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Original Article

Eszopiclone for the treatment of primary insomnia: a systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials

Liang Liang [a, 1], Yabing Huang [b, 1], Rong Xu [c], Yanyan Wei [a], Ling Xiao [a], Gaohua Wang [a, *]

[a] Department of Psychiatry, Renmin Hospital of Wuhan University, Hubei Zhang Road (formerly Ziyang Road), Wuchang District No. 99, Jiefang Road 238, Wuhan, Hubei province, China
[b] Department of Pathology, Renmin Hospital of Wuhan University, Hubei Zhang Road (formerly Ziyang Road), Wuchang District No. 99, Jiefang Road 238, Wuhan, Hubei province, China
[c] Department of Medical Oncology, People's Hospital of Xinjiang Uygur, Urumqi, China

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ABSTRACT

Study objective: In this study, we performed a systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials to evaluate the efficacy and safety of eszopiclone for the treatment of primary insomnia.
Methods: We searched MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials and PubMed from inception to June 2018. Additionally, we searched the ClinicalTrials.gov trials register for other relevant trials. According to participants, intervention, comparison, outcome (PICO) criteria, studies were included that focused on: adults diagnosed with primary insomnia, aged 18–65 and > 65 years; eszopiclone for the treatment of primary insomnia; comparison were made between eszopiclone and placebo; as well as primary outcomes, secondary outcomes, and adverse effects.
Results: A total of six randomized trials involving 2809 patients with primary insomnia were included in our analysis. Our analysis suggested that eszopiclone was associated with significant improvements in subjective sleep latency, wake after sleep onset, number of awakenings, total sleep time at one week, two weeks, one month, three months and six months. Meanwhile, eszopiclone was associated with increased quality of sleep, ability to function, daytime alertness and sense of physical well-being at one week, one month, three months and six months. Dizziness and unpleasant taste were the most common adverse effects in elderly subgroup. Alternately, non-elderly patients may be more prone to adverse effects such as infection, pharyngitis, somnolence, unpleasant taste and dry mouth.
Conclusion: This meta-analysis showed that eszopiclone is an effective and safe therapy option for patients with primary insomnia, especially in elderly patients. However, due to the high clinical heterogeneity in some outcomes, further standardized preparation, large-scale and rigorously designed trials are needed.

1. Introduction

Insomnia is a common problem that affects approximately 9–15% of the general population worldwide [1]. Both psychological and pharmacological treatments have proven efficacy for chronic insomnia. Recent clinical guidelines recommend some pharmacological treatment options for insomnia, mainly including benzodiazepines (BZD), non-benzodiazepines or 'Z'-drugs and certain antidepressants [2,3]. Although the short-term efficacy of benzodiazepines (BZD) and non-benzodiazepines has been demonstrated in a large number of randomized controlled trials, they have a high chance of producing side effects, such as dry mouth (44%), dizziness (18%), fatigue (11%) and lethargy (5%) [4].

Eszopiclone is a non-benzodiazepine hypnotic agent of the cyclopyrrolone family. It is recently approved for the treatment of insomnia in the United States and Japan [5,6]. Recently, however,

Abbreviations: CI, Confidence intervals; BZD, benzodiazepines; SMD, standardized mean differences; MD, mean difference; RR, risk ratio; TSO, time to sleep onset; TST, total sleep time; SQ, quality of sleep; WASO, wake after sleep onset; SL, sleep latency; IVRS, interactive voice response system; ISI, Insomnia Severity Index; MQ, morning questionnaire; PSG, Polysomnography.

* Corresponding author.
E-mail address: wgh6402@163.com (G. Wang).

[1] Liang Liang and Yabing Huang are equally contributed to this work.

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the US Food and Drug Administration (FDA) has issued a warning regarding the risk of next-day impaired activities requiring mental alertness and revised recommended starting dose at 1 mg. The selectivity of cyclopyrrolones presents greater benefits compared to benzodiazepines, as the former sustains the hypnotic effect while producing significant anxiolytic and/or muscle relaxation effects [7]. Previous studies have showed that eszopiclone is efficacious in reducing sleep latency and improving sleep efficiency in a model of transient insomnia and in a six-month study of chronic insomnia [8,9]. To our knowledge, there have been many randomized trials, but no systematic review or meta-analysis has been performed to summarize the results of current studies on overall efficacy and safety of eszopiclone for treatment of primary insomnia.

