

# Therapeutic efficacy of zolpidem combined with cognitive-behavioral therapy on primary insomnia

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## Abstract

**Background:** In this study, we intend to assess the efficacy of zolpidem combined with cognitive-behavioral therapy (CBT) for patients with primary insomnia (PI).

**Methods:** A predefined search strategy will be used to search for associated literature from inception to the July 1, 2019: PubMed, EMBASE, Cochrane Library, Scopus, Web of Science, Google Scholar, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure with no language limitation. In addition, we will also retrieve reference lists of included studies and relevant reviews, as well as the conference proceedings. All randomized controlled trials related to the zolpidem and CBT for PI will be included. Two authors will perform study selection, data collection, and study quality, respectively. We will also apply RevMan 5.3 software for statistical analysis.

**Results:** This study will provide a comprehensive overview of the available evidence of the benefits and safety of zolpidem and CBT for PI. Primary outcomes are sleep quality and severity of sleep disorders. Secondary outcomes consist of sleep-onset latency, total sleep duration, sleep efficiency, and frequency and adverse events.

**Conclusion:** The results of this study will inform clinical and policy decisions regarding the benefits and harm of zolpidem and CBT for patients with PI.

**PROSPERO registration number:** PROSPERO CRD42019142796.

**Abbreviations:** CBT = cognitive behavioral therapy, PI = primary insomnia, RCTs = randomized controlled trials.

**Keywords:** cognitive-behavioral therapy, efficacy, primary insomnia, randomized controlled trial, safety, zolpidem

## 1. Introduction

Primary insomnia (PI) is a very serious sleep disturbance.<sup>[1,2]</sup> This disorder comprises of acute, subchronic and persistent insomnia according to the duration of PI.<sup>[3–6]</sup> Such condition is often secondary to the multiple factors, including headache, anxiety, depression, cardio-cerebrovascular diseases, or psychiatric issues.<sup>[8–13]</sup> It has been estimated that about 10% to 20% of the population worldwide suffer from poor sleep quality,<sup>[14]</sup> and

approximately 50% of those population experience more than 1 month.<sup>[14]</sup> The incidence of PI is more likely to affect female than male individuals.<sup>[15,16]</sup>

A variety of managements can be used to treat PI, such as eszopiclone, doxepin, acupuncture, physical exercise, zolpidem, and cognitive-behavioral therapy (CBT).<sup>[17–24]</sup> However, there is still limited efficacy of those single therapies. Thus, it is very important to apply combined treatments for the treatment of patients with PI, such as combination of zolpidem and CBT.<sup>[25–28]</sup> However, the efficacy is still inconclusive. Therefore, this study aims to assess the efficacy and safety of zolpidem and CBT for the treatment of patients with PI systematically.

## 2. Methods

### 2.1. Inclusion criteria for study selection

**2.1.1. Study types.** All randomized controlled trials (RCTs) of zolpidem and CBT for the management of PI will be included without language or publication status limitation.

**2.1.2. Participant types.** All participants with diagnosed PI will be included without limitation of gender, age, and ethnic background.

**2.1.3. Intervention types.** The therapy used in the experimental group includes combination of zolpidem and CBT.

The control group can be any interventions, except any forms of zolpidem and CBT.

**2.1.4. Outcome types.** Primary outcomes are sleep quality and severity of sleep disorders, as assessed by Pittsburgh sleep quality index or other relevant scales.

YS and BL contributed equally to this study.

No ethical approval is needed. Findings will be disseminated at a peer-reviewed journal or conference proceedings.

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**Table 1**  
**Search strategy of PubMed database.**

| Number | Search terms                  |
|--------|-------------------------------|
| 1      | Sleep                         |
| 2      | Sleeplessness                 |
| 3      | Insomnia                      |
| 4      | Wakeful                       |
| 5      | Early awakening               |
| 6      | Somnambul                     |
| 7      | Somnipathy                    |
| 8      | Sleep initiation dysfunction  |
| 9      | Or 1–8                        |
| 10     | Non-pharmacological treatment |
| 11     | Cognitive                     |
| 12     | Behavioural therapy           |
| 13     | Intervention                  |
| 14     | Treatment                     |
| 15     | Or 10–14                      |
| 16     | Zolpidem                      |
| 17     | Edluar                        |
| 18     | Zolpimist                     |
| 19     | Ambien CR                     |
| 20     | Ambien                        |
| 21     | Intermezzo                    |
| 22     | Or 16–21                      |
| 23     | Randomized controlled trial   |
| 24     | Controlled trial              |
| 25     | Clinical trial                |
| 26     | Placebo                       |
| 27     | Sham                          |
| 28     | Randomly                      |
| 29     | Randomized                    |
| 30     | Trial                         |
| 31     | Study                         |
| 32     | Or 23–31                      |
| 33     | 9 and 15 and 22 and 32        |

Secondary outcomes consist of sleep-onset latency, total sleep duration, sleep efficiency, and frequency and adverse events.

