Review Article

Efficacy and safety of Zolpidem in the treatment of insomnia disorder for one month: a meta-analysis of a randomized controlled trial

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Article history:
Received 19 June 2021
Received in revised form
30 August 2021
Accepted 7 September 2021
Available online 20 September 2021

Keywords:
Insomnia
Zolpidem
Placebo
RCT

1. Introduction

Insomnia is becoming the concern of health problems. An early cross-sectional survey of the insomnia epidemic in 10 countries around the world found that 24% of people reported poor sleep, of which 45.4% of the respondents in China experienced varying degrees of insomnia in the past month [1]. In addition, studies have reported that about 23.2% of adults in the United States suffer from insomnia [2]. Currently, insomnia disorder is one of the most common sleep disorders and one of the common mental illnesses. The prevalence of insomnia disorder is about 10.8%—15.1% [3]. Patients with insomnia often suffer from sleep disturbances. Most patients with insomnia often suffer from daytime dysfunction, cognitive decline, emotional problems, etc., which bring serious burdens to patients and their families, and even social medical care and the global economy.

Methods of treating insomnia disorder include cognitive behavioral therapy, drug therapy and physical therapy. Early drug treatments were mainly benzodiazepines, but due to their causes of cognitive decline, falls, impaired psycho-motor speed, sleep structure changes, drug dependence, and rebound insomnia [4—8], they were gradually being replaced by non-benzodiazepines. At present, the more commonly used non-benzodiazepine drugs in clinical are zopiclone, eszopiclone, zolpidem and zaleplon. Among them, zolpidem is used more. Zolpidem is a short-acting non-benzodiazepine hypnotic, belonging to the class of imidazopyridines. Used for lack of sleep, transient insomnia, chronic insomnia. Although there are reports that approved doses of Zolpidem (10 mg for adults and 5 mg for the elderly) are consistently effective in reducing sleep
latency (SL) and increasing total sleep time (TST) in patients with insomnia, and it can also effectively improve the quality of sleep [9,10]. However, clinically, its efficacy and safety are still worried by users. Moreover, there is currently a lack of meta-analysis on the efficacy and safety of zolpidem in the treatment of insomnia after 1 month or even longer.

In order to evaluate the efficacy and safety of zolpidem in the treatment of adult insomnia disorder, we conducted a systematic review and meta-analysis of standard randomized placebo-controlled trials.

2. Materials and methods

2.1. Search strategy and inclusion criteria

We searched PubMed, EMBASE, MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials and web of science from the beginning to May 13, 2021. The search terms are (“insomnia” OR “insomniac” OR “sleepless” OR “sleep”) AND (“Zolpidem” OR “SL 80.0750” OR “Zolpi Lich” OR “Zolpidem Tartrate” OR “Zolpidem Hemitartrate” OR “Zolpimist” OR “Ambien” OR “Stilnoct” OR “Stilnox”) AND (“Randomized controlled trial” OR “randomized” OR “random” OR “randomly” OR “RCT”). In addition, we also searched the ClinicalTrials.gov trials register to obtain the original data of other relevant trials and some documents that met the standards.

All included studies meet the following criteria: (1) People aged 18 and above; (2) According to Diagnostic and Statistical Manual of Mental Disorders (DSM) [11–13] or International Classification of Sleep Disorders (ICSD) [14,15] or International Classification of Diseases (ICD) [16,17] diagnostic system diagnosed as primary insomnia or met the diagnosis of primary insomnia; (3) zolpidem as a monotherapy and a randomized controlled trial with placebo; (4) English literature; (5) The duration of zolpidem intervention is 1 month. Publications that do not have full text or data, overlaps or repetitions are excluded, and studies on other diseases that accompany insomnia are also excluded.

2.2. Data extraction and quality assessment

Two reviewers independently assessed whether the study met the inclusion requirements according to the Cochrane Reviewer Handbook [18]. When there was a disagreement, two reviewers discussed with the third reviewer to decide whether the article should be adopted. The extracted information as follows: (1) Information about the selected candidates; (2) Related information on intervention measures (dose for each group); (3) Research characteristics (diagnostic system, research design). According to the Cochrane Handbook for Systematic Reviews of Interventions for bias assessment [19], the ratings of the included trials are divided into “high”, “low”, and “unclear”.