To assess the efficacy and safety of Eszopiclone for the treatment of primary insomnia, we conducted a systematic review and meta-analysis of all available randomised treatment trials.

2. Methods

2.1. Literature search and selection criteria

We searched MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials and PubMed from inception to June 2018, using the grouped terms ("insomnia" OR "insomniac" OR "sleepless" OR "sleep") and ("eszopiclone" OR "zopiclone" OR "cyclopyrrolone"). Additionally, we searched the ClinicalTrials.gov trials register for other relevant trials. No language restrictions were applied. For this meta-analysis, we followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) in reporting this systematic review [10].

Inclusions criteria of the trials were as follows: randomized controlled trials (RCTs) were chosen; patients suffering from primary insomnia; comparisons were made between eszopiclone and placebo; and reporting data of subjective measures in both eszopiclone and placebo groups. We excluded trials of: uncontrolled, non-randomised or quasi-randomised nature; when data were still unavailable after attempting to contact the authors; and when two studies with overlapping populations or duplicated data. We incorporated all randomized, controlled trials that investigated the efficacy and safety of eszopiclone for the treatment of primary insomnia. We excluded a Japanese treatment trial in adults because individual patient data were not available [11]. Furthermore we excluded trials that examined the efficacy of eszopiclone for any entities other than primary insomnia (ie, healthy subjects, mood disorders and insomnia with other comorbid diseases). According to participants, intervention, comparison, outcome (PICO) criteria [12], inclusions criteria of the trials were as follows: patients suffering from primary insomnia, as diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (DSM) [13,14], International Classification of Diseases [15], or International Classification of Sleep Disorders [16]. Eszopiclone for the treatment of primary insomnia (<65, 3 mg; >65, 2 mg). Comparisons were made between eszopiclone and placebo, and reporting data of subjective measures in both eszopiclone and placebo groups for primary outcomes, secondary outcomes, and adverse effects.

Two independent authors conducted the search and selected relevant publications independently. When meeting disagreements, final selection of articles was discussed by the two authors.

2.2. Data extraction and quality assessment

Data were extracted independently by two authors. For each selected study, the extracted information as followed: (1) patients' characteristics (age and sex); (2) study characteristics (diagnostic system, study design and study settings); and (3) information on interventions (doses and durations of drugs given to each group). Study quality was assessed by the Cochrane Collaboration's risk-of-bias method, rating as 'adequate', 'inadequate' or 'unclear' in each domain [17].

2.3. Outcomes and statistical analysis

The primary outcome was subjective sleep latency (SL). The secondary outcomes included other subjective parameters and next-day function. Subjective parameters included subjective wake after sleep onset (WASO), subjective number of awakenings (Awakenings), subjective total sleep time (TST), and subjective quality of sleep (SQ). Next-day function included ability to function, daytime alertness and sense of physical well-being. Adverse events were also compared between each group. Comparisons of eszopiclone and placebo for all sleep and daytime measures were performed on ranked data over the double blind period using an analysis of variance (ANOVA) model with treatment and site as fixed effects. The outcomes all trials reported at one week, two weeks, one month, three and six months are presented. Secondary outcomes except SQ, Ability to function, Daytime alertness and Sense of physical well-being were combined using mean differences (MD). Dichotomous outcomes were combined using risk ratios (RRs). Since baselines values are balanced between groups, efficacy was evaluated by end points data on each outcomes in this meta-analysis [18]. Heterogeneity was predefined as I^2>50%. A random-effect model was used if heterogeneity was observed in this meta-analysis. We collected the data at each time point which was based either on intention-to-treat analysis or available case analysis. A two-sided P value of less than 0.05 was considered statistically significant if not specifically stated. All analyses were done with the Stata software version 13.0 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Overall summary of included studies

Through a full search of databases and manually search, totally 1206 relevant citations were identified initially. Six randomized, placebo-controlled trials of the efficacy of eszopiclone were selected based on our inclusion and exclusion criteria [19–24] (Table 1). A total of 2809 patients with primary insomnia, based on DMS-IV-TR criteria, were included in this analysis. The flow diagram was shown in Fig. 1. The study durations varied from one week to six months. All trials used parallel design. Three trials administered 3 mg to patients aged <65 years (nonelderly) and three trials administered 2 mg to those ≥ 65 years (elderly).

