SLEEPJ, 2021, 1–11

doi: 10.1093/sleep/zsab077
Advance Access Publication Date: 26 March 2021
Original Article

ORIGINAL ARTICLE

The effect of non-benzodiazepine sedative hypnotics on CPAP adherence in patients with OSA: a systematic review and meta-analysis

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Abstract

Study Objectives: This meta-analysis aimed to explore the effect of non-benzodiazepine sedative hypnotics (NBSH) on continuous positive airway pressure (CPAP) adherence in patients with obstructive sleep apnea (OSA).

Methods: We conducted a systematic search through PubMed, Medline, the Cochrane Library, EMBASE, Scopus and ClinicalTrials (all searched from inception to August 15, 2020). Publications were limited to articles, clinical conferences and letters, including randomized controlled trials and retrospective studies. We used a random-effects model to calculate the odds ratio (OR) and mean difference (MD) with corresponding confidence interval (CI). Subgroup analyses were conducted to analyze the sources of heterogeneity.

Results: Eight studies fulfilled the inclusion and exclusion criteria for patients newly diagnosed with obstructive sleep apnea. Overall, the use of NBSH was associated with increased use of CPAP per night (MD = 0.62 h; 95% CI = 0.26–0.98) and use for more nights (MD = 12.08%; 95% CI = 5.27–18.88). When a study seriously affecting heterogeneity was removed, more patients adhered well with CPAP use (pooled OR = 2.48; 95% CI = 1.75–3.52) with good adherence defined as CPAP use for >4 h/night on >70% of nights. Among prescribed NBSHs, eszopiclone showed the most significant effect on CPAP adherence.

Conclusion: CPAP adherence may increase in OSA patients treated with non-benzodiazepine sedative hypnotics especially eszopiclone. The effect of zolpidem and zaleplon on CPAP adherence requires further investigation by larger scale, randomized, controlled trials.

Statement of Significance

Continuous positive airway pressure (CPAP) therapy is currently the gold standard treatment for obstructive sleep apnea (OSA). The longer patients use CPAP, the greater the benefit. Nonetheless, adherence to CPAP is less than ideal. The improvement of CPAP adherence with non-benzodiazepine sedative hypnotics (NBSH) is controversial. Our review and meta-analysis demonstrated that NBSHs especially eszopiclone, may improve CPAP adherence in patients with OSA. There is a need for large prospective studies with long term follow-up to determine the effects of zolpidem and zaleplon on CPAP adherence. It is also important to determine whether the severity of OSA affects CPAP adherence with NBSH.

Key words: obstructive sleep apnea; non-benzodiazepine sedative hypnotics; CPAP; adherence; eszopiclone; zolpidem; zaleplon

Submitted: 18 October, 2020; **Revised:** 22 March, 2021

Introduction

Obstructive sleep apnea (OSA) is a potentially serious sleep disorder. It causes breathing to repeatedly stop and start during sleep and is likely to result in excessive daytime sleepiness, gastroesophageal reflux disease [1], nocturia [2] and high blood pressure. The prevalence of OSA with apnea–hypopnea index (AHI) ≥5 has been reported to be 9%–38% with men more often affected [3]. Awareness of OSA has also increased, with the popularization of related information.

It is strongly recommended that clinicians use continuous positive airway pressure (CPAP) for ongoing treatment of OSA in adults [4]. The longer CPAP is used, the greater the benefits. Nonetheless, adherence with treatment has been less than ideal under for various reasons. Recently, average adherence to CPAP has been reported to be 4.5 h per night [5]. Despite numerous advances in machine dynamics including softer masks, quieter pumps, and improved portability, adherence to CPAP remains poor and a concern for clinicians. No meaningful improvement in adherence rates in the research setting has been discernible over the two decades of data available since objective CPAP monitoring was introduced, with adherence rates generally ranging from 30% to 60 % [5, 6]. Initial treatment of OSA requires early identification of difficulties with CPAP use, as adherence over the first few days has been shown to predict long-term adherence [7–9]. Therefore, intervention and improvement in early CPAP use seem to be a potentially effective method to improve adherence.

Non-benzodiazepine sedative hypnotics (NBSH) mainly includes zolpidem, zaleplon, and eszopiclone. It has been reported that NBSH can promote sleep onset and continuity without altering sleep architecture [12]. Regardless of their baseline AHI (mild, moderate, severe, or no OSA), most patients do not develop any polysomnographically evident worsening of existing AHI when using NBSH [10]. As opposed to benzodiazepines that have potential adverse effects, such as decreased wakefulness, airway muscle tone, and ventilation response to hypoxemia [11], NBSH are safer during the initial treatment phase of CPAP in OSA. Nonetheless, the efficacy on CPAP adherence has been controversial in some studies [12–19], and thus a meta-analysis is warranted.

Methods

Standard protocol approval and registration

The systematic review followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [20]. The protocol was registered in the Prospero database (registration number CRD42020207574)

Search strategy

Index terms such as medical subject headings (MeSH) and free text were utilized to capture a broad range of literature. Index terms were limited to those identified in the title, abstract and keywords. We conducted a systematic search through PubMed, Medline, EMBASE, Scopus, Cochrane Database of Systematic Reviews and ClinicalTrials (all searched from inception to August 15, 2020). The search terms are described in the supplemental materials (Tables S1–S3).

Study selection

Titles and abstracts were independently reviewed by two authors (D.H.W. and Y.K.T.) to select eligible studies. Duplicates from different databases were removed. The full text of the eligible studies was retrieved and studies were excluded if the inclusion criteria were not met. Again, two authors reviewed the full texts independently. Any disagreements were resolved through discussion, and a third author was available to arbitrate if necessary.

