Frontiers in Neuroendocrinology 52 (2019) 22–28

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Exogenous melatonin as a treatment for secondary sleep disorders: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Melatonin
Secondary sleep disorders
Meta-analysis
Sleep onset latency
Total sleep time
Sleep efficiency

ABSTRACT

Melatonin is a physiological indoleamine involved in circadian rhythm regulation and it is currently used for secondary sleep disorders supported by empirical evidence. A small amount of evidence and some controversial results have been obtained in some randomized controlled trials (RCT). The objective of this meta-analysis is to determine the efficacy of exogenous melatonin versus placebo in managing secondary sleep disorders. Literature retrieval of eligible RCT was performed in 5 databases (PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Web of Science). In total, 7 studies of 205 patients were included. Pooled data demonstrate that exogenous melatonin lowers sleep onset latency and increases total sleep time, whereas it has little if any effect on sleep efficiency. Although, the efficacy of melatonin still requires further confirmation, this meta-analysis clearly supports the use of melatonin as a management for patients with secondary sleep disorders.

1. Introduction

Sleep disorders, or somnipathy, are serious public health problems that cause a prominent economic burden worldwide. More than 10% individuals in Western societies have sleep disorders (Auld et al., 2017; Gervais et al., 2017). Conventional drugs usually have a short half-life and a hangover effect that might contribute to a poor compliance (Walters and Lader, 1971). Implementation of non-pharmacotherapy such as cognitive and relaxation therapy is usually a complex process influenced by multiple factors. Thus, an exogenously-administered agent that mimics the actions of an endogenous molecule might serve to cure or improve sleep disorders.

Melatonin, discovered by Aaron Lerner, is an chronobiotic that modulates circadian rhythms (Suhner et al., 2001; Keijzer et al., 2014) and has a wide variety of other functions (Carrier et al., 2017; Reiter et al., 2017, 2014; Yang et al., 2014; Yu et al., 2018). In humans, melatonin enhances darkness-related behavior and induces soporific effects. For example, melatonin has been tested in secondary sleep disorders (namely secondary insomnia) caused by sleep restriction (e.g., shiftwork, jet lag) without organic diseases (Buscemi et al., 2006; Liira et al., 2014). Previous studies have demonstrated that melatonin has a hypnotic action on secondary sleep disorders (Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002) with no known adverse effects (Suhner et al., 2001; van Geijlswijk et al., 2010).

Primary sleep disorders are rarely markedly improved by exogenous drug treatment, as a result of the existence of protopathy (Zhang et al., 2016). A previous meta-analysis by Buscemi reported that melatonin is ineffective in relieving sleep problems. Buscemi et al. (2006) explored sleep disorders resulting from organic and non-organic factors and concluded that melatonin has no effects, which contradicts the conclusions of some randomized controlled trials (RCT) (Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Wright et al., 1998). Sample sizes of previously published studies were usually small and the results were inconsistent (Beaumont et al., 2004; Folkard et al., 1993; Suhner et al., 2001). However, some of the recent findings published suggest that melatonin is a potent drug candidate for secondary sleep disorders (Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002). Thus, an updated meta-analysis with a different focus is needed

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https://doi.org/10.1016/j.yfrne.2018.06.004
Received 17 February 2018; Received in revised form 7 June 2018; Accepted 13 June 2018
Available online 15 June 2018
0091-3022/

to provide the latest evidence for clinical psychiatrists and neurologists. This systematic review summarizes the current data that investigated the roles of exogenous melatonin, versus placebo, in the treatment of secondary sleep disorders.

2. Methods

2.1. Study protocol

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

2.2. Search strategy

A systematic search was performed on PubMed, Embase, Cochrane Register for Systematic Reviews databases, ClinicalTrials.gov, and Web of Science with no language limitations (published between Jan 1, 1950 and Sep 19, 2017). Search terms included “melatonin”, or “5-methoxytryptamine”, or “ramelteon” in combination with “sleep disorders”, or “sleep disturbance”, or “sleep dysfunction”. For example, the search strategy in PubMed was as follows: “((melatonin[MeSH Terms] OR methoxytryptamine[Text Word])) AND (sleep disorder[MeSH Terms] OR secondary sleep disorder[Text Word] OR sleep dysfunction[Text Word] OR sleep disturbance[Text Word] OR sleep[Text Word])) AND (random allocation[MeSH Terms] OR randomized[Text Word] OR randomly[Text Word] OR placebo[Text Word] OR crossover[Text Word] OR cross-over[Text Word])”. Moreover, the references of relevant studies, reviews, editorials, letters, and conference abstracts were also searched. The research work was done independently and in duplicate.