3.2. Risk of bias in included studies

All studies were of high methodological quality according to the Cochrane Risk of Bias Criteria. All trials had adequate sequence generation, allocation concealment, and blinding of outcome assessors. All studies disclosed the involvement of industry sponsorship. The results of the quality assessment of the studies, according to the GRADE checklist, are shown in Table 5.

3.3. Primary outcome analysis

Five trials yielded data on SL in the eszopiclone group compared with placebo group with a total of 2501 completed patients 19, 20, 22–24. Eszopiclone was associated with reduced SL at one week, two weeks, one month, three months, six months compared with placebo (Table 2 and Fig. 2).

Table 1
Characteristics of included studies.

No.	1st Author (year)	Mean age, y (range)/% female	Diagnostic system	Design	Sample size (Treatment/ Control)	Eszopiclone treatment	Major sleep outcome measures	Source of participants	Inclusion criteria	SL (Baseline)		P value	Assessment time points	Run-in period	Intention-to-treat	Risk of bias
										Eszopiclone (2 mg/3 mg)	Placebo					
1	Krystal (2003) [19]	44.3 (21–69)/ 63.2%	DSM IV, primary insomnia	Double-blind, 2-parallel arms (3 mg; PBO)	788 (593/195)	Dose:3 mg Duration:six months	IVRS	Out-patient	TST<6.5 h per night SL > 30 min >1 month	90.6 (79.6)	96.1 (94.7)	0.6137	one week,one month,three months,six months	NR	Yes,LOCF	A,A,A,A,A,A,A
2	McCall (2006) [20]	71.5 (64–86)/ 67.4%	DSM IV, primary insomnia	Double-blind, 2-parallel arms (2 mg; PBO)	264 (136/128)	Dose:2 mg Duration:two weeks	IVRS, PSG, MQ	NR	TST<6.5 h per night SL > 30 min >1 month	88.6 (65.6)	106.9 (93.9)	0.151	two weeks	NR	NR	A,A,A,A,A,A,A
3	Zammit (2004) [21]	39.8 (21–64)/ 64.5%	DSM IV, primary insomnia	Double-blind, 3-parallel arms (2 mg; 3 mg; PBO)	308 (104/105/99)	Dose:2 mg/3 mg Duration:six weeks	IVRS, PSG, MQ	NR	TST<6.5 h per night SL > 30 min >1 month	69.4(58.9)/ 70.5(49.8)	81.2 (61.3)	0.313	two weeks, onw month	NR	Yes	A,A,A,A,U,I,A
4	Walsh (2007) [23]	46.0 (21–64)/ 60.8%	DSM IV, primary insomnia	Double-blind, 2-parallel arms (3 mg; PBO)	830 (550/280)	Dose:3 mg Duration:six months	IVRS	NR	TST<6.5 h per night SL > 30 min >1 month	77.0 (48.0)	83.2 (55.0)	0.589	one month,three months,six months	NR	NR	A,A,A,A,A,A,A
5	Sonia (2009) [22]	71.6 (65–85)/ 62.6%	DSM-IV-TR, primary insomnia	Double-blind, 2-parallel arms (2 mg; PBO)	388 (194/194)	Dose:2 mg Duration:12 weeks	PSG, MQ	Out-patient	TST<6 h ≥ 3 night per week WASO ≥ 3 night per week	75.68 (56.6)	82.17 (74.1)	0.513	three months	NR	Yes,LOCF	A,A,A,A,A,A,A
6	Scharf (2005) [24]	72.3 (65–85)/ 57.6%	DSM IV, primary insomnia	Double-blind, 3-parallel arms (1 mg; 2 mg; PBO)	231 (72/79/80)	Dose:1 mg/2 mg Duration:two weeks	IVRS	NR	TST<6.5 h per night SL > 30 min >1 month	119.1 (170)	131.9 (175)	0.591	one week, two weeks	NR	Yes	A,A,A,A,A,A,A

DSM, Diagnostic and Statistical Manual of Mental Disorders; PBO, placebo; IVRS, interactive voice response system; PSG, Polysomnography; MQ, morning questionnaire; NR, no report; TST, total sleep time; SL, sleep latency; LOCF, last observation carried forward; Risk of bias (Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, Incomplete outcome data, Selective reporting, Other bias); A, adequate; I, in adequate; U, Unclear.