Inclusion and exclusion criteria

Inclusion criteria

(1) Adult patients newly diagnosed with OSA by PSG (AHI ≥ 5). (2) At least one NBSH (zaleplon, zolpidem, and eszopiclone) included in the study. (3) Clearly the definition of the experimental and control groups. (4) At least one of the following outcome measurements included: nights of CPAP use, CPAP use per night and the number of patients or percentage who showed good adherence with CPAP. (5) Include abstracts or letters if the required information was included.

Exclusion criteria

(1) The study mentioned only the effect of NBSH on the AHI or other treatment of CPAP. (2) Patients regularly used a sedative or had other concomitant conditions such as PTSD and insomnia. (3) Patients received treatment other than an NBSH, such as remote monitoring.

Data extraction

Information was collected for each publication and included first author, publication year and type, study design, number of patients, age, percentage of male, body mass index (BMI), apnea–hypopnea index (AHI), study duration, blinding, dropout rate, experimental, and control group.

Statistical methods

Review Manager Software (version 5.3) was used to analyze the statistics. The various methodologies such as study design and protocols may result in heterogeneity of studies. The random-effects model was used if significant heterogeneity was found; otherwise, the fixed-effects model was applied. Higgins I^2 test was used to assess the heterogeneity. An I^2 value of 25%–50% was considered low heterogeneity, an I^2 value of 50%–75% as moderate heterogeneity, and an I^2 value >75% as high heterogeneity. We also sought to perform subgroup analysis to determine the sources of heterogeneity. The pooled mean difference (MD) of each study and corresponding 95% confidence interval (CI) was used to estimate the percentage of nights use and CPAP use per day. Odds ratio (OR) and 95% CI were used to estimate the number of patients with good adherence.

Quality assessment

We used Review Manager Software (version 5.3) with Cochrane Handbook for Systematic Reviews of Interventions to assess study quality and the risk of bias of randomized controlled

trials (RCT). The Newcastle–Ottawa Scale (NOS) [21] scoring system was used to assess retrospective reviews. Stata 13 (StatCorp LP, College Station, Texas) with trim and fill method was conducted to evaluate the publication bias. Trim and fill method is a nonparametric approach that first trims the smaller studies that cause a funnel plot's asymmetry after estimating the suppressed number, so that the overall effect estimate produced by the remaining studies can be considered minimally impacted by publication bias, and then to fill imputed missing studies in the funnel plot based on the bias-corrected overall estimate. Finally, effect size and its variance based on the filled symmetric funnel plot is estimated [22–24].