2.3. Eligibility criteria

Studies meeting the following criteria were included: (a) study design is double-blind RCT (crossover or parallel); (b) populations were adult patients with secondary sleep disorders secondary accompanying sleep restriction; (c) intervention comparisons of melatonin versus placebo; (d) outcomes analyzed for nocturnal sleep without diurnal disturbance; (e) enrolled studies report any or all of the following nocturnal sleep outcomes: I. sleep onset latency (the length of time between full wakefulness to sleep onset), II. total sleep time (total time spent asleep in bed), III. sleep efficiency (total sleep time/total time spent in bed). Sleep onset latency was the primary outcome. Total sleep time and sleep efficiency were secondary outcomes.

The exclusion criteria were: (a) articles not peer-reviewed or published; (b) populations that included children (< 18 years); (c) studies that were repeatedly published or had qualitative outcomes; (d) outcomes that analyzed daytime instead of the night sleep. There was no limit on sample size, trial duration, et al. Preliminarily, retrieved results were subjected to a title and abstract screening for inclusion by two independent reviewers (Li & Jiang). Full-text retrieval was performed to determine eligibility using a standardized data abstraction form by the two independent reviewers. Disagreements regarding the inclusion of studies were discussed between the two reviewers (Li & Jiang) and ultimately decided by the third reviewer (Han).

2.4. Data extraction

Two reviewers (Li & Jiang) independently extracted relevant data with a standardized form, including study characteristics and main outcomes. Disagreement was resolved through discussion with a third author (Han). Characteristics of patients such as age, research site, sample size, study design, duration, dosage, and clinical outcomes were collected. Clinical outcomes included continuous variables of sleep onset latency (mean [SD]), total sleep time (mean [SD]), and sleep efficiency (mean [SD]). Two reviewers also independently assessed the risk of bias of enrolled studies using The Cochrane Collaboration’s tool for assessing risk of bias (Higgins et al., 2011). Three types of risk (low risk of bias, unclear risk of bias, and high risk of bias) were identified depending on the following domains: (a) random sequence generation (selection bias), (b) allocation concealment (selection bias), (c) blinding of participants and personnel (performance bias), (d) blinding of outcome assessment (detection bias), (e) incomplete outcome data (attrition bias), (f) selective reporting (reporting bias), (g) other biases. Disagreement was resolved by a third reviewer (Han).

2.5. Statistical analysis

The efficacy of exogenous melatonin versus placebo was evaluated on three continuous outcomes: sleep onset latency (mean [SD]), total sleep time (mean [SD]), and sleep efficiency (mean [SD]). We calculated results for continuous outcomes as mean differences (MD) with 95% confidence intervals (CI), comparing the change from baseline for both melatonin and placebo. All tests were two tailed and a P value of less than 0.05 was deemed statistically significant. Data were analyzed by the latest Cochrane collaboration Review Manager analysis software version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). According to the knowledge from evidence-based medicine and Cochrane Handbook for Systematic Review of Interventions (version 5.1), the weight of enrolled studies depends on the value of mean, [SD], and total sample size. The Z-test determined an overall significance of therapeutic effect versus placebo with values of $P < 0.05$. Heterogeneity was assessed using chi-squared test and I^2 test in accordance with Cochrane collaboration's guidance for assessing heterogeneity in meta-analyses. Data were considered heterogeneous if chi-squared test yielded $P < 0.10$ and $I > 50\%$. Random effects model (REM) was utilized when heterogeneity was absent; otherwise, the fixed effects model (FEM) was chosen. If we identified sufficient trials ($N \geq 10$), a funnel plot was utilized to test potential publication bias.