Table 2
Summary of primary outcome analysis.

Parameters	Timepoint	Outcomes (95% CI)	Heterogeneity			Sample size (Treatment/Control)	
			P(Q)		I2, %		
SL	one week	−38.53 [−48.54, −28.51]	0.52	1	0	439/191	MD
	two weeks	−22.98 [−36.70, −9.27]	0.36	1	0	215/208	MD
	one month	−21.96 [−27.66, −16.25]	0.34	1	0	908/391	MD
	three months	−18.01 [−23.27, −12.74]	0.27	2	23	1052/534	MD
	six months	−20.26 [−25.99, −14.54]	0.44	1	0	908/391	MD

CI, confidence interval; SL, sleep latency; MD, mean difference.

Table 3
Summary of secondary outcome analysis.

Parameters	Timepoint	Outcomes (95% CI)	Heterogeneity			Sample size (Treatment/Control)	
WASO	one week	−29.85 [−42.61, −17.10]	0.28	1	15	439/191	MD
	two weeks	−11.74 [−22.94, −0.55]	0.83	1	0	215/208	MD
	one month	−16.88 [−22.75, −11.02]	0.85	1	0	908/391	MD
	three months	−17.36 [−22.18, −12.54]	0.87	2	0	1052/534	MD
	six months	−11.77 [−23.53, −0.01]	0.1	1	64	908/391	MD
Awakenings	one week	−0.34 [−0.59, −0.09]	0.14	1	54	439/191	MD
	two weeks	−0.30 [−0.53, −0.07]	1	1	0	215/208	MD
	one month	−0.77 [−1.05, −0.48]	0.75	1	0	908/391	MD
	three months	−0.40 [−0.71, −0.08]	0.06	2	64	1052/534	MD
	six months	−0.55 [−0.81, −0.29]	0.52	1	0	908/391	MD
TST	one week	51.81 [37.70, 65.91]	0.7	1	0	439/191	MD
	two weeks	30.63 [16.72, 44.53]	0.82	1	0	215/208	MD
	one month	45.94 [37.68, 54.21]	0.41	1	0	908/391	MD
	three months	39.26 [31.76, 46.76]	0.52	2	0	1052/534	MD
	six months	43.23 [34.29, 52.18]	0.54	1	0	908/391	MD
SQ	one week	1.38 [1.03, 1.73]	0.17	1	43	439/191	SMD
	one month	1.20 [1.00, 1.40]	1	1	0	908/391	SMD
	three months	0.88 [0.46, 1.31]	0.007	2	80	1052/534	SMD
	six months	1.11 [0.89, 1.32]	0.2	1	38	908/391	SMD
Ability to function	one week	0.93 [0.60, 1.26]	0.04	1	76	439/191	MD
	one month	0.70 [0.51, 0.89]	1	1	0	908/391	MD
	three months	0.68 [0.51, 0.86]	0.34	2	7	1052/534	MD
	six months	0.74 [0.54, 0.95]	0.38	1	0	908/391	MD
Daytime alertness	one week	0.91 [0.33, 1.50]	0.09	1	64	439/191	MD
	one month	0.73 [0.54, 0.93]	0.64	1	0	908/391	MD
	three months	0.80 [0.63, 0.98]	0.08	2	60	1052/534	MD
	six months	0.87 [0.67, 1.08]	0.07	1	69	908/391	MD
Sense of physical well-being	one week	0.73 [0.39, 1.06]	0.25	1	25	439/191	MD
	one month	0.57 [0.37, 0.77]	0.65	1	0	908/391	MD
	three months	0.70 [0.53, 0.88]	0.53	2	0	1052/534	MD
	six months	0.74 [0.53, 0.95]	0.39	1	0	908/391	MD

CI, confidence interval; WASO, wakefulness after sleep onset; Awakenings, number of awakenings; TST, total sleep time; SQ, quality of sleep; SMD standardized mean differences ; MD mean differences.