Results

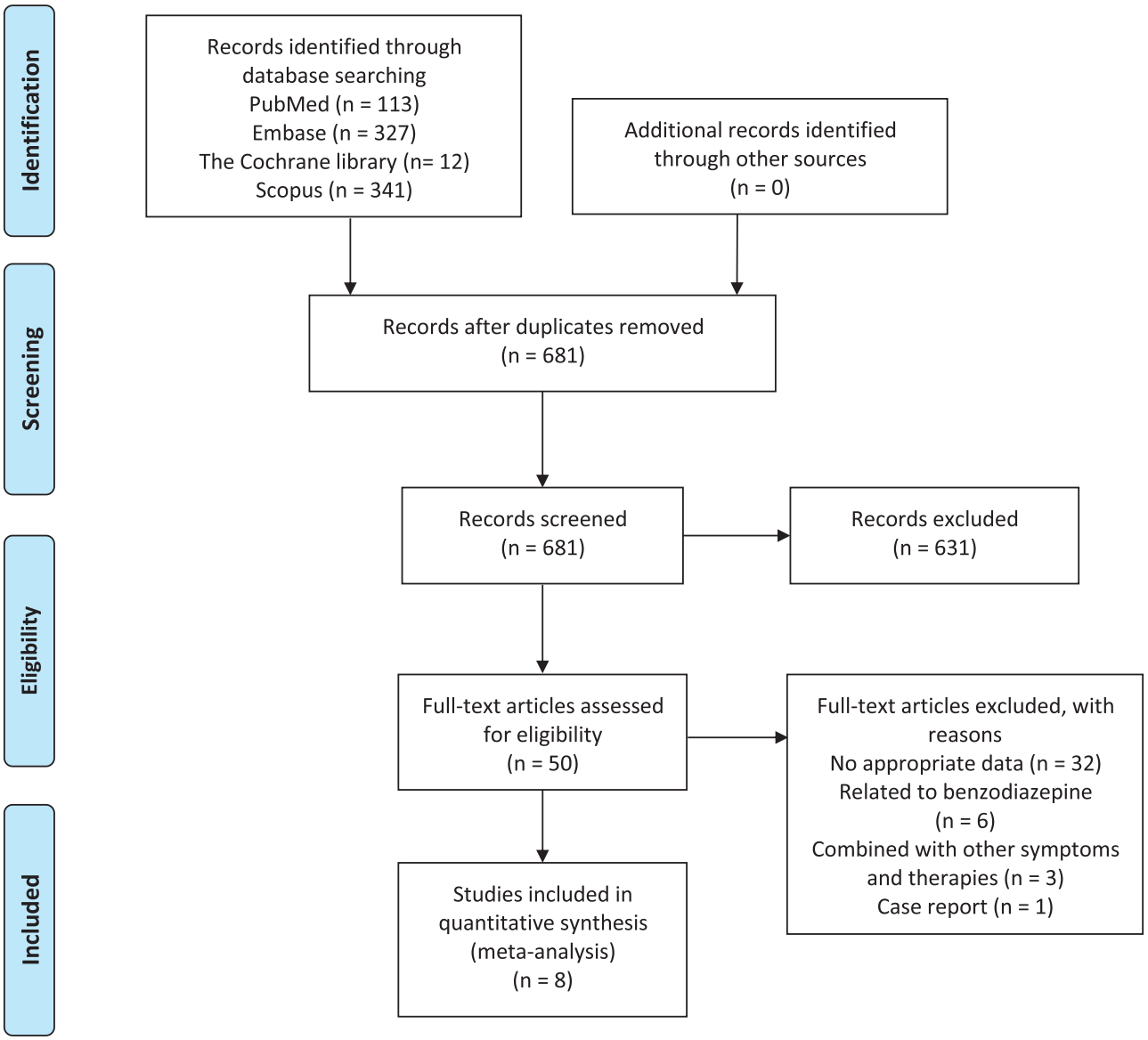
Study selection

According to our search strategy, 793 potentially relevant articles were identified from the electronic databases. After excluding duplicates, 681 articles remained. 631 articles that did not meet the inclusion criterion were excluded after reading the titles and abstracts. After reading the full text of the remaining 50 articles, 32 were excluded because of no appropriate data, 6 were related to benzodiazepine, 3 combined other symptoms and therapies, and 1 was a case report. Eight eligible studies were finally identified [12–19]. The selection process is shown in Figure 1 and detailed information of each study in Table 1.

Finally, after excluding the number of dropouts reported in each study, the meta-analysis comprised a sample size of 1,203 patients and included six RCTs and two retrospective cohort studies. Five studies used eszopiclone, two used zolpidem and one study used zaleplon to evaluate the effect of NBSH on CPAP adherence.

Meta-analysis results

Eight studies reported the effect of NBSH on CPAP use per night and the forest plot is shown in Figure 2, a. Prescription of an NBSH significantly improved the length of CPAP use per



AQ6

Figure 1. The flow diagram of identifying studies through systemic search in multiple databases.

AQ5 **Table 1.** Study characteristics

Source, year	Publication type	Study design	*n*	Age (years)	%male	BMI (kg/m²)	AHI (events/h)	Experimental	Control	Study duration (weeks)	Blinding	Dropout rate (%)	Main outcome
Bradshaw 2006 12	Article	RCT	48	38.2 ± 7.4	100	35.2 ± 5.2	35.4 ± 25.3	Zolpidem	Placebo	4	Double blind	-	Nights of CPAP use %, CPAP use per night h, Good compliance %
Collen 2009 13	Article	Retrospective study	400	47.0 ± 7.7	78	30.3 ± 3.7	41.1 ± 25.1	Eszopiclone	No pre-med	4–6	–	21	CPAP use per night h, Good compliance %
Lettieri-1 2009 14	Article	RCT	160	45.7 ± 7.3	78.6	30.4 ± 4.0	36.9 ± 23.0	Eszopiclone	Placebo	24	Double blind	25	CPAP use per night h, Good compliance %
Lettieri-2 2009 15	Article	RCT	114	44.9 ± 6.7	79	–	29.2 ± 24.3	Eszopiclone	Placebo	4–6	Double blind	16.2	Nights of CPAP use %, CPAP use per night h, Good compliance %
Shah 2009 16	Conference abstract	RCT	136	45.6 ± 9.0	–	30.4 ± 5.3	36.1 ± 27.7	Eszopiclone	Placebo	24	Double blind	-	Nights of CPAP use %, CPAP use per night h
Park 2013 17	Article	RCT	134	49.8 ± 11.3	68.6	35.9 ± 8.7	21.1 ± 20.6	Zaleplon	Placebo	4	Double blind	29.1	Nights of CPAP use %, CPAP use per night h
Holley 2017 18	Article	Retrospective study	397	42.2 ± 10.1	72.9	28.8 ± 4.5	14.9 ± 14.0	Zolpidem	No pre-med	4	–	25.6	CPAP use per night h, Good compliance %
Schmickl 2020 19	Article	RCT	153	44 ± 7	76	30.3	–	Eszopiclone	Placebo	2	–	30.1	CPAP use per night h

BMI, body mass index; AHI, apnea hypopnea index; CPAP, continuous positive airway pressure.

night with a pooled mean difference (0.62 h; 95% CI = 0.26–0.98; $p = 0.0008$). Four studies reported that NBSH increased the percentage nights of CPAP use [12, 15–17] (12.08%; 95% CI = 5.27–18.88; $p = 0.0005$, Figure 2, b). With good adherence with CPAP defined as use for >4 h/night on >70% of nights, five studies reported non-significant results of NBSH (OR = 1.23; 95% CI = 0.70–2.17; $p = 0.47$, Figure 2, c), but this result had a high heterogeneity of 88%. It indicated that one or more studies may have influenced the result and sensitivity analysis would be conducted to evaluate it.

Subgroup analysis

Study design

Eight studies reported the effect of NBSH on CPAP use per night, six RCTs and two cohort studies. The results of the RCTs produced statistically significant results (0.77 h; 95% CI = 0.36–1.18; $p = 0.0002$) while findings of the cohort studies were insignificant (0.23 h; 95% CI = –0.95–1.40; $p = 0.71$). The forest plot of the subgroup analysis is shown in Figure 3, a.