2.3. Outcome indicators and data analysis

The primary efficacy outcomes were the change in TST from baseline and the change in SL from baseline. The secondary outcome were the change in wake-time after sleep onset (WASO) from baseline and the change in sleep quality assessed by visual analog scales (VAS) from baseline. Safety assessment was mainly the adverse reactions that occur during the intervention process. If we observed heterogeneity (I²>50%) in this meta-analysis, a random effects model would be used. P value < 0.05 indicated statistical significance. All analyses were performed using Stata 16.

3. Results

3.1. Characteristics of included studies

Through searching PubMed, EMBASE, MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials and web of science, 1334 related citations were obtained. In addition, 28 studies with results were obtained by searching the ClinicalTrials.gov trials register. According to our inclusion and exclusion criteria, we finally determined 6 randomized controlled trials [20–25] that met zolpidem monotherapy and were placebo-controlled, with a total of 1068 participants. The characteristics of the included studies ware shown in Table 1. The flow chart was shown in Fig. 1. Four of the trials gave 10 mg zolpidem to patients <65 years old (non-elderly), one trial gave 6.25 mg zolpidem to women >55 years old and men >65 years old (elderly) patients, and the other gave 59–85 years old of zolpidem. 5 mg of zolpidem in female patients.

3.2. Bias risk assessment of included studies

According to Cochrane’s risk of bias assessment criteria, 4 studies were high quality and 2 studies were unclear. Four of the six studies described methods of random sequence generation and allocation concealment. The research quality evaluation was shown in Table 2.

3.3. Primary outcome analysis

In all included studies [20–25], zolpidem was compared with placebo in terms of total sleep time relative to baseline. A total of 973 patients completed the collection of TST data. Overall, compared with placebo, zolpidem treatment of patients with insomnia disorder had a more significant increase in TST (p = 0.000), which was statistically significant (Fig. 2). When performing subgroup analysis, we found that the change in TST of non-elderly patients was not statistically significant (p = 0.105). In the elderly group of zolpidem for one month, the increase in TST was more significant than that in the placebo group (p = 0.000). In addition, there were 5 studies in this study that compared the sleep latency from baseline. A total of 974 patients completed the sleep latency statistics. Compared with placebo, zolpidem was more significantly related to the decrease in SL after one month of treatment (p = 0.000) (Fig. 3). A subgroup analysis showed that there was no significant difference between SL and placebo after zolpidem treatment in the non-elderly group. The change of SL in the elderly group showed that the reduction was more obvious after zolpidem treatment.

3.4. Secondary outcome analysis

Compared with placebo, the amount of change in the secondary outcome WASO after zolpidem treatment from the baseline value was not statistically significant (p = 0.106) (Fig. 4). The same subgroup analysis of the secondary indicators found that the WASO changes in the non-elderly group after zolpidem treatment were not significantly different from placebo.

In addition, we also analyzed the change in sleep quality assessed by VAS from baseline and found that the sleep quality of patients taking zolpidem improved more significantly than that of the placebo group (p = 0.016) (Fig. 5).

3.5. Adverse events

In this study, five studies reported adverse reactions, but one of these five studies only briefly described them. Therefore, the
A comparison of adverse reactions was only carried out in the remaining four items [21,23–25]. Compared with placebo, common adverse events in the adult group included Headache, Nasopharyngitis, Dizziness, Fatigue, Dyspepsia, Nausea, Abdominal pain upper, etc. (Table 3), but these adverse events were not significantly different between zolpidem and placebo groups. Common adverse events in the elderly include Headache, Somnolence, Dizziness, Myalgia, Upper resp infection, Nausea, etc. There was no significant difference in adverse events between zolpidem and placebo.

### 4. Discussion

In clinical practice, many medical workers use zolpidem to treat insomnia disorder or symptoms of insomnia. Therefore, it is necessary to comprehensively analyze the effectiveness and safety of zolpidem. This study showed that zolpidem was related to the improvement of TST, SL and sleep quality, and had no significant statistical significance with the change of WASO. Regardless of the non-elderly subgroup or the elderly subgroup, there was no