3. Results

3.1. Study characteristics

The initial search by two reviewers (Li & Jiang) identified 1223 database records and 13 additional records (Fig. 1). 900 records remained after removing 336 duplicates. Then, the title and abstract of remained literature were screened, and 812 records were excluded due to review article, meta-analyses/systematic review, case-control studies, cross sectional studies, or unrelated topics. Thereafter, 88 full-text articles were assessed for eligibility and 81 records were excluded with reasons: children (n = 21), insufficient end points (n = 32), non-randomized studies (n = 10), and irrelevant reports (n = 18). Eventually, 7 RCT (Beaumont et al., 2004; Folkard et al., 1993; James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Wright et al., 1998; Yoon and Song, 2002) were included, their characteristics were listed in Table 1.

3.2. Systematic review

These 7 studies of 205 participants were conducted in USA (n = 4) (Beaumont et al., 2004; James et al., 1998; Suhner et al., 2001; Wright et al., 1998), England (n = 1) (Folkard et al., 1993), Republic of Korea (n = 1) (Yoon and Song, 2002), and Iran (n = 1) (Sadeghniiat-Haghighi et al., 2016), published between 1993 and 2016 (Table 1). All studies were double-blind RCT that used standard experimental/control groups (melatonin/placebo). The mean age of participants ranged from 29 (Folkard et al., 1993; James et al., 1998; Yoon and Song, 2002) to 41.3 (Suhner et al., 2001). The sample size ranged from 12 (Yoon and Song, 2002) to 74 (Suhner et al., 2001). Participants include medical staffs (James et al., 1998; Wright et al., 1998; Yoon and Song, 2002), police

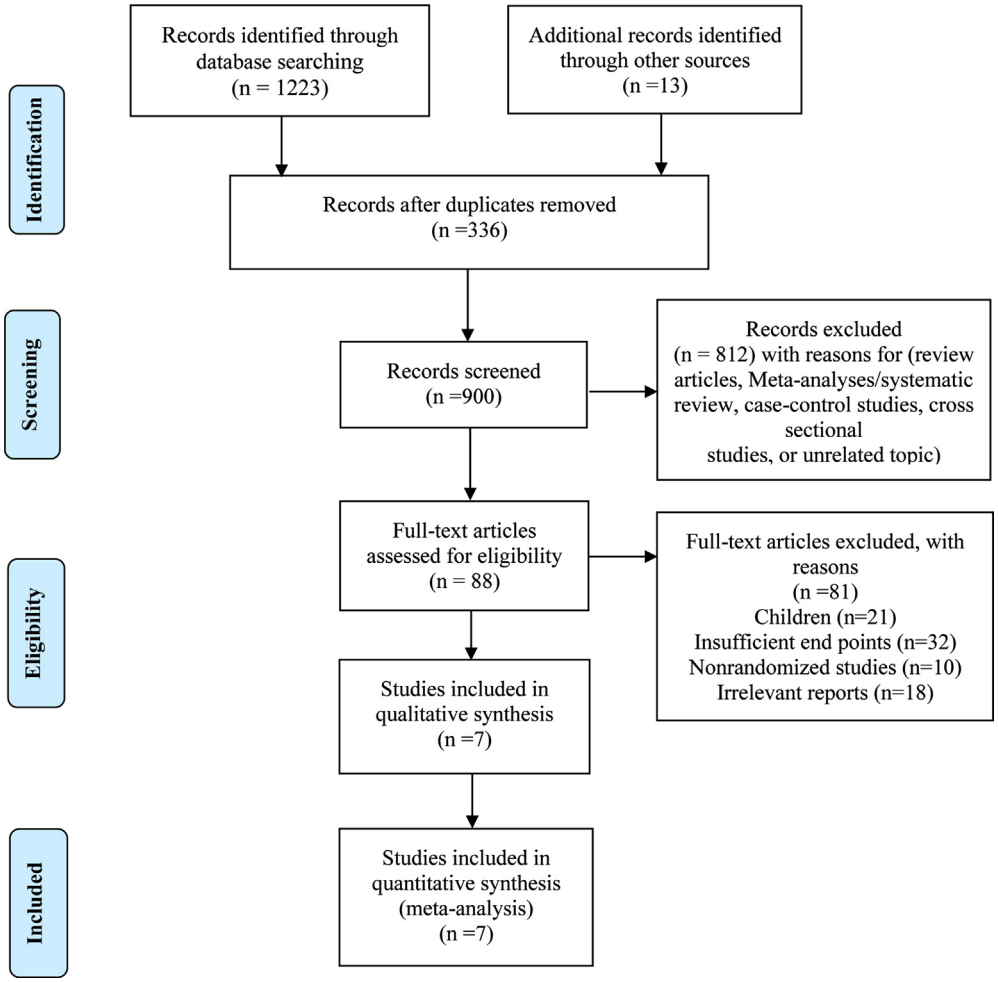

Fig. 1. Flowchart of study screening.