Type of NBSH

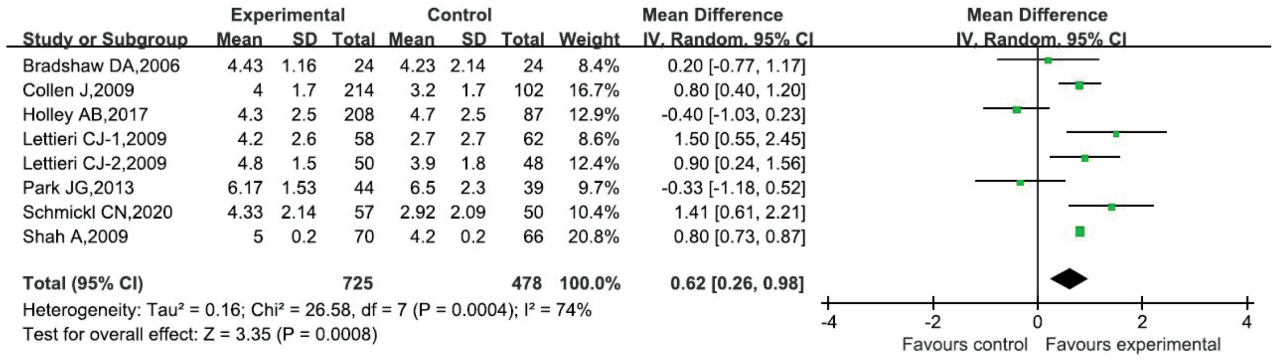
In the eight studies, five used eszopiclone, two used zolpidem, and one used zaleplon. Zaleplon showed a non-significant effect on CPAP adherence in the study reported by Park et al. [17]. No additional study about zaleplon could verify this effect. The study was therefore excluded from this subgroup analysis. Overall results revealed that eszopiclone significantly improved daily CPAP use (0.83 h; 95% CI = 0.70–0.96; $p < 0.00001$) but results were insignificant for zolpidem (–0.22 h; 95% CI = –0.76–0.32; $p = 0.42$) under the random-effects model. The forest plot for the subgroup analysis is shown in Figure 3, b.

Sensitivity analysis

Following subgroup analysis of study design, the coupled forest plots of CPAP use per day show that the heterogeneity differed for RCTs ($I^2 = 60\%$) and retrospective study ($I^2 = 90$) design. Neither of the two retrospective studies [13, 18] was blinded and may have been affected by confounding factors such as selection bias as well as drug differences. Different retrospective studies had greater heterogeneity than RCTs.

In the forest plot of the percentage of nights CPAP use, the results significantly influenced the pooled results (I^2 decreased from 73% to 0%) when we removed Park's study [17]. In their study, zaleplon showed a non-significant effect on the percentage of nights CPAP use which may account for high heterogeneity. The forest plot is shown in Figure 4, a.

(a)



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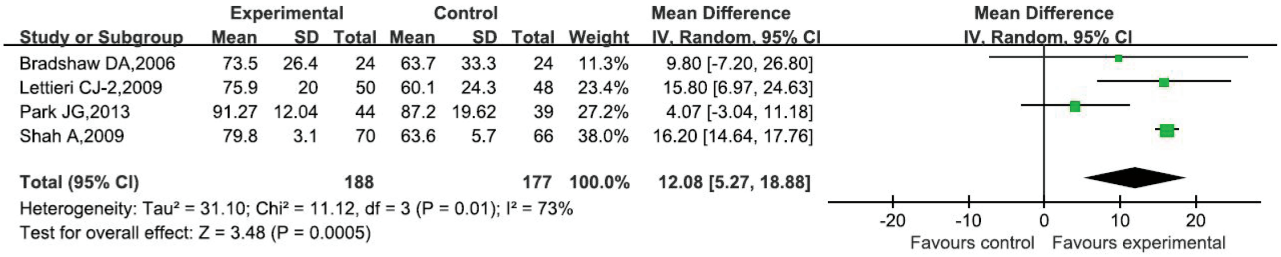

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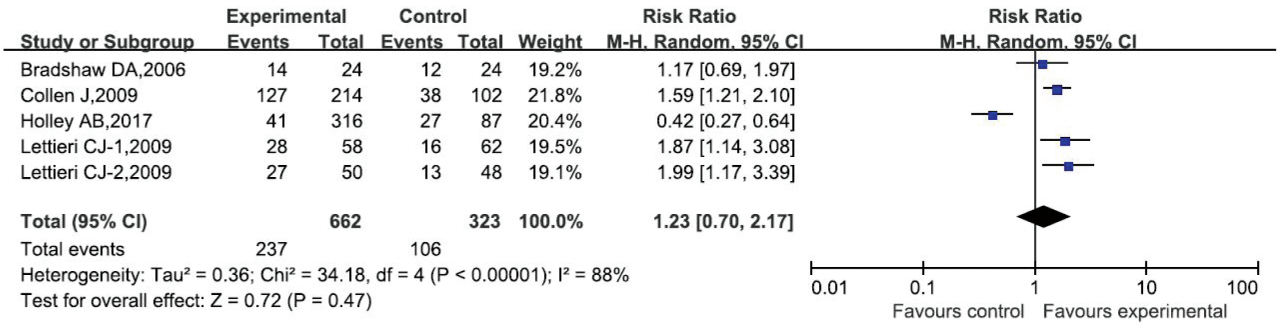


Figure 2. Meta-analysis of CPAP adherence in OSA patients with NBSH compared with controls; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea. (a) CPAP use per night; (b) percentage of nights use; (c) good adherence.