3.4. Secondary outcome analysis

Eszopiclone was associated with significant improvements in all secondary outcomes (WASO, Awakenings and TST) at one week, two weeks, one month, three months and six months respectively. And eszopiclone was associated with increased SQ at one week, one month, three months, six months compared with placebo. In the next-day function, eszopiclone was associated with increased ability to function, daytime alertness and sense of physical well-being at one week, one month, three months, six months compared with placebo (Table 3).

3.5. Adverse effects

In this study, all six trials reported adverse and clinical events associated with eszopiclone treatment. Commonly reported events included accidental injury, back pain, dizziness, dry mouth, pain, rash, somnolence, arthralgia, anxiety, headache, unpleasant taste, dyspepsia, infection and pharyngitis. There were subgroups of two eszopiclone regimens: 3 mg for nonelderly and 2 mg for elderly.

Elderly patients receiving eszopiclone were more likely to report dizziness, unpleasant taste compared to those receiving placebo. In nonelderly subgroup, while, patients receiving eszopiclone were more likely to get infection, pharyngitis, somnolence, unpleasant taste, dry mouth (Table 4).

4. Discussion

To our knowledge, this was the first meta-analysis focused on efficacy and safety of eszopiclone on primary insomnia compared to placebo. This study indicated that eszopiclone was associated with improvements in SL, WASO, Awakenings, TST, SQ, Ability to function, Daytime alertness and Sense of physical well-being. Compared to placebo groups, nonelderly patients receiving eszopiclone were more likely to report unpleasant taste, dry mouth, somnolence, infection and pharyngitis. While, elderly patients were more likely to get dizziness and unpleasant taste.

Previous meta-analysis showed that sleep latency was reduced (95%CI, −12.37–26.00 min) with non-benzodiazepine hypnotics in treatment of insomnia [7]. However, it was hardly significant. The

Table 4
Subgroup analysis by adverse and clinical event.

Adverse effect	2 mg for elderly		Relative risk (95% CI)	Heterogeneity		
	No. of adverse events/Total No. of participants			P(Q)	df	I2, %
	eszopiclone	Placebo				
Back pain	6/327	8/319	1.16 [0.07, 20.10]	0.07	1	69
Dizziness*	25/327	5/319	5.19 [1.96, 13.75]	0.81	1	0
Dry mouth	17/327	6/319	2.65 [0.55, 12.69]	0.12	1	59
Pain	13/327	8/319	1.59 [0.64, 3.91]	0.64	1	0
Rash	7/327	9/319	0.75 [0.27, 2.03]	0.31	1	3
Somnolence	17/409	19/402	0.87 [0.44, 1.70]	0.45	2	0
Arthralgia	9/327	2/319	4.48 [0.96, 20.85]	0.63	1	0
Anxiety	9/327	2/319	3.82 [0.94, 15.56]	0.65	1	0
Headache	63/273	57/274	1.14 [0.76, 1.72]	0.76	1	0
Unpleasant taste*	26/215	1/208	19.44 [3.69, 102.29]	0.45	1	0
Dyspepsia	8/273	8/274	0.89 [0.34, 2.34]	0.61	1	0
Adverse effect	3 mg for nonelderly		Relative risk (95% CI)	Heterogeneity		
	No. of adverse events/Total No. of participants			P(Q)	df	I2, %
	eszopiclone	Placebo				
Accidental injury	70/1141	28/475	1.01 [0.64, 1.60]	0.3	1	7
Back pain	78/1246	28/574	1.40 [0.53, 3.69]	0.05	2	68
Dyspepsia	75/1141	28/475	1.10 [0.70, 1.73]	0.8	1	0
Headache	211/1246	87/574	1.06 [0.80, 1.39]	0.77	2	0
Infection*	185/1141	47/475	1.87 [1.04, 3.38]	0.11	1	62
Pain	115/1141	41/475	1.18 [0.81, 1.72]	0.04	1	77
Pharyngitis*	92/1141	21/475	1.80 [1.11, 2.94]	0.6	1	0
Somnolence*	110/1246	17/574	3.16 [1.86, 5.36]	0.87	2	0
Unpleasant taste*	298/1246	17/574	11.53 [4.62, 28.75]	0.08	2	61
Dizziness	63/698	10/294	2.29 [0.83, 6.32]	0.19	1	42
Dry mouth*	45/698	5/294	4.01 [1.54, 10.46]	0.67	1	0

CI, confidence interval; No, number. Asterisks (*) indicate a statistical significance.