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**Table 1**

**Characteristics of included studies.**

<table>
<thead>
<tr>
<th>NO.</th>
<th>1st Author (year)</th>
<th>Sample size (zolpidem/Placebo)</th>
<th>Age, y (range)</th>
<th>Design</th>
<th>Diagnostic system</th>
<th>Dose of zolpidem</th>
<th>Duration of treatment</th>
<th>Major sleep outcome measures</th>
<th>TST Change from baseline</th>
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<td>1</td>
<td>Allain (2001) [20]</td>
<td>124/121</td>
<td>25–64</td>
<td>RCT</td>
<td>DSM-IV</td>
<td>10 mg</td>
<td>4w</td>
<td>Sleep diary</td>
<td>74.6 ± 77.7</td>
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<td></td>
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<td></td>
<td>18–64</td>
<td></td>
<td>DSM-5</td>
<td>10 mg</td>
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<td>52.7 ± 50.3</td>
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<td>2</td>
<td>Dauvilliers (2020) [21]</td>
<td>60/60</td>
<td>25–64</td>
<td>RCT</td>
<td>DSM-IV</td>
<td>10 mg</td>
<td>4w</td>
<td>Sleep Diaries</td>
<td>69.2 ± 74.9</td>
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<td></td>
<td></td>
<td>DSM-5</td>
<td>10 mg</td>
<td></td>
<td>Nightcap</td>
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<tr>
<td>3</td>
<td>Jacobs (2004) [22]</td>
<td>15/15</td>
<td>25–64</td>
<td>RCT</td>
<td>DSM-IV</td>
<td>10 mg</td>
<td>4w</td>
<td>Sleep Diaries</td>
<td>70.0 ± 64.9</td>
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<td></td>
<td>DSM-IV</td>
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<td>Nightcap</td>
<td>51.8 ± 69.3</td>
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<td></td>
<td>DSM-IV</td>
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<tr>
<td>4</td>
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<td>Only female 59–85</td>
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<td>DSM III-R</td>
<td>5 mg</td>
<td>4w</td>
<td>Morning Questionnaire</td>
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<tr>
<td>5</td>
<td>Monti (1994) [24]</td>
<td>8/8</td>
<td>20–85</td>
<td>RCT</td>
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<td>4w</td>
<td>PSG</td>
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<td></td>
<td>DSM-IV</td>
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<td>Sleep Diaries</td>
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<tr>
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<td>Female ≥ 55</td>
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**Fig. 1.** Flow diagram of the included studies.
significantly different in the occurrence of adverse events after one month of zolpidem and placebo treatment.

Earlier studies showed that compared with placebo, after short-term treatment with Zolpidem, the TST, SL and sleep quality of patients with insomnia were significantly improved [26–31]. This was consistent with the findings of this study. However, McCall et al. found that the increase in subjective total sleep time and the decrease in sleep latency in the placebo group were clinically significant [32]. In addition, a meta-analysis found that after non-benzodiazepine hypnotic drugs and placebo treated adult insomnia, the polysomnography and subjective sleep latency of the two groups were significantly reduced, and the drug group changed more than the placebo group [33]. This meant that zolpidem was equally effective in treating insomnia for one month, and the drug group changed more than the placebo group [33]. This meant that zolpidem was equally effective in treating insomnia for one month, and the drug group changed more than the placebo group [33]. This meant that zolpidem was equally effective in treating insomnia for one month, and the drug group changed more than the placebo group [33]. This meant that zolpidem was equally effective in treating insomnia for one month, and the drug group changed more than the placebo group [33]. This meant that zolpidem was equally effective in treating insomnia for one month, and the drug group changed more than the placebo group [33]. However, some studies had found that after zolpidem treatment, there was no difference between WASO and objective wake-up time during sleep (WTDS) and other objective indicators of sleep maintenance [29]. Another study found that compared with placebo, the improvement of WASO after one week of zolpidem treatment was statistically significant, while after two weeks of treatment, the difference between the two groups was not statistically significant [31]. And this study found that there was no significant difference in the improvement of WASO between the two groups.

In the subgroup analysis, we observed that the TST and SL change values of the non-elderly group were not statistically different between the zolpidem and placebo groups. However, in this study by Nowell et al., it was found that there was a statistically significant difference in the improvement of TST and SL in adults after receiving zolpidem treatment [35]. It might be in contrast to the fact that we only compared the included studies (except for the Monti et al. study, which only had objective indicators [24]), but did not compare objective indicators. Of course, it could not be ruled out that the effect of zolpidem in the treatment of adult insomnia patients is not as obvious as the difference between the elderly group and the improvement of TST and SL. We need more data to verify it in the future.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of Outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
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<tr>
<td>Jacobs (2004)</td>
<td>Low</td>
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<tr>
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<td>Low</td>
<td>Low</td>
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<tr>
<td>Monti (1994)</td>
<td>Low</td>
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<tr>
<td>Rosenberg (2019)</td>
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</table>

**Fig. 2.** Change in TST from baseline of zolpidem vs. placebo.
Fig. 3. Change in SL from baseline of zolpidem vs. placebo.