## 2.2. Data sources and search methods

Eight databases of PubMed, EMBASE, Cochrane Library, Scopus, Web of Science, Google Scholar, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure will be comprehensively searched from inception to the July 1, 2019 with no language limitation for the RCTs regarding zolpidem and CBT for PI. The detailed strategy for PubMed is presented in Table 1. Any modified search strategies will be applied for other electronic databases. Relevant conference proceedings, reference list of eligible studies, and relevant reviews will also be searched.

## 2.3. Data collection

**2.3.1. Study selection.** Two authors will independently carry out study selection according to the previous designed eligibility criteria. All literature records will be scanned and all obvious disqualified studies will be excluded through the titles and abstracts. The final full text will be read to judge whether they meet all inclusion criteria. Any inconsistencies between 2 authors will be solved by another author via discussion. The process of study selection will be presented in the flowchart.

**2.3.2. Data extraction.** Two authors will independently extract the data via a standardized data form. Any disagreements will be checked and arbitrated by a third author through discussion. This sheet includes basic general information (authors, titles, year of publication, age, etc), disease duration, study setting, study methods, sample size, treatment details, comparators, outcome details, adverse events, and conflicts of interest.

**2.3.3. Dealing with missing data.** We will correspond with the primary author to inquire the missing or insufficient or unclear data. If we can not obtain those data, only available data will be analyzed and its potential impact will be discussed.

## 2.4. Assessment of risk of bias

Two authors will independently assess the risk of bias using the Cochrane Risk of Bias Tool. Any discrepancies between 2 authors will be solved by a third author via discussion. This tool consists of 7 aspects and each one will be categorized into 3 levels of high, unclear, or low risk of bias.

## 2.5. Measures of treatment effect

For continuous data, a standard mean difference and 95% confidence interval will for calculation. For dichotomous outcomes, a rate ratio and 95% confidence interval will be expressed for treatment effect measurement.

## 2.6. Assessment of heterogeneity

We will use  $I^2$  test to identify heterogeneity among included studies. If a value of  $I^2$  less than 50%, it will be regarded as acceptable. Otherwise, if an  $I^2$  value exceeds 50%, it will be considered as substantial. At the same time, subgroup analysis will be performed to explore the potential causes of heterogeneity.

## 2.7. Data synthesis and analysis

RevMan 5.3 software will be employed to compute the data pooling when a meta-analysis is provided. If  $I^2 \leq 50\%$ , a fixed-effects model will be used for data pooling. If  $I^2 > 50\%$ , a random-effects model will be used to perform data pooling, and subgroup analysis will be conducted. If data are limited or significant heterogeneous to pool after subgroup analysis, we will summarize findings in a narrative review.

## 2.8. Subgroup analysis

According to the different treatments, controls, and outcomes, subgroup analysis will be carried out to explore the resources of heterogeneity if eligible studies are sufficient.

## 2.9. Sensitivity analysis

We will conduct sensitivity analysis to identify the robustness of outcome results by removing low-quality studies.

## 2.10. Reporting bias

We will perform the Funnel plot<sup>[29]</sup> and Egger regression test<sup>[30]</sup> to identify any possible reporting bias if more than 10 trials entered.

### 3. Discussion

PI is one of the most frequency disorders among general population. A variety of managements are used for the treatment of PI. Zolpidem and CBT have been used in various clinical conditions, including PI. To the best of our knowledge, the efficacy and safety of zolpidem and CBT have not been clearly elucidated systematically yet. Therefore, it is very necessary to carry out a high-quality study systematically, and the process of this study will be presented in the diagram. It is expected that this study can provide rigorous and objective evidences of the efficacy and safety of zolpidem and CBT for patients with PI.

#### Author contributions

**Conceptualization:** Ying Song, Bing Liang.

**Data curation:** Ying Song, Bing Liang.

**Formal analysis:** Bing Liang.

**Funding acquisition:** Ying Song.

**Investigation:** Ying Song.

**Methodology:** Bing Liang.

**Project administration:** Ying Song.

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**Supervision:** Ying Song.

**Validation:** Ying Song, Bing Liang.

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**Writing – original draft:** Ying Song, Bing Liang.

**Writing – review and editing:** Ying Song, Bing Liang.

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