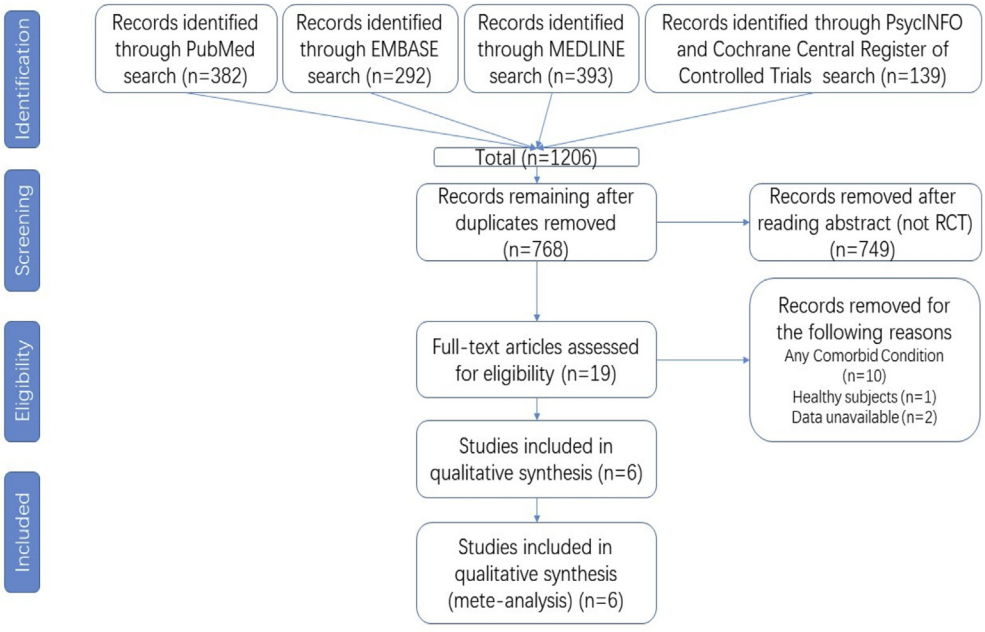

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram.

non-benzodiazepine hypnotics showed an effect similar to other drugs on sleep-initiation. Some other meta-analyses showed that sleep latency was also reduced with BDZ (95% CI, 3.44–16.60 min) and exogenous melatonin treatments (95% CI, 2.29–8.71 min) [25,26]. In this study, our results showed that eszopiclone tended to produce significant shortening of sleep latency at all timepoints. However, there was one characteristic point should be mentioned. Huedo-Medina et al., showed that there were no significant effects of non-benzodiazepine hypnotics were found in secondary outcomes [7]. In fact, randomized placebo-controlled trials on eszopiclone suggested that significant and sustained improvements in WASO, Awakenings, TST and SQ compared with placebo. Moreover, monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of

Table 5
Study quality as assessed by grading of recommendations, assessment, development and evaluation (GRADE) checklist.

Risk of bias evidence	Quality assessment					Certainty of grade
		Inconsistency	Indirectness	Imprecision	Other grade consideration	
Krystal (2003) [19]	Case-control	Not relevent	Not serious	Not serious	none	High
McCall (2006) [20]	Case-control	Not relevent	Not serious	Not serious	none	High
Zammit (2004) [21]	Case-control	Not relevent	Not serious	Not serious	none	Moderate
Walsh (2007) [23]	Case-control	Not relevent	Not serious	Not serious	none	High
Sonia (2009) [22]	Case-control	Not relevent	Not serious	Not serious	none	High
Scharf (2005) [24]	Case-control	Not relevent	Not serious	Not serious	none	High