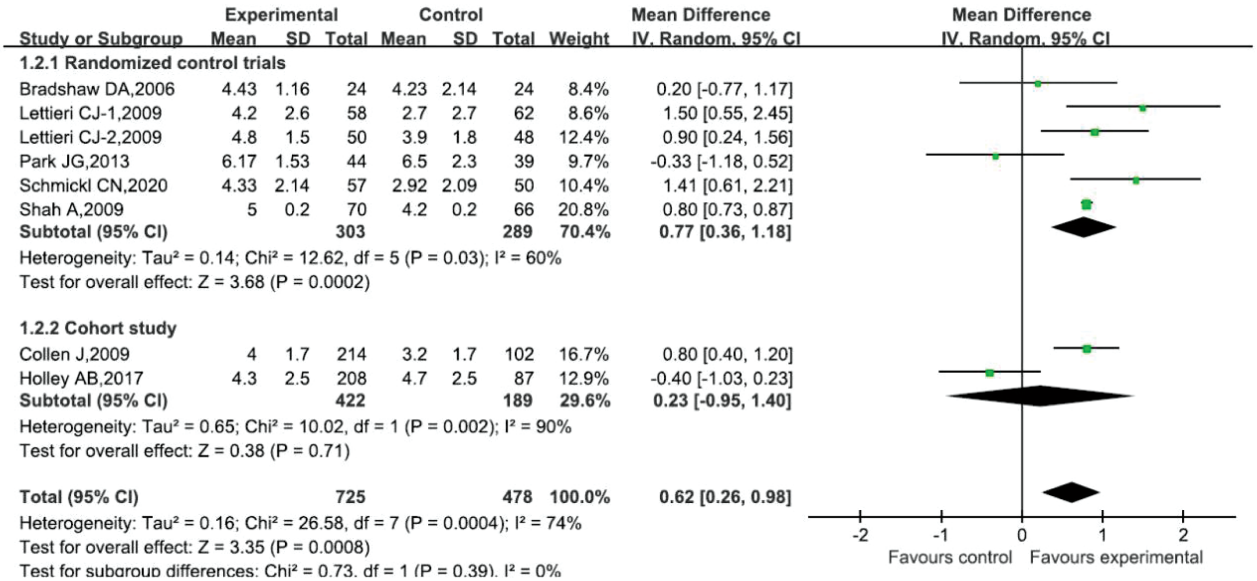
In the forest plot of the number of patients with good adherence, results were significantly influenced by the removal of the study by Holley [18] (I^2 decreased from 88% to 0%). After removal, the results indicated that more patients used CPAP with good adherence (pooled OR = 2.48; 95% CI = 1.75–3.52). The forest plot is shown in Figure 4, b. This would appear to be a plausible result with a low heterogeneity. The study by Holley accounted for heterogeneity, validated in the funnel plot (Figure 5). There are several possible reasons for this. First, the study could not exclude selection bias, patients were governed by specific characteristics that could influence results. The willingness of patients to take drugs prior to CPAP may have differed with more choosing to take zolpidem than pre-medication, and consequent different sample sizes between groups and altered deviation. Second, patients in this study had a lower AHI (14.9 ± 14.0 events/h) compared with the other six studies. This may have resulted in a limited treatment effect of zolpidem on CPAP adherence.

Moreover, when we conducted the subgroup analysis according to the type of NBSH use, the heterogeneity of CPAP use per day was dramatically decreased in eszopiclone (I^2 = 8%) and zolpidem (I^2 = 3%). It turned out that the results of the same drugs were highly consistent across studies.

Risk of bias

Based on the trim and fill method, no missing studies were imputed in the filled symmetric funnel plot (Figure 6). The analysis indicated that the imputed MD was 0.621 (95% CI = 0.257–0.984), consistent with the primary meta-analysis with no trimming performed. Therefore, no study needed to be statistically corrected for funnel plot asymmetry. The detailed results are described in the supplemental materials (Table S4). The methodological quality of included RCTs is shown in Figure 7, and the quality of cohort studies in Table 2. There was a high risk

(a)



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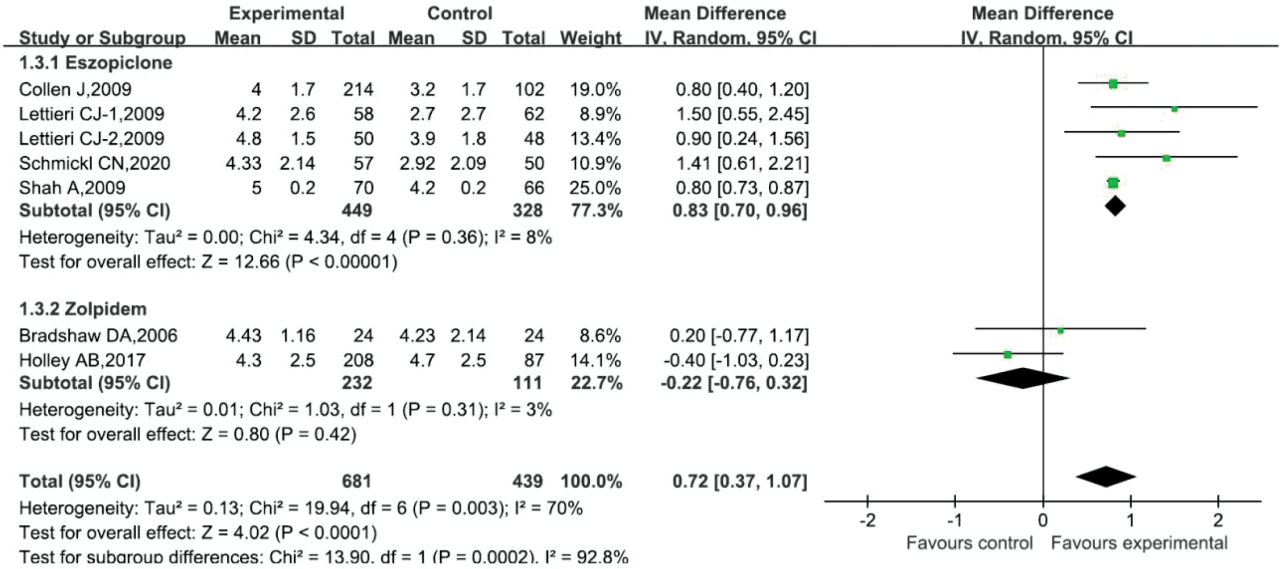


Figure 3. Meta-analysis of subgroup in CPAP use per day. NBSH, non-benzodiazepine sedative hypnotics. (a) Study design; (b) type of NBSH.