(Folkard et al., 1993), workers (Sadeghniiat-Haghighi et al., 2016) after shift-work, and pilots (Beaumont et al., 2004), travelers (Suhner et al., 2001) after jet lag.

All studies reported the efficacy of melatonin in sleep onset latency. 3 studies reported the efficacy of melatonin in total sleep time (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). 3 studies reported the efficacy of melatonin in sleep efficiency (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). The dosage of melatonin ranged from 3 (Sadeghniiat-Haghighi et al., 2016) to 6 mg (James et al., 1998; Yoon and Song, 2002), among which 5 mg was the most frequently used (Beaumont et al., 2004; Folkard et al., 1993; Suhner et al., 2001; Wright et al., 1998). The duration of treatment ranged from 3 (Sadeghniiat-Haghighi et al., 2016) to 9 days (Beaumont et al., 2004).

3.3. Sleep onset latency

Sleep onset latency is the primary outcome in this meta-analysis. All studies assessed the efficacy of melatonin in sleep onset latency. Pooled analysis of 7 studies (N = 154) demonstrate that exogenous administration of melatonin lowers sleep onset latency (Total mean difference: −2.48 min, 95% CI: −4.56, −0.40, Fig. 2), versus placebo. The overall estimated score of melatonin treatment is significant (Z = 2.33, P = 0.02). No significant heterogeneity was present across these studies (Chi^2 = 7.54, P = 0.27, I^2 = 20%).

3.4. Total sleep time

Total sleep time was the secondary outcome in this meta-analysis. 3 studies reported the efficacy of melatonin in total sleep time (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). Analysis of the 3 studies (N = 71) suggest that exogenous administration of melatonin increases total sleep time (Total mean difference: 29.27 min, 95% CI: 6.68, 51.86, Fig. 3). The overall estimated action of melatonin is significant (Z = 2.54, P = 0.01). No significant heterogeneity was present across the 3 studies (Chi^2 = 2.71, P = 0.26, I^2 = 26%).

3.5. Sleep efficiency

Sleep efficiency was also the secondary outcome in this meta-analysis. 3 studies reported the efficacy of melatonin in sleep efficiency (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). Analysis of the 3 studies (N = 71) suggested that exogenous melatonin has no meaningful actions on sleep efficiency (Total mean difference: 1.46, 95% CI: −0.43, 3.35, Fig. 4). The Z value of melatonin is 1.52 (P = 0.13). No significant heterogeneity was present across the 3 studies (Chi^2 = 2.03, P = 0.36, I^2 = 1%).

3.6. Risk of bias

Figs. 5 and 6 show the risk of bias across 7 trials. 100% studies have a low risk of bias on random sequence generation, blinding of participants and personnel, and selective reporting. 3 (Beaumont et al., 2004;

Table 1
Characteristic of included studies.

Study	Groups	Participants	Total number	Number (exp)	Age (years)	Research site	Study design	Duration of treatment (day)	Dosage (mg)	Outcomes	Reference
Beaumont et al, 2004	Melatonin/ Placebo	Pilots after a seven-time zone eastbound flight	18	9/9	35.3 ± 8.1 (19–47)	USA	RCT, parallel	9	5	1–3	Beaumont et al. (2004)
Folkard et al, 1993	Melatonin/ Placebo	Police officers after night shift	14	7/7	29 ± 7 (21–48)	England	RCT, parallel	7	5	1	Folkard et al. (1993)
James et al, 1998	Melatonin/ Placebo	Emergency medical staffs after night shift	22	22/22	29 ± 7 (20–41)	USA	RCT, crossover design	4	6	1	James et al. (1998)
Sadeghniiat-Haghighi et al, 2016	Melatonin/ Placebo	Shift workers	50	50/50	32.9 ± 8 (24–52)	Iran	RCT, crossover design	3	3	1–3	Sadeghniiat-Haghighi et al. (2016)
Suhner et al, 2001	Melatonin/ Placebo	Travelers after a jet lag	74	35/39	41.3 (18–68)	USA	RCT, parallel	4	5	1	Suhner et al. (2001)
Wright et al, 1998	Melatonin/ Placebo	Emergency physicians after night-shift work	15	15/15	38.6 (32–45)	USA	RCT, crossover design	4	5	1	Wright et al. (1998)
Yoon et al., 2002	Melatonin/ Placebo	Nurses after night-shift work	12	12/12	29 ± 7 (21–48)	Republic of Korea	RCT, crossover design	4	6	1–3	Yoon and Song (2002)