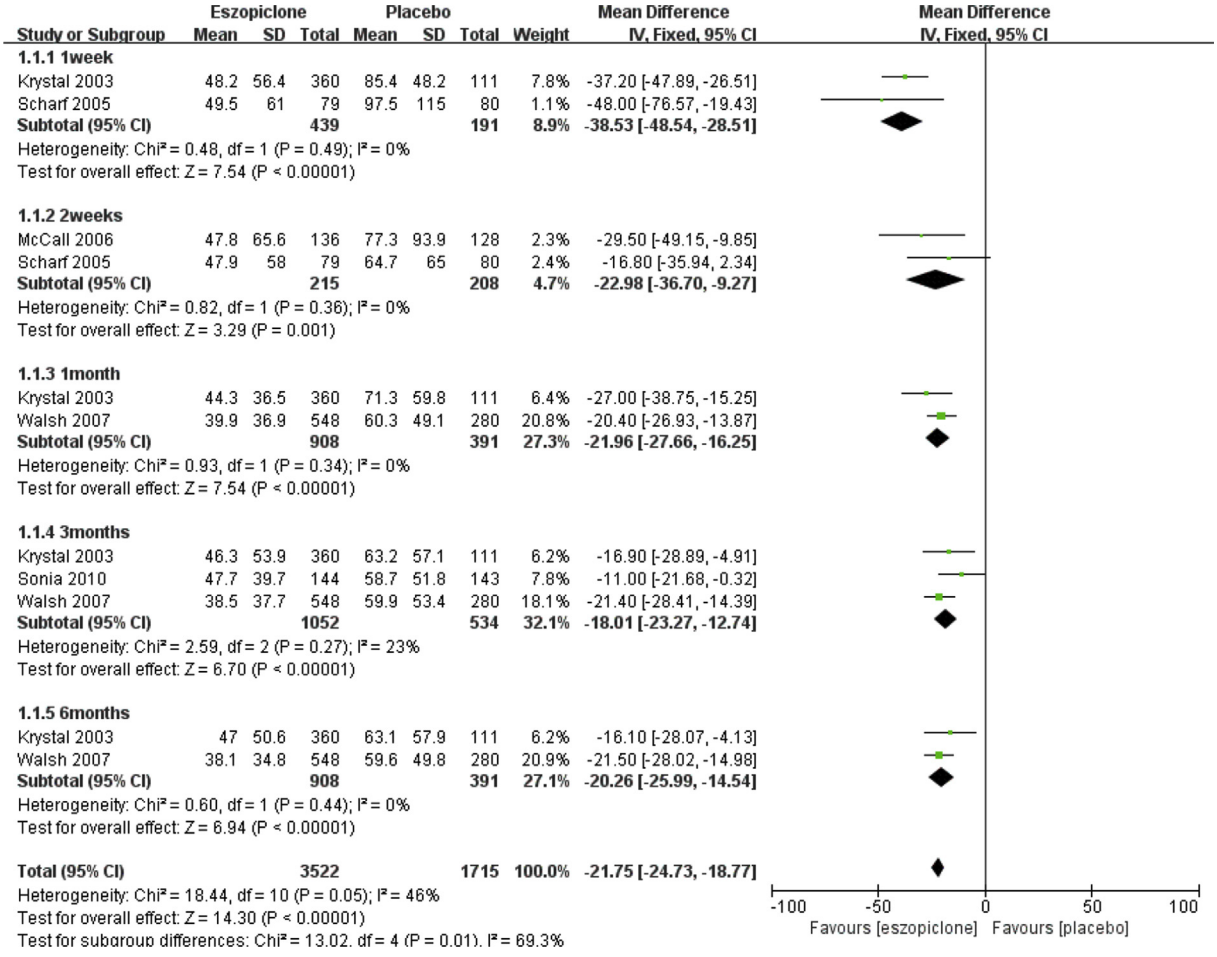

Fig. 2. Meta-analysis results for primary efficacy outcomes of eszopiclone compared with placebo.

eszopiclone than with placebo. This meta-analysis and these facts suggested that the efficacy of eszopiclone in treatment of insomnia disorder. Those meta-analyses on the other treatments included trials with short durations, and most of these duration were less than of around four weeks. However, the durations of these trials on eszopiclone ranged from two weeks to six months. Therefore, our meta-analysis showed the efficacy of the long-term use of eszopiclone in treatment of insomnia disorder.

