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UROLOGY - REVIEW

Efficacy and safety of desmopressin in women with nocturia: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Purpose To evaluate the efficacy and safety of desmopressin treatment in women with nocturia.

Methods The PubMed, EMBASE, ISI web of knowledge, and the Cochrane Controlled Trial Register of Controlled Trials were searched from their inception date till April, 2019. The meta-analysis was performed by Revman 5.3. This review also stratified each outcome by dose (< 25 μg, 25 μg versus > 25 μg) to explore the differences in the dose response for orally disintegrating tablet (ODT).

Results Seven publications with seven trials were included in this review. The methodological quality of these trials was fair, and four studies had low risk of bias. The number of nocturnal voids per night was significantly decreased by desmopressin when compared to the control [6 trials, Weighted Mean Difference (WMD) = 0.41, $P < 0.00001$], and the difference between < 25, 25 and > 25 μg dose ODT groups was also significant ($P = 0.03$). The duration of first sleep period was significantly increased by desmopressin [4 trials, WMD = 66.64, $P < 0.00001$], and the difference between these three doses ODT was not significant ($P = 0.15$). Overall, the risk ratios (RR) for 33% responder rate showed significance when compared with desmopressin to controls [3 trials, RR = 1.30, $P = 0.0003$]. The number of total adverse events was similar in both desmopressin and control groups [5 trials, RR = 0.95, $P = 0.59$], otherwise, showed no significant difference between different ODT dose groups ($P = 0.82$).

Conclusions Desmopressin had certain efficacy and adequate safety in women with nocturia. The exploration of appropriate dose for female patients, and other influential factors, such as age should be conducted and considered in future.

Keywords Efficacy · Safety · Desmopressin · Nocturia · Gender differences · Meta-analysis

Introduction

Nocturia is one of the most troublesome lower urinary tract symptoms, and is defined as the need to wake to void once or more per night according to the International Continence Society [1]. Adults aged over 50 generally awake 1.5–2 times overnight, and those with nocturia account for approximately 68% [2]. Based on the degree of bother, the number of night voids is defined as clinically significant nocturia if it is twice or more voids per night [3]. It is associated with a multifactorial etiology, and nocturnal polyuria is one of the major components responsible for the cause of up to 70% of nocturia. The incidence of nocturia increases with age and demonstrates significant adverse events in adults including reduced quality of life, increased risk of falls and mortality [4].

Conservative treatments focused on fluid restriction and behavioral modification, while the evidences of pharmacotherapy with alpha blockers and anticholinergic medications for nocturia also showed ambiguous results [5, 6]. Desmopressin (esamino-8-D-arginine vasopressin) is a selective vasopressin receptor two agonist with antidiuretic activity. This can be used to treat nocturia, especially in adults with nocturia [7, 8]. But due to pure water accumulation, and dilution of the body sodium, it causes hyponatremia. This is defined as a potentially lethal metabolic condition that

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causes even death secondary to the use of desmopressin for nocturia in older adults [9].

Desmopressin has most recently been formulated as an orally disintegrating tablet (ODT), which is administered sublingually without water. This formulation is associated with increased bioavailability, allowing lower dosing than with the original. According to a previous study, a gender difference was observed with regard to desmopressin ODT sensitivity in adults when used at low doses. The decrease in nocturnal urine volume in patients treated with desmopressin ODT over 28 days was significantly larger for women than for men at the lower desmopressin melt doses of 10 and 25 µg. There were a greater proportion of desmopressin prescriptions to women than men for the lowest dose, which was consistent with greater sensitivity to desmopressin in women [10]. Increasing incidence of hyponatremia is observed with increasing doses, and at the highest dose level of 100 µg, the decrease in serum sodium was approximately twofold greater in women over 50 years age than in men [11]. The reason for this might be due to that the analysis of efficacy and safety of desmopressin for nocturia should be based on different genders. The benefits and harms of desmopressin use in men with benign prostatic hyperplasia have been proved, while not in women [9]. Hence, this meta-analysis and systematic review aimed to evaluate the efficacy and safety of desmopressin in women with nocturia, and explore the differences in the dose response for desmopressin ODT.