Suhner et al., 2001; Wright et al., 1998) and 4 (Folkard et al., 1993; James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002) studies have a low and unclear risk of bias on allocation concealment, respectively. 1 (Wright et al., 1998) and 6 (Beaumont et al., 2004; Folkard et al., 1993; James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002) studies have a low and unclear risk of bias on blinding of outcome assessment, respectively. As for the incomplete outcome data, 2 (Beaumont et al., 2004; Yoon and Song, 2002), 2 (Folkard et al., 1993; Wright et al., 1998), and 3 (James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001) studies have a low, unclear, and high risk of bias on incomplete outcome data, respectively. 4 (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002), 2 (Folkard et al., 1993; James et al., 1998), and 1 (Wright et al., 1998) studies have a low, unclear, and high risk of bias on other bias, respectively. Other bias (Higgins et al., 2011) might include the following situations: (1) There was no description of the ingested drug monitoring by physicians, which could result in performance bias. (2) The authors state any important concerns about bias not covered in the other domains in the tool. (3) Bias due to problems not covered elsewhere exists.

4. Discussion

4.1. Main findings

In this meta-analysis of 7 studies that analyzed exogenous melatonin versus placebo in the treatment of secondary sleep disorders, we found that melatonin reduces sleep onset latency and increases total sleep time (Figs. 2 and 3). However, based on current data, melatonin has no actions on sleep efficiency of patients with secondary sleep disorders (Fig. 4). Overall, these data demonstrate that melatonin improves sleep quality with respect to sleep onset latency and total sleep time, which lends support to melatonin as a potential approach to secondary sleep disorders.

4.2. Interpretation

Secondary sleep disorders, namely secondary insomnia caused by sleep restriction, have caused a huge economic and social burden in the world (Liira et al., 2014). The management of secondary sleep disorders remains a big issue in clinical psychiatry and sleep medicine. So far, there are no effective treatments for secondary sleep disorders. Pharmacotherapies usually have a short half-life and a hangover effect. Non-pharmacotherapies (e.g., cognitive therapy and relaxation therapy) are complex and patients usually have poor compliance with them. Therefore, the low toxicity may facilitate melatonin as a therapeutic candidate for secondary sleep disorders (Jan et al., 2009; Li et al., 2017).

This meta-analysis was conducted under the guidance of PRISMA (Moher et al., 2009). The search strategy of this meta-analysis is thorough and the inclusion criteria are broad. Both MeSH Terms and Text Word were utilized in databases from PubMed, Embase, Cochrane Library, et al., which includes a wide variety of publications from 1950 to 2017 (Robinson, 2005). Enrolled studies were analyzed by two authors (Li & Jiang) independently using unitive criteria and disagreement was solved through discussion with a third author (Han). Based on previous works (Chan et al., 2011; Nathan et al., 2017), this review also provides a general introduction for all enrolled studies in Section Systematic review and has mentioned Buscemi's work in Section Introduction. In Buscemi's work, secondary sleep disorders were clearly distinguished from those accompanying sleep restriction. In this review, secondary sleep disorders are referred to as sleep disorders accompanying sleep restriction (e.g. shift work and jet lag). Compared to Buscemi's work in 2006, this meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

