyses on the primary outcomes, if possible: a) exclusion of cross-over trials; b) exclusion of open-label and single-blind studies; c) exclusion of studies with high-risk bias.

Country(ies) involved: China.

Keywords: pharmacological, non-pharmacological, insomnia.

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