Eszopiclone is now available in a generic form in the United States as of May 2014 and approved by the US Food and Drug Administration for the treatment of insomnia in nonelderly and elderly adults [27]. Meanwhile, growing age has been identified as a risk factor for primary insomnia. In the United States, the clinical trials included both short- and long-term studies but did not incorporate long-term research in elderly patients [20,24]. In previous studies, eszopiclone was effective for sleep induction and maintenance at 3 mg for non-elderly patients and 2 mg for elderly patients [20–24]. In this meta-analysis, the results showed that eszopiclone in treatment of all patients with chronic insomnia significantly improved SL, WASO, Awakenings, TST, SQ, Ability to function, Daytime alertness and Sense of physical well-being. Similarly, in the six-month study of eszopiclone in nonelderly adults with chronic insomnia showed that outcomes consistent with trial results of two-weeks study for elderly patients. Therefore, the subgroup analysis showed that elderly and nonelderly patients in eszopiclone treatment had similar efficacy with respect to all outcomes, which is relevant to actual practice.

This meta-analysis suggested that eszopiclone is associated with some adverse effects. Some other studies showed that the use of

benzodiazepine hypnotics increases the odds ratio of traffic accident risk up to 1.19 [28,29]. Uemura et al. suggested a significant difference in some functions between the use of hypnotics and placebo in the healthy elderly [30]. According to our subgroup analysis, the incidences of AEs were higher in nonelderly patients. Infection, pharyngitis, somnolence, unpleasant taste and dry mouth were the most common side effects in nonelderly patients, while dizziness and unpleasant taste were common in elderly patients. Overall, the incidences of adverse events were relatively lower in elderly patients than nonelderly patients. Thus, eszopiclone has been shown to be safety for primary insomnia in elderly patients. Recently, the recommended starting dose of eszopiclone for difficulty falling asleep, proposed by the FDA, was 1 mg at bedtime. For elderly patients, it can be increased to 2 mg if indicated. Both eszopiclone 1 mg and 2 mg reduced latency to sleep and increased TST. In addition, eszopiclone was well-tolerated for up to 12 weeks of continuous use by elderly patients. Tolerance to the hypnotic effect of eszopiclone 2 mg for 12 weeks did not develop. Overall, 2 mg eszopiclone is a safe and well-tolerated treatment option for elderly patients with insomnia.

Our meta-analysis has several strengths. First, all trials included in this study were of high-quality and low risk in most components of the Cochrane risk of bias tool. Second, subjective parameters including SL, TST, WASO and Awakings were examined in this study. In some systematic reviews, such subjective parameters for insomnia have been examined. The Cochrane Collaboration has emphasized the need to maintain a focus on patient-reported outcomes, which necessitated a look at subjective parameters. Third, this meta-analysis is the first to our knowledge to examine the efficacy and safety of eszopiclone for primary insomnia management.

This study also had some limitations. First, the number of trials included in the analysis was small. This impeded examination for the causes of high statistical heterogeneity in some pooled outcomes. Nevertheless, it should be emphasized that these have largest trials conducted to investigate the pharmacological treatment of primary insomnia. Secondly, although the research time points were comprehensive, study durations of included trials were short in this study. However, it should be noted that the durations of the trials on eszopiclone were relatively longer among the randomized placebo-controlled trials than other pharmacological treatments of primary insomnia. Third, our meta-analysis only had aggregate data due to lack of patient-level data that precluding investigation on the statistical heterogeneity for some outcomes. Fourth, we did not ask the drug company whether there are unpublished data. Despite all this, the directions for these outcomes were consistent with those in the original studies, and this discrepancy will not disaffirm the efficacy of eszopiclone in treatment of primary insomnia that original studies have shown.

Given that insomnia is a chronic disorder. Efficacy of long-term use of eszopiclone for primary insomnia should be examined through future clinical trials. Despite our exhaustive research, no studies have compared eszopiclone and other hypnotic agents for insomnia management. Overall, to determine the place of eszopiclone in the treatment of primary insomnia, comparative effectiveness studies with eszopiclone and other agents should also be conducted.

Authors'contribution

In this study, Liang Liang, Yabing Huang and Gaohua Wang performed search and wrote the manuscript, Yanyan Wei, Rong Xu and Ling Xiao prepared tables and figures. Thanks to my co-authors. All authors critically reviewed the paper and approved the final version of the manuscript.

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Conflict of interest

All authors have no conflict of interest to declare. There was no external grant or financial support for this study.

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.2019.03.016.

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