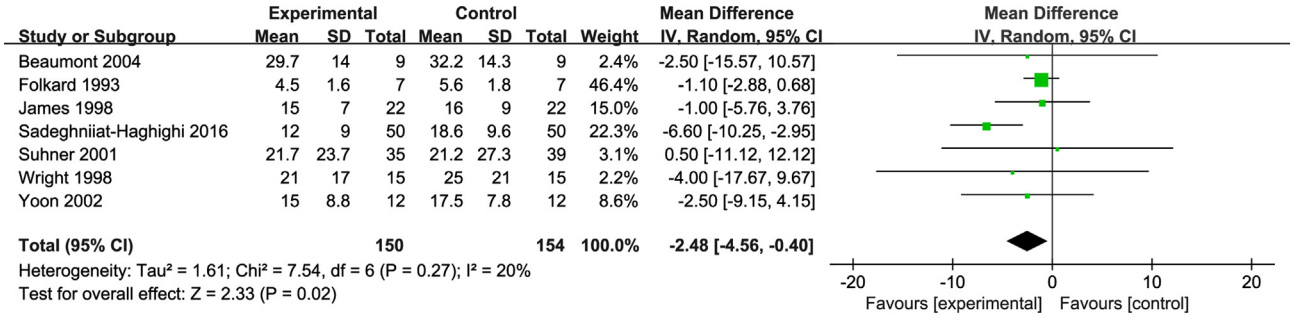

Fig. 2. Effects of melatonin on SOL. This forest plot demonstrates that exogenous administration of melatonin lowers sleep onset latency. SOL, sleep onset latency.

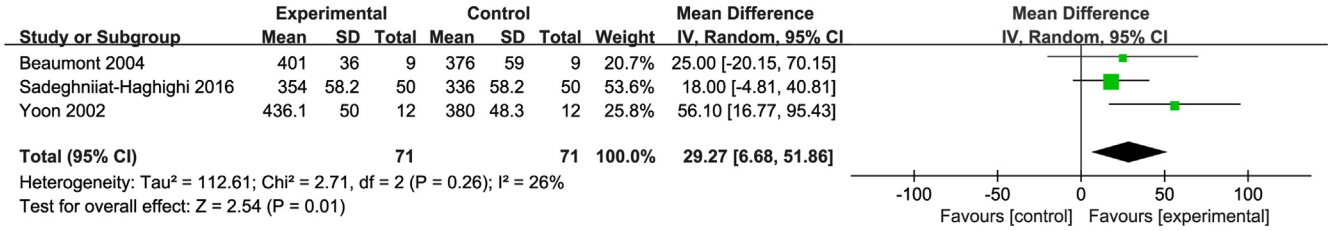

Fig. 3. Effects of melatonin on TST. This forest plot suggests that exogenous administration of melatonin increases total sleep time. TST, total sleep time.

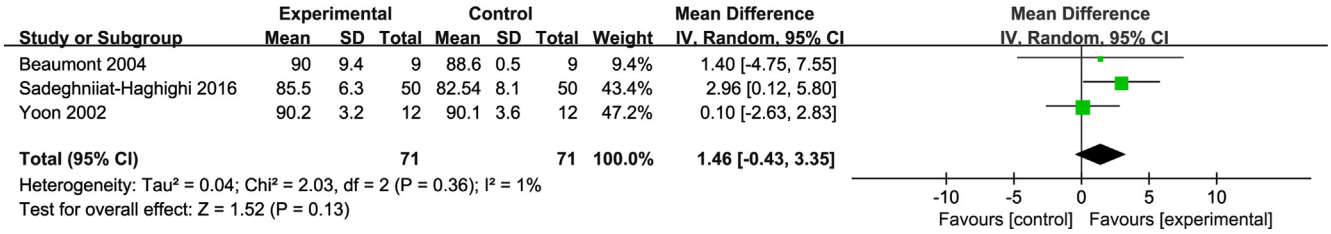

Fig. 4. Effects of melatonin on SE. This forest plot reveals that melatonin has no significant effects on sleep efficiency. SE, sleep efficiency.

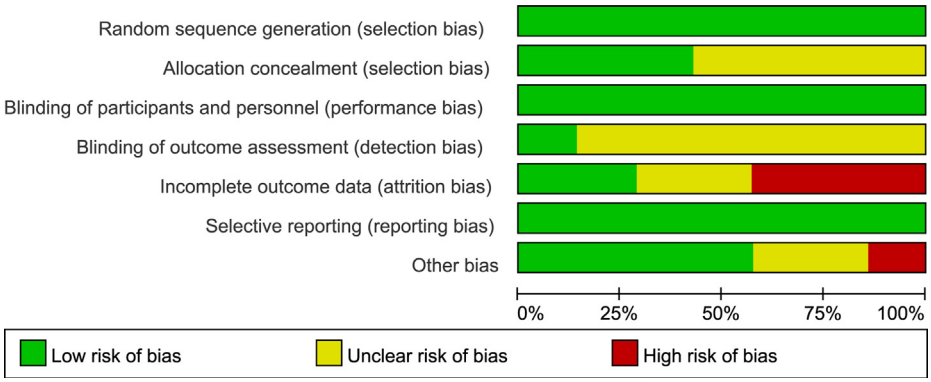

Fig. 5. Risk of bias graph. This figure shows review authors' judgements about each risk of bias item presented as percentages across all included studies.