Materials and methods

A systematic review was performed according to the Cochrane Systematic Reviews Guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [12, 13].

Search strategy

PubMed, EMBASE, ISI web of knowledge, and the Cochrane Controlled Trial Register of Controlled Trials were searched from their inception date till April, 2019 to identify randomized controlled trials (RCTs) that assessed the efficacy and/or safety of desmopressin for the treatment of nocturia in women. The following search terms were used: desmopressin, Minirin, DDAVP, nocturnal polyuria, nocturnal enuresis, nocturia, randomized controlled trial, RCT. The references for all eligible articles, including related systematic reviews were searched manually for additional relevant articles.

Study selection criteria

Inclusion/exclusion criteria were defined and applied according to Population, Intervention, Comparison, Outcomes, and Study (PICOS).

Participants Eligible patients were females older than 18 years with nocturia (two or more voids per night), and were determined by at least 3-day patient-held diaries. Nocturia is defined according to the International Continence Society as the need to wake to void once or more per night. Nocturia that occurs twice or more per night can have substantial adverse effects on the patient's quality of life (QOL), and in many cases require treatment [1, 14].

Intervention Desmopressin administration, dose and course of treatment were not limited.

Comparison All types of comparisons could be accepted, including the placebo or other treatments.

Outcomes The efficacy outcomes included number of nocturnal voids per night after treatment, duration of the first sleep period, and 33% responder rate. The safety outcome was the incidence of total adverse events (AEs). The number of nocturnal voids per night after treatment was the primary outcome, and the others were secondary outcomes.

Study Any published or unpublished RCTs were selected.

The trials that enrolled participants without any gender constraint, and the analyses with different genders separately were also included on the premises of randomization. We excluded studies in children and in specialized populations such as patients with multiple sclerosis.

Study selection

Two reviewers independently conducted the study selection based on the inclusion criteria. After deleting the duplications, they screened the titles and abstracts for all identified potential studies. All articles with possible relevance were then retrieved in full-text for comprehensive assessment with inclusion criteria. Any disagreement between them was resolved by discussion or by reaching a consensus with a third reviewer.

Data collection

Two reviewers independently extracted the data, and disagreement was resolved by discussion or consensus was reached with the help of a third reviewer. All study

characteristics and data, such as study population, sample size, and outcome data, were extracted according to a predefined form. Duplicate publications and missing data were dealt with by utilizing the methods from the Cochrane Collaboration Guidelines [12].

Quality assessment

Methodological quality and risk of bias were assessed in accordance with the Cochrane Collaboration Guidelines for the risk of bias by two reviewers independently, and disagreements were resolved by a third reviewer [12]. The items for the risk of bias were divided into seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other types of biases. The bias was described either as a low or high risk of bias; and "unclear" if the risk of bias was unclear.

Statistical analysis

Statistical analysis was performed by two reviewers independently. The meta-analysis was performed by Revman 5.3. The results were expressed as risk ratios (RR) for dichotomous outcomes. For continuous outcomes with change data, weighted mean difference (WMD) or the standardized mean difference (SMD) was used, with 95% confidence intervals (CI). The SMD was applied if the outcome data were not recorded in a congress method. A fixed-effects model was used if there was no significant heterogeneity; otherwise, a random-effects model was used. Cochrane's χ^2 test and I^2 were used to assess heterogeneity. It was assumed if the P value was less than 0.10 of the χ^2 test. If the I^2 value was above 75%, there was considerable level of heterogeneity [12]. Each outcome in this meta-analysis was stratified by dose (< 25 µg, 25 µg versus > 25 µg) to explore the dose response difference for only desmopressin ODT considering the bioavailability of different dosage forms. Publication bias was tested by Begg's funnel plot and Egger's publication bias plot [15, 16]. They were performed using STATA 15.0 software (StataCorp, College Station, TX).