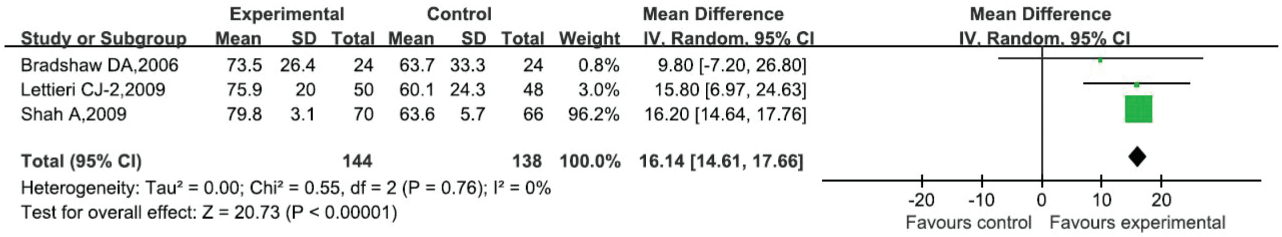
of bias (attrition bias) in the studies by Bradshaw et al. [12] and Lettieri et al. [14]. Bradshaw et al. enrolled a limited number of patients (24 in each group) and the sample size may not have been adequately powered to detect a difference between the experimental and control groups. In the Lettieri et al.'s study, about one-quarter of patients dropped out during the 24-week follow up and did not initiate or have smart card data that due to participants not returning their smart card. Assuming zero use of CPAP for all missing data points, this may actually lead to an underestimation of the effect of eszopiclone on CPAP adherence.

Discussion

This meta-analysis suggests that NBSH significantly improves CPAP adherence, including CPAP use per night, the percentage of the night used and the number of patients with good adherence. The included studies excluded OSA patients who regularly used a sedative and did not assess insomnia symptoms. Following our meta-analysis, we predicted that combination with NBSH treatment would benefit CPAP adherence for OSA patients with insomnia symptoms.

Eszopiclone, zolpidem and zaleplon are newer generation NBSHs prescribed for regular treatment of insomnia, with a high affinity for the BZ/GABA$_A$ receptor [25]. Long-term use of NBSH has been shown to be safe with minimal side effects and no tolerance, withdrawal, dependence, or rebound insomnia [26–28]. The administration of NBSH in OSA patients significantly increased sleep efficiency, reduced sleep latency, and decreased wake time after sleep onset [10]. NBSH also increase the respiratory-arousal threshold as a result of the shift of sleep

(a)



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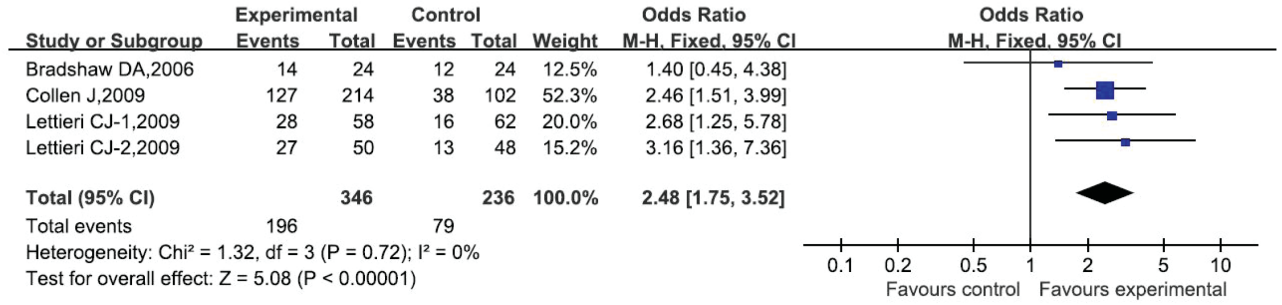

Figure 4. Sensitivity analysis of NBSH on the percentage of nights uses and good adherence. (a) percentage of nights use; (b) good adherence.

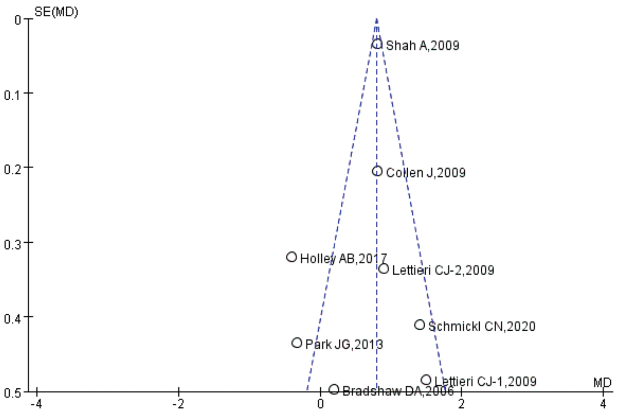

Figure 5. Funnel plots of publication bias in the analysis of CPAP use per night.

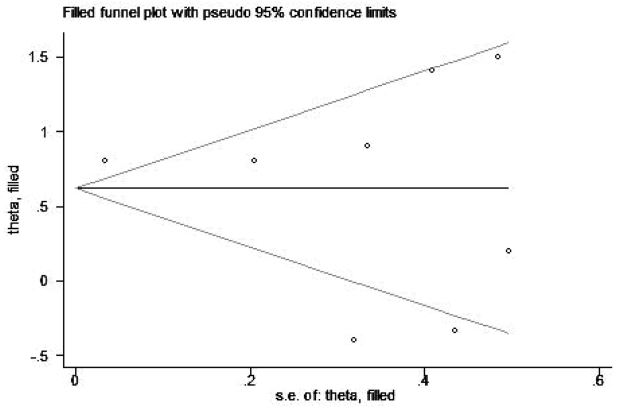

Figure 6. Funnel plots of trim and fill method in the analysis of CPAP use per night.

from stage 1 to stage 2 with no reduction in the amount of stage 3 sleep [29, 30]. In addition, NBSH have no significant adverse effect on AHI or mean and nadir SaO_2 in OSA patients [8, 31]. As such, the use of NBSH are considered safe in patients with long-term CPAP therapy during sleep.