and aimed to explore the new literature and provide a different emphasis. Thus, there is a difference of included studies between this review and other meta-analysis. So far, the safety issues of melatonin in pediatrics remain a big concern (Kennaway, 2015) and there is a lack of RCTs on long-term usage of melatonin in pediatrics. Thus, children (< 18 y) are excluded in this article, which is in accordance with previous meta-analysis (Brzezinski et al., 2005). Risk of bias of enrolled studies were assessed using The Cochrane Collaboration's tool (Figs. 5 and 6) (Higgins et al., 2011) and the overall risk of bias is low or unclear. Besides, we also searched for unpublished and commercially-sponsored work during searching. These data are excluded due to the absence of peer review and potential interacted interest.

Strikingly, the strong effect of melatonin seems to be opposed to the results of the present study. Based on previous studies and hypothesis, the following explanations may address this question: (1) The studies on the sleep induction effect of melatonin are mainly conducted in animals (Fisher et al., 2008; Fisher and Sugden, 2009), instead of human beings. (2) The meta-analysis articles are based on RCTs, some of which demonstrated that the effects of melatonin are not strong (Folkard et al., 1993; James et al., 1998; Yoon and Song, 2002), (mean difference < 5 min compared to the controls (Wade et al., 2007; Zhdanova et al., 2001)). (3) Different eligibility criteria in those meta-analysis articles contribute to different enrolled population.

As shown in Fig. 2, pooled data reveal that compared to placebo, exogenous melatonin lowers sleep onset latency (Total mean difference: −2.48 min, 95% CI: −4.56, −0.40, I^2 = 20%). The heterogeneity is less than 50% and is not significant, suggesting a good homogeneity among the enrolled studies. Auld's work evaluates the effects of

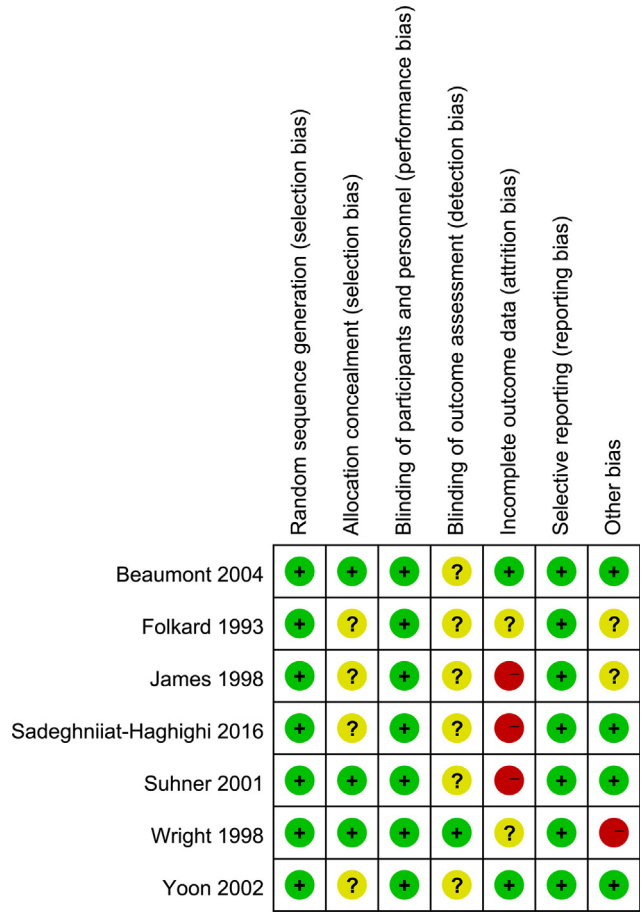

Fig. 6. Risk of bias summary. This figure shows review authors' judgements about each risk of bias item for each included study.