Results

Initially, 1059 potentially relevant articles were identified. Of these, 528 articles were excluded due to different publications. Of the remaining 531 articles, 439 articles were excluded after evaluating the titles and abstracts. Eighty-five articles were excluded as they did not meet the inclusion

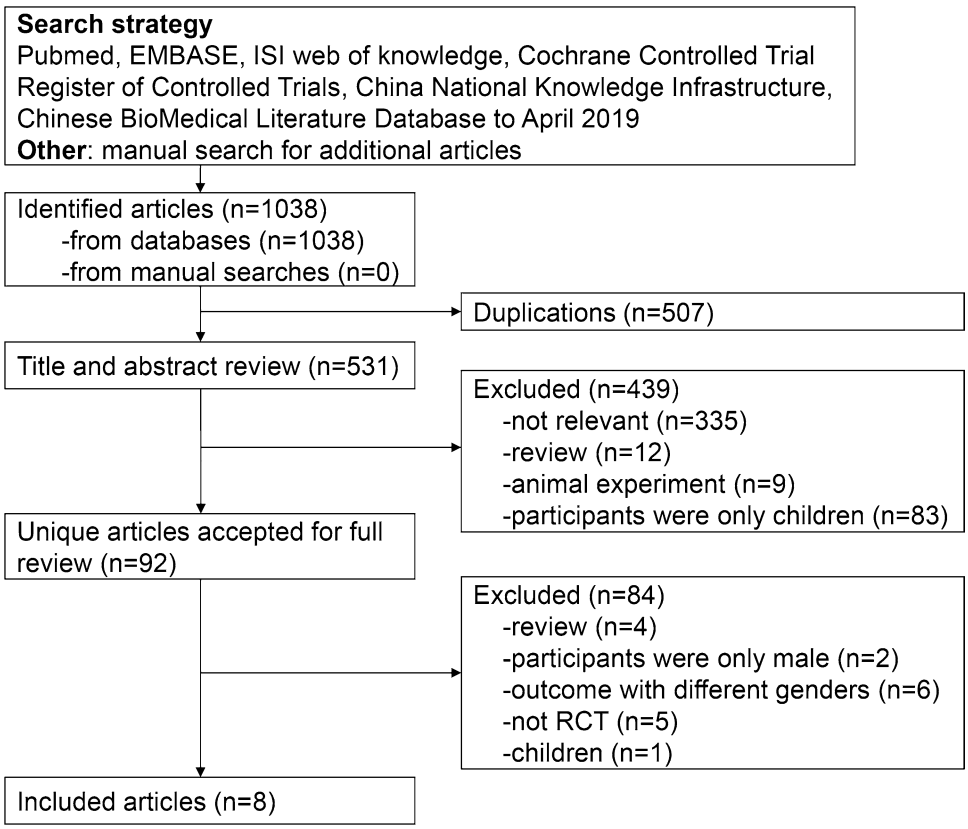

Fig. 1 Summary of literature identification and selection process

criteria after reading the full texts. Finally, seven studies with seven trials were included in this review [17–23]. The selection process of the studies is shown in Fig. 1.

All studies included were published between 2003 and 2018, and all of them were in English. These studies are conducted in USA, Canada, Japan, Denmark, Sweden, United Kingdom, and Netherlands. The study by Weiss et al., was a post hoc analysis of [21, 22].

Study characteristics

Most of the trials enrolled women alone, except one trial that enrolled participants without gender constraint, and analyzed with different genders separately on the premise of randomization [19]. One trial used a nasal spray, one with acetate, while the others used desmopressin ODT. All these trials compared desmopressin with placebo plus complementary therapy or not. While, the dose of desmopressin ranged from 10 to 400 μg, with duration from 3 weeks to 3 months. Two trials only included old female participants, and the remaining included females aged ≥ 18 years. The sample sizes ranged from 25 to 341. The characteristics of trials included in the present meta-analysis are given in Table 1.

Quality assessment

Methodological quality of these included trials was not bad generally. The methodological quality of the trials is presented in Fig. 2.