Bradshaw et al. first suggested that zolpidem could not improve CPAP adherence in OSA patients [12]. Nonetheless, all study subjects were male so the influence of gender could not be determined. Similar findings were reported by Holley et al. in a retrospective review [18]. Park et al. showed that adherence with CPAP in both the experimental group (zaleplon) and a control group (placebo) was relatively high although there was no significant difference, making it challenging to discern an additive contribution of zaleplon when the control group was highly satisfied [17]. Since only Park et al. evaluated the effect of zaleplon on CPAP adherence, the evidence on the efficiency of zaleplon is insufficient. In addition to the above studies, other studies including RCT and retrospective study have shown improvements in CPAP adherence. From our meta-analysis, eszopiclone showed the most significant and stable improvement in CPAP adherence (0.83 h; 95% CI = 0.70–0.96; $p < 0.00001$), compared with zolpidem. According to previous studies, the onset of action of zaleplon, zolpidem and eszopiclone was after 15–30, 15, and 15–30 min, respectively. The action duration of zaleplon and zolpidem was short, with a mean elimination half-life of 1 and 1.5–4.5 h [32]. Nonetheless, following a single 3mg dose of eszopiclone, the mean elimination half-life was approximately 6 h in adults and increased to 9 h in adults ≥65 years after a single 2 mg dose [33]. Clearly, eszopiclone has much longer action duration than zaleplon and zolpidem. Since the prevalence of rapid eye movement (REM)-related OSA ranged from 13.5% to 36.7% [34] and respiratory events tend to worsen during REM that prevails during the second half of the night [35], the action of zaleplon and zolpidem may be wearing off at the time when it is most needed and may worsen the

initial experience with CPAP. Therefore, long-acting medication like eszopiclone might significantly improve CPAP adherence.

CPAP use per night as an average over total study nights, was one of the main outcomes in studies reviewed. This outcome was influenced by actual hours of CPAP use each night and the nights of CPAP use. In Collen's study [13], patients who used eszopiclone during their CPAP titration had longer total sleep time (344.7 ± 41.9 min vs 313.7 ± 51.2 min, $p < 0.0005$), similar to the results of the study by Lettieri et al. (350.9 ± 33.6 min vs 319.7 ± 48.7 min, $p < 0.0007$) [15]. These results suggest that eszopiclone could increase sleep duration and may have contributed to the increased actual hours of CPAP use per night. Otherwise, CPAP titration and initial experience also appeared to be a crucial factor in determining its subsequent use [36, 37]. In our meta-analysis, the prescription of an NBSH increased the percentage of nights when CPAP was used [12, 15–17] (12.08%; 95% CI = 5.27–18.88; $p = 0.0005$). Presumed reasons for the improved adherence with nights of CPAP use included a more effective CPAP titration, a better initial experience with CPAP, and increased patient confidence that CPAP would improve sleep efficiency.

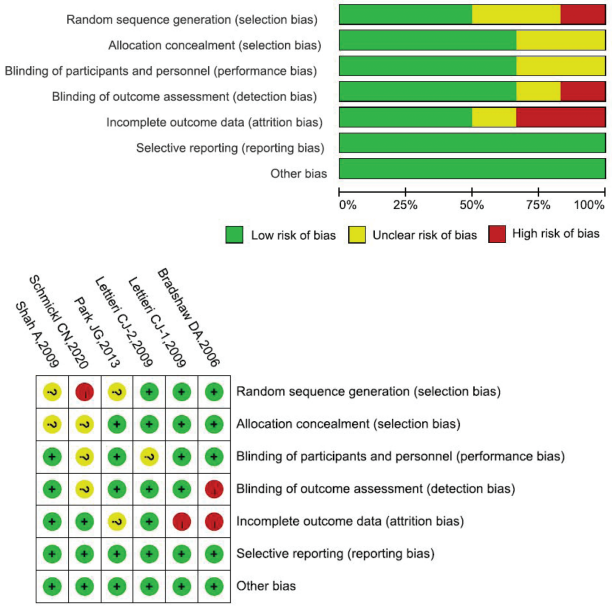

Figure 7. Risk of bias summary and graph: review of authors' judgments about each risk of bias item for each included study. The PRISMA guidelines require an analysis of potential biases that would lead to underestimation or overestimation of the true intervention effect. Referring to the PRISMA guidelines, the authors judged the risk of bias (low, unclear, high risk of bias) for the following items for each included study: selection bias, blinding of the participants and personnel, detection bias, attrition bias, reporting bias, and other bias. Shown are the authors' judgments about each risk of bias item for each study (upper part) and as percentages across all included studies (lower part).

Good adherence or adequate adherence is commonly defined as use for at least 4 h per night for at least 70% of nights. This is also the standard used by some countries to authorize continued reimbursement for PAP after the initial 90 days of therapy [38, 39]. The definition of good adherence is scientific since some improvement in symptoms and complications in OSA patients is associated with the duration of CPAP use. The data demonstrated that CPAP use for more than 4 h could improve subjective sleepiness, 6 h could improve objective sleepiness, and >7 h could significantly improve quality of life [40].

Furthermore, improvements may be seen in OSA patients with some adverse cardiovascular events by reducing 24-h ambulatory mean blood pressure [41]. Use of PAP for at least 6 h per night might also result in clinically improved memory in patients with previous verbal memory impairment [42]. It appears beneficial to increase duration of CPAP use per night, especially beyond the recommended 4 h. However, how the duration of use specifically affects the efficacy of CPAP requires further verification.