melatonin on primary sleep disorders and concluded a total mean difference of −5.05 min (95% CI: −8.51, −1.59) (Auld et al., 2017). Brzezinski's study assessed the effects of exogenous melatonin on sleep (including primary and secondary outcomes). The total mean difference of sleep onset latency are −4.0 min (95% CI: −2.5, −5.4) (Brzezinski et al., 2005). The result of this meta-analysis is similar to previous results (Auld et al., 2017; Brzezinski et al., 2005). Overall, despite the statistically significant mean differences, 2.48 min for secondary insomnia patients is not clinically relevant, which requires further studies to evaluate its efficacy.

Fig. 3 shows that melatonin increases total sleep time (Total mean difference: 29.27 min, 95% CI: 6.68, 51.56, I^2 = 26%). The heterogeneity is also non-significant among the included studies. Fig. 4 shows that melatonin has no significant actions on sleep efficiency (Total mean difference: 1.46, 95% CI: −0.43, 3.35, I^2 = 1%). It is clear that total sleep time is increased and sleep onset latency is reduced. Notably, the sleep efficiency does not increase. The following explanations may account for the observations reported. On one hand, the enrolled studies of Figs. 2 and 4 are different. Seven studies are included in Fig. 2, whereas three are inlcuded in Fig. 4. Sleep efficiency is not provided by the Folkard's study (Folkard et al., 1993), or in 3 other studies (James et al., 1998; Suhner et al., 2001; Wright et al., 1998). Thus, only 3 studies are included in Fig. 4. This difference might contribute to the insignificance of sleep efficiency. Conversely, the enrolled studies and sample size in Figs. 2 and 4, as well as the total number of individuals is small. Risk of bias of enrolled 7 studies are summarized in Figs. 5 and 6, according to The Cochrane Collaboration's tool (Higgins et al., 2011), which bears a high risk of bias on attrition bias and other biases across the 7 studies. Of note, the researches by James, Sadeghniiat-Haghighi, Suhner, and Wright have a high risk of bias (James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Wright et al., 1998), which also contribute to the suspicion of literature quality, which needs further study.

4.3. Limitations

There are some limitations to this review. Firstly, unpublished studies were excluded in this meta-analysis, which may increase the publication bias (Kicinski et al., 2015). Secondly, although data analysis revealed that melatonin reduces sleep onset latency and increases total sleep time, these results need additional support from additional RCT. The reduced time of sleep onset latency is not clinically significant. Third, each study does not adjust for the same confounders, such as duration of administration and dosage, therapeutic period, and gender, which requires further well-designed RCT where these issues are taken into consideration.

4.4. Conclusion

This meta-analysis is dedicated to elucidating the effects of exogenous melatonin, compared to the placebo, on the nocturnal outcomes of secondary sleep disorders. Meta-analysis of the data from a series of studies with small sample size demonstrates that exogenous melatonin improves the sleep quality of secondary sleep disorders. Based on the current advantages of melatonin in the management of secondary sleep disorders, it is hoped that there will be a tremendous growth in the use of melatonin application worldwide. Besides, little evidence is available regarding the adverse effects of long-term use of melatonin (Brzezinski, 1997; Zisapel, 2018). Clinicians should be alert to these shortcomings but also aware of the potential role of melatonin in clinical psychiatry and sleep medicine. Although further studies are needed to establish the optimal approach to this treatment in clinic, this meta-analysis clearly supports the use of melatonin as a management for patients with secondary sleep disorders as a complementary therapy.

5. Authors' contributions

Yang Y designed the study. Li T and Jiang S searched the literature and wrote the manuscript. Li T and Yang Z verified the data and participated in the resolution of disagreements. Han MZ, Lv JJ, and Deng C extracted and analyzed the data. Yang Z draw the picture. Reiter RJ revised the manuscript. All authors read the manuscript with critical revision

6. Disclosures

All authors declare no competing interests. The National Natural Science Foundation of China and China Postdoctoral Science Foundation have no roles in the design, data collection and analysis, writing of the report, or approval of the manuscript.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (81500263 and 81673578) and China Postdoctoral Science Foundation (2016T90973 and 2015M572681). We are indebted to the authors of the primary studies. Furthermore, we sincerely appreciate the hard work from the distinguished editors and reviewers.

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