Most of these trials reported an adequate method of randomization, except two trials failed to report the method of randomization [17, 23]. Over half of these did not have an adequate description of allocation concealment [17, 20, 23]. All studies included blinding of participants and personnel, and the same with blinding of outcome assessment. All relevant trials have adequately addressed incomplete outcome data. Three trials reported that the study was free of suggestions of selective outcomes reporting, as the trials were registered on http://www.clinicaltrials.gov; while the others had no description. Other biases were suspected in five trials as they were sponsored by Ferring Pharmaceuticals A/S [18–21, 23].

Efficacy outcomes

Primary outcome

Due to small statistical heterogeneity between the trials, the fixed-effects model was applied. All the seven trials reported the number of nocturnal voids per night after treatment, and the number of nocturnal voids was significantly decreased by desmopressin treatment [6 trials, 919 participants, WMD = −0.41, 95% CI = −0.54 to −0.29, $P < 0.00001$]. The reduction in the number of nocturnal voids was −0.24 in < 25 μg desmopressin ODT dose group [2 trials, 104 participants, WMD = −0.24, 95% CI = −0.70 to 0.21, $P = 0.29$], −0.27 in 25 μg desmopressin ODT dose group [4 trials, 451 participants, WMD = −0.27, 95% CI = −0.44 to −0.10, $P = 0.002$], and −0.64 in > 25 μg desmopressin ODT dose group when compared to controls [3 trials, 339 participants, WMD = −0.64, 95% CI = −0.86 to −0.41, $P < 0.00001$], with significant difference between these three dosage groups ($P = 0.03$). The comparison of reduction in the number of nocturnal voids per night is shown in Fig. 3, and the subgroup analysis for desmopressin ODT in Fig. 4.

Secondary outcome

The duration of the first sleep period was significantly increased after desmopressin treatment [4 trials, 571 participants, WMD = 66.64, 95% CI = 49.62–83.67, $P < 0.00001$]. The results showed an improvement of 19.85 in the low-dose ODT group (< 25 μg dose) [2 trials, 86 participants, WMD = 19.85, 95% CI = –36.22 to 75.92, $P = 0.49$], 38.35 in the moderate-dose ODT group (25 μg dose) [3 trials, 173 participants, WMD = 38.35, 95% CI = 6.59–70.11, $P = 0.02$], and 83.59 in the high-dose ODT group (> 25 μg dose) [3 trials, 265 participants, WMD = 71.82, 95% CI = 43.01–100.62, $P < 0.00001$]. Meanwhile, the difference between these three doses ODT showed no significant differences ($P = 0.15$). Comparison of the change in duration of the first sleep period is presented in Fig. 5, and the subgroup analysis for desmopressin ODT in Fig. 6.

Only three trials reported 33% responder rate, and all of them were desmopressin ODT [20, 21]. Overall, the difference of RR for 33% responder rate showed significant differences [3 trials, 708 participants, RR = 1.30, 95% CI = 1.13–1.50, $P = 0.0003$] between the desmopressin ODT group and control group. When stratified by dose, the RR for 33% responder rate showed no significance in any ODT dose groups ($P = 0.48$). The results of comparison for 33% responder rate are presented in Fig. 7.

Safety outcome

Five RCTs with the safety of desmopressin in the treatment of nocturia were included in the analysis. The results revealed that the number of total AEs was similar in both desmopressin and control groups [5 trials, 646 participants, RR = 0.95, 95% CI = 0.79 to 1.15, $P = 0.59$]. There was no significant difference between different dosage groups ($P = 0.87$). The comparison of the incidence of AEs is presented in Fig. 8, and the subgroup analysis for desmopressin ODT in Fig. 9.