Fig. 4. Change in WASO from baseline of zolpidem vs. placebo.

Fig. 5. Change in sleep quality assessed by VAS from baseline of zolpidem vs. placebo.
Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline indicated that when clinicians use zolpidem as a treatment for adult sleep onset and sleep maintenance insomnia, there was less certainty about treatment outcome and appropriateness [36]. Although there were differences in the outcome of the non-elderly group, compared with baseline, the TST of the zolpidem group increased and the SL decreased. Overall, this meta-analysis showed that zolpidem treatment of patients with insomnia disorder could increase their TST and reduce SL, and the improvement in sleep maintenance remained to be determined.

In terms of adverse events, our study found no significant difference between zolpidem and placebo. Nevertheless, Headache, Nasopharyngitis, Dizziness, Fatigue, Dyspepsia, Nausea, Abdominal pain upper, etc. were also more common in adults after receiving zolpidem treatment. The more common adverse events in the elderly include Headache, Somnolence, Dizziness, Myalgia, Upper resp infection, and Nausea. Both the elderly and non-elderly people should be alert to the adverse reactions after the use of zolpidem, to avoid the occurrence of safety accidents due to adverse reactions such as dizziness, fatigue, fatigue, and drowsiness. Because, there were researches reported that the use of zolpidem significantly increased the risk of injury [37–39]. As a short-term FDA-approved drug for the treatment of insomnia disorder, zolpidem can effectively improve TST and SL in patients with insomnia. The specific use plan should be carried out in accordance with the standards approved by the FDA, paying attention to the difference in the blood concentration of zolpidem between men and women. Some studies have shown that zolpidem can reduce slow-wave sleep [40,41]. In addition, studies have shown that zolpidem can also depress rapid eye movement (REM) sleep [42]. Therefore, in the long-term use of zolpidem to treat insomnia, it is also necessary to consider its impact on sleep structure.

Our meta-analysis had many advantages. Firstly, all the studies included in this study are high-quality and low-risk studies after Cochrane’s risk of bias assessment, and the remaining two are unclear. Secondly, this study evaluated TST, SL, WASO, and sleep quality, and compared it with the conclusions of zolpidem that improved TST, SL, WASO and sleep quality reported by most previous studies. In addition, this study focused on evaluating the efficacy and safety of zolpidem in the treatment of patients with insomnia for one month, and provides a reference for the clinical use of zolpidem to treat insomnia for a longer period of time.

There were some limitations in this study. First of all, we only analyzed and compared subjective indicators, but did not analyze objective indicators. When we use zolpidem to treat insomnia disorders for a long time, we should consider its impact on sleep structure, especially slow-wave sleep. Furthermore, the number of studies we included in the analysis is small, and the total number of subjects is also small, so we need to further expand the sample size for analysis. Third, we had not been able to obtain the most original data of all studies, only the aggregated data, so we couldn't conduct statistical heterogeneity surveys of certain outcomes. Nonetheless, these shortcomings will not negate the efficacy of zolpidem in the treatment of insomnia as shown by the original research.

5. Conclusion

According to the results of our meta-analysis, zolpidem is an effective and safe therapy option to treat insomnia disorder for one month. However, when using zolpidem to treat insomnia, its effect...
on sleep structure should be considered. In the future, it is necessary to further pass large-scale clinical trials to compare the effectiveness and safety of zolpidem in the treatment of insomnia from both subjective and objective indicators and evaluate its effect on sleep structure.

Author contribution

Tiang Xing: performed search, Wrote original draft preparation, prepared tables and figure. Yixian Cai: performed search, conducted statistical analysis and prepared tables and figures. Zhijin Hong: performed search, Supervision.

Acknowledgments

We thank Prof. Jiayang Pan for his support with technical issues. And we also thank for the financial support by National Natural Science Foundation of China (grant numbers: 81871036).

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.09.005.

References