Educational, supportive and behavioral interventions may improve CPAP use by patients with OSA. Educational interventions include videos, group education sessions, an individual explanation of polysomnography (PSG) reports [43–45]. Supportive interventions mainly include telemonitoring using various formats and platforms [46, 47]. Behavioral interventions include Motivational Enhancement Therapy (MET) aimed at resolving

Table 2. NOS for assessment of quality of included studies—cohort studies

Quality assessment criteria	Acceptable (*)	Collen J 2009	Holley AB 2017
Selection			
Representativeness of the exposed cohort?	Representative of average adult in community (age/sex/BMI/being at risk of disease)	*	*
Selection of the non-exposed cohort?	Drawn from the same community as the exposed cohort	*	*
Ascertainment of exposure?	Secured records, structured interview	*	*
Demonstration that outcome of interest was not present at start of study?	Yes	*	*
Comparability			
Study controls for regular use of hypnotics and sedatives?	Yes	*	*
Study controls for additional risk factor?	Age, sex, BMI, AHI, severity of OSA	–	–
Outcome			
Assessment of outcome?	Independent blind assessment, record linkage	*	*
Was follow-up long enough for outcomes to occur?	Follow-up >1 month	*	*
Adequacy of follow up of cohorts?	Complete follow-up or subjects lost to follow up unlikely to introduce bias	–	–
Total score		7	7

NOS, Newcastle-Ottawa scale; BMI, body mass index; AHI, apnea–hypopnea index; OSA, obstructive sleep apnea.

ambivalence towards treatment and a combination of various motivational strategies [48–50]. In Askland's meta-analysis, educational interventions increased the duration of CPAP use (MD = 0.85 h; 95% CI = 0.06–1.64), based on six studies with 698 participants. Supportive intervention increased average hours of CPAP use per night (MD = 0.91 h; 95% CI = 0.57–1.25), based on seven studies with 735 participants. Behavioral interventions increased average hours of CPAP use (MD = 1.32 h; 95% CI = 0.93–1.72), based on six studies with 525 participants [51]. Saraç et al. suggested that educational interventions predicted CPAP compliance (OR = 3.6; 95% CI = 1.2–10.6; p = 0.020) [52]. Nonetheless, Tamisier et al. reported that multimodal telemonitoring intervention had no effect [53]. As above, there were a variety of interventions to improve CPAP adherence that paid high attention to urge OSA patients with large individual differences to insist on using CPAP initiatively and did not have definitive conclusions. A CPAP device records the time when the mask is being worn and fails to distinguish the duration of wake from sleep. There are times when a patient is awake and not using CPAP. All the above interventions had only limited benefits of CPAP and did not improve sleep efficiency. NBSH reduces sleep latency and lowers the arousal threshold. This may benefit patients with OSA by increasing sleep duration and effective CPAP use. Moreover, patients with OSA may be more willing to use CPAP if the initial experience is improved by the addition of an NBSH. Therefore, the benefits of NBSH combined with other interventions on CPAP adherence should be targeted at patients with OSA.

Based on the above analysis, we suggest that clinicians may routinely prescribe a single 3 mg dose of eszopiclone to patients with OSA prior to CPAP titration and for the following 2 weeks of CPAP therapy. Average CPAP adherence over six months should be encouraged in patients with OSA. Otherwise, those patients who are prescribed an NBSH can benefit from more hours of CPAP that will improve objective sleepiness and quality of life. Of note though, long-term use of NBSH may impose psychological and financial burdens on patients. In Rösner's meta-analysis [54], the statistically significant adverse events of eszopiclone were an unpleasant taste, dry mouth, somnolence, anxiety and dizziness. There was no significant difference between eszopiclone and placebo in the occurrence of serious adverse events (RD = 0.00, 95% CI = 0.01–0.01; participants = 4,289; studies = 12; I^2 = 0%). Long-term use of NBSH is associated with certain risks. Therefore, whether OSA patients should take NBSH before each use of CPAP and therapeutic dosing need to be carefully discussed and further investigated.

There are some potential limitations in the meta-analysis that should be noted when interpreting the results of our study. First, the CPAP device and mask comfort might differ between studies. Second, we did not analyze the severity of OSA in subgroups. Third, although heterogeneity was significantly reduced after we performed subgroup analysis based on drugs, the sample size of zolpidem and zaleplon was insufficient. Last, the included studies did not use scales to assess the degree of the initial experience, so could not directly determine the correlation between initial experience and subsequent CPAP adherence. Many trials showed a gradual decline in long-term adherence over time or terminated interventions [48, 55–57]. Whether continuous treatment with NBSH can maintain good adherence with CPAP, and how long can early treatment with NBSH have a significant effect on CPAP adherence are both unclear. Thus, the relationship between NBSH and long-term adherence with CPAP could not be determined in this meta-analysis. Our results still require further confirmation by larger scale, randomized, controlled trials with three drugs and more parameters.

Conclusions

In summary, CPAP adherence should be encouraged in patients with OSA. Administration of non-benzodiazepine sedative hypnotics, especially eszopiclone, significantly improves CPAP adherence in OSA patients. The benefits of zolpidem and zaleplon in CPAP adherence remain a matter for debate and require evaluation by larger scale, randomized, controlled trials.

Acknowledgments

D.H.W. designed the study. S.Z. and Y.K.T. extracted the data and ran the analysis. D.H.W. wrote the first draft of the article. Y.H.C., S.Z., D.J.M., Y.T.L., S.W.L., X.F.S., X.N.W., C.L.L. contributed equally. All authors read and approved the final manuscript.

Disclosure Statement

Financial Disclosure: All authors declared no conflict of interest.
Non-financial Disclosure: None.

Funding: This work was supported by the Natural Science Fou ndation of Guangdong Province China (No. 2019A1515010981). The funding bodies had no role in design, data collection and analysis, or interpretation of the findings.

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