Table 1 The characteristics of trials included in the present meta-analysis

Study	Country	Study population	Sample size	Treatment	Control	Follow-up	Outcome
Hilton (1982) [17]	United Kingdom	Women with nocturia (≥ 2 nocturnal voids)	11/14	Desmopressin, orally, 20 μg, 6 weeks	Placebo, orally, 6 weeks	6 weeks	No. of nocturnal voids, nocturnal urine output, diurnal urine output, diurnal urinary frequency, incidence of urinary symptoms, AEs
Lose (2003) [18]	Denmark, Sweden, United Kingdom, Netherlands	Women with nocturia (≥ 2 nocturnal voids, nocturia index score > 1), aged ≥ 18 years	72/72	Desmopressin, orally, 0.1, 0.2, or 0.4 mg, 3 weeks	Placebo, orally, 3 weeks	3 weeks	No. of nocturnal voids, duration of first sleep period, nocturnal diuresis, ratio of nocturnal/24-h urine volume, ratio of nocturnal/day urine volume, AEs
Weiss (2012) [19]	USA, Canada	≥ 18 years of age, with an average of ≥ 2 voids	66/73/65/71/66	Desmopressin, orally, 10, 25, 50, or 100 μg, 4 weeks	Placebo, orally, 4 weeks	4 weeks	No. of nocturnal voids, duration of first sleep period, 33% responder rate, N-QoL, nocturnal/total urinary volume, AEs, serum sodium
Yamaguchi (2013) [20]	Japan	Women with nocturia (≥ 2 nocturnal voids), aged 55–75 years	12/12/9/9/11	Desmopressin, orally, 10, 25, 50, or 100 μg, 28 days	Placebo, orally, 28 days	28 days	No. of nocturnal voids, duration of first sleep period, nocturnal urine volume, Pittsburgh Sleep Quality Index, N-QoL, Nocturnal Polyuria Index, AEs, serum sodium
Sand (2014) and Weiss (2018) [21, 22]	USA, Canada	Women with nocturia (≥ 2 nocturnal), aged ≥ 60 years	133/128	Desmopressin, orally, 25 μg, 3 months	Placebo, orally, 3 months	1 week, 1, 2, and 3 months	No. of nocturnal voids, 33% responder rate, N-QoL, Work Productivity and Activity Impairment Questionnaires, self-rated sleep quality, AEs, serum sodium
Rovner (2018) [23]	USA	Women with overactive bladder and nocturia, with nocturia (≥ 2 nocturnal voids), aged ≥ 18 years	45/52	Desmopressin, orally, 25 μg + Tolterodine, orally, 4 mg, 3 months	Placebo + Tolterodine, orally, 4 mg, 3 months	1, 2, and 3 months	No. of nocturnal voids, duration of first sleep period, 33% responder rate, nocturnal void volume, EuroQoL Group 5 Dimensions Questionnaire, Sleep Rating Scale, Nocturia Impact Diary, AEs

AEs adverse events, *N-QoL* nocturia QoL questionnaire

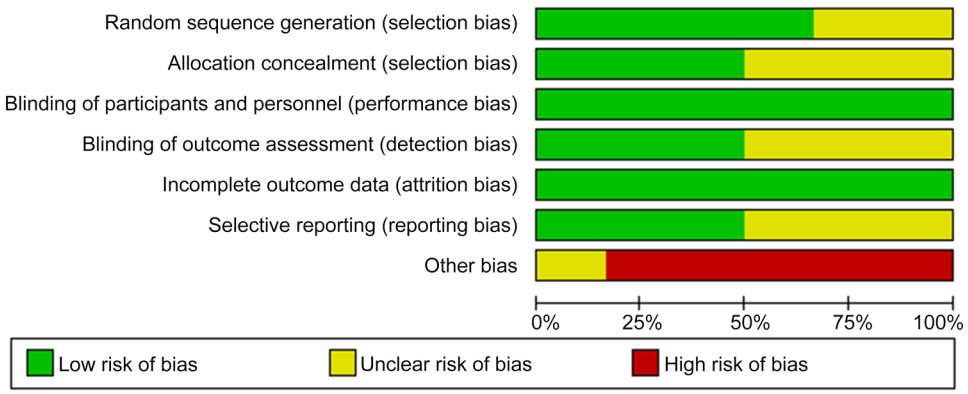

Fig. 2 Risk of bias of included trials according to the Cochrane Collaboration Guidelines

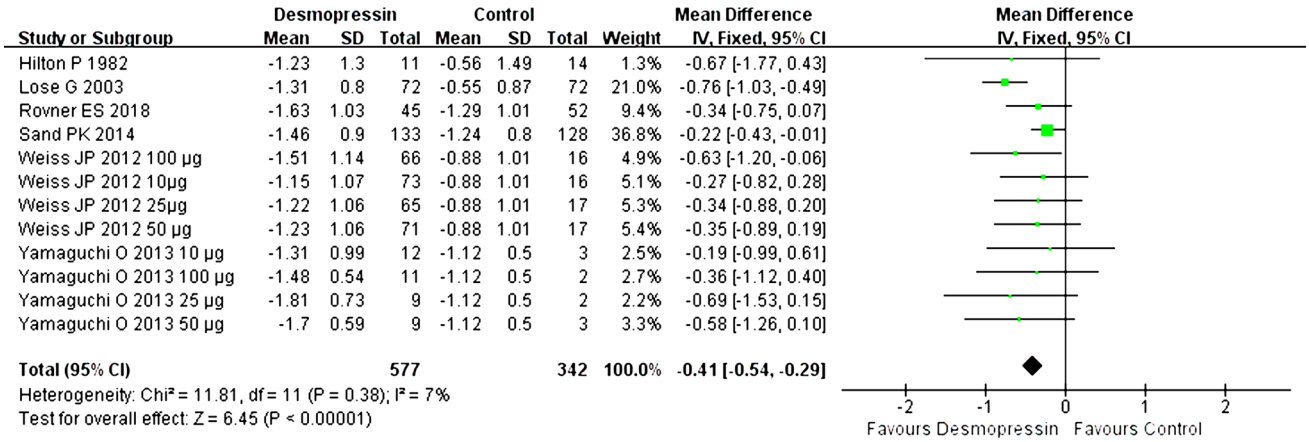

Fig. 3 Comparison of reduction in the number of nocturnal voids per night

Publication bias

All *P* values of Egger and Begg tests were > 0.05, showing publication bias that was not evident in various other meta-analyses. The results of Begg's funnel plot and Egger's publication bias plot are shown in Figs. 10 and 11.

Discussion

Summary of evidences

Seven trials with 1016 women with nocturia that met our inclusion criteria were identified. Of these, four studies had low risk of bias. The findings of our systematic review indicated that desmopressin might be effective to relieve nocturia in women with a dose of ≥ 25, and the adverse events associated with desmopressin might be neglected. Female patients taking desmopressin had 0.46 lesser voids per night than those taking placebo or other controls. What is more, the time of the first sleep period in female participants with desmopressin had an hour more than the controls. Statistically significant benefits were observed with doses 25-µg desmopressin ODT, but their magnitude was smaller than those with > 25 µg dose ODT for the number of nocturnal voids per night after treatment. There were some benefits in the placebo group also, and these might be due to restricted water intake at bedtime or other lifestyle modifications [24]. On the other hand, we did not find any evidence that the higher dose more likely induces AEs.

The desmopressin dose selection for the benefit

There was a doubt that the dose of < 25 µg ODT had a notable pharmacodynamic effect in nocturia. One study indicated that the response reached a plateau at 25-µg desmopressin ODT in female patients, and higher doses (50 and 100 µg) did not provide any further reduction in the mean number of nocturnal voids [20]. The response to 10-µg desmopressin ODT showed no significant differences from placebo. These findings are consistent with those of Juul et al., which reported the responses to 25-µg desmopressin ODT in female nocturia patients to be at the

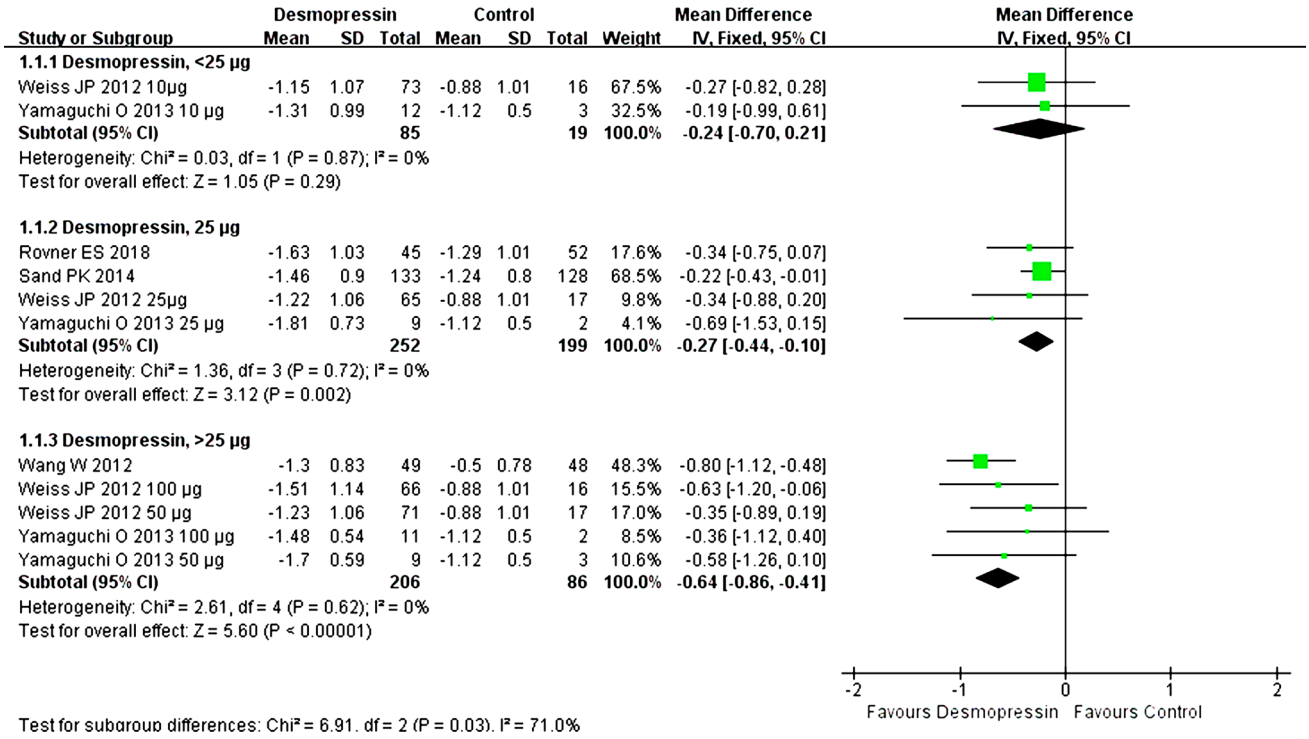

Fig. 4 Dose subgroup analysis of desmopressin ODT for the number of nocturnal voids per night

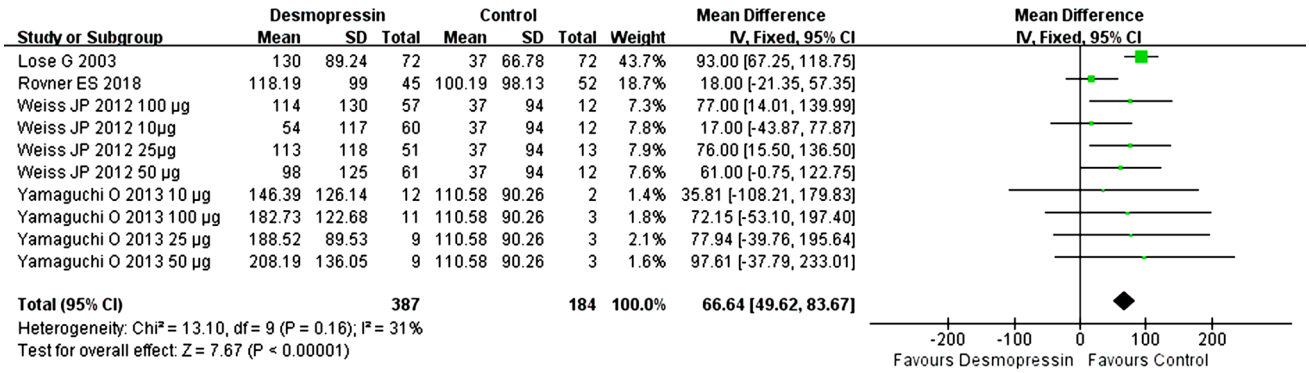

Fig. 5 Comparison of change in the duration of first sleep period

upper plateau phase of the S-formed dose–response curve, and increasing doses of desmopressin did not provide any additional clinical efficacy [11]; while our review found that the dose > 25 µg had larger curative effect than that < 25 µg ODT. While the data from another study about dose response revealed that the doses of > 25 µg ODT were significantly superior ($P \leq 0.05$) to placebo in females, but the doses of 100 µg had a larger efficacy than the doses of 25 µg [19]. All these included trials were just an exploration rather than the curative effect test, as the sample sizes were too small, and so Yamaguchi et al. enrolled not greater than 12 participants in each group.

The desmopressin dose selection for the harm

This review could not find any evidence that the higher doses more likely induce AEs. But the harm due to desmopressin could not be neglected. Hyponatremia is an important potential complication of this treatment. While no such meta-analysis has been conducted in our study,

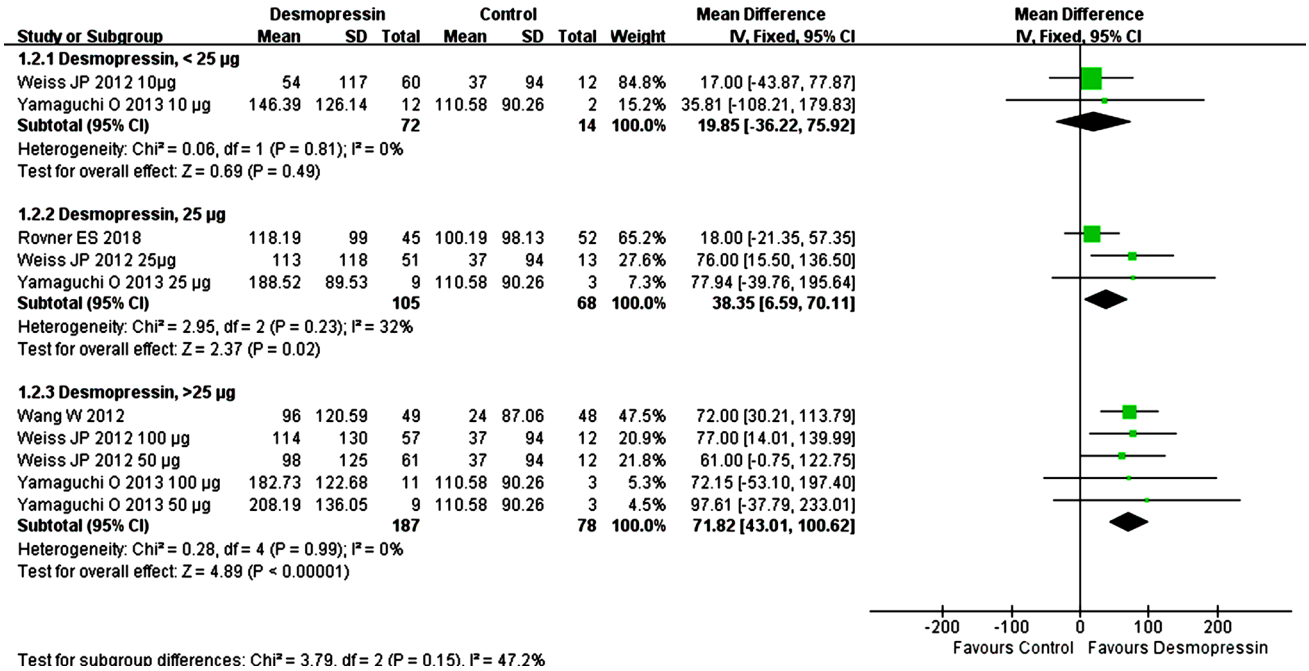

Fig. 6 Dose subgroup analysis of desmopressin ODT for the duration of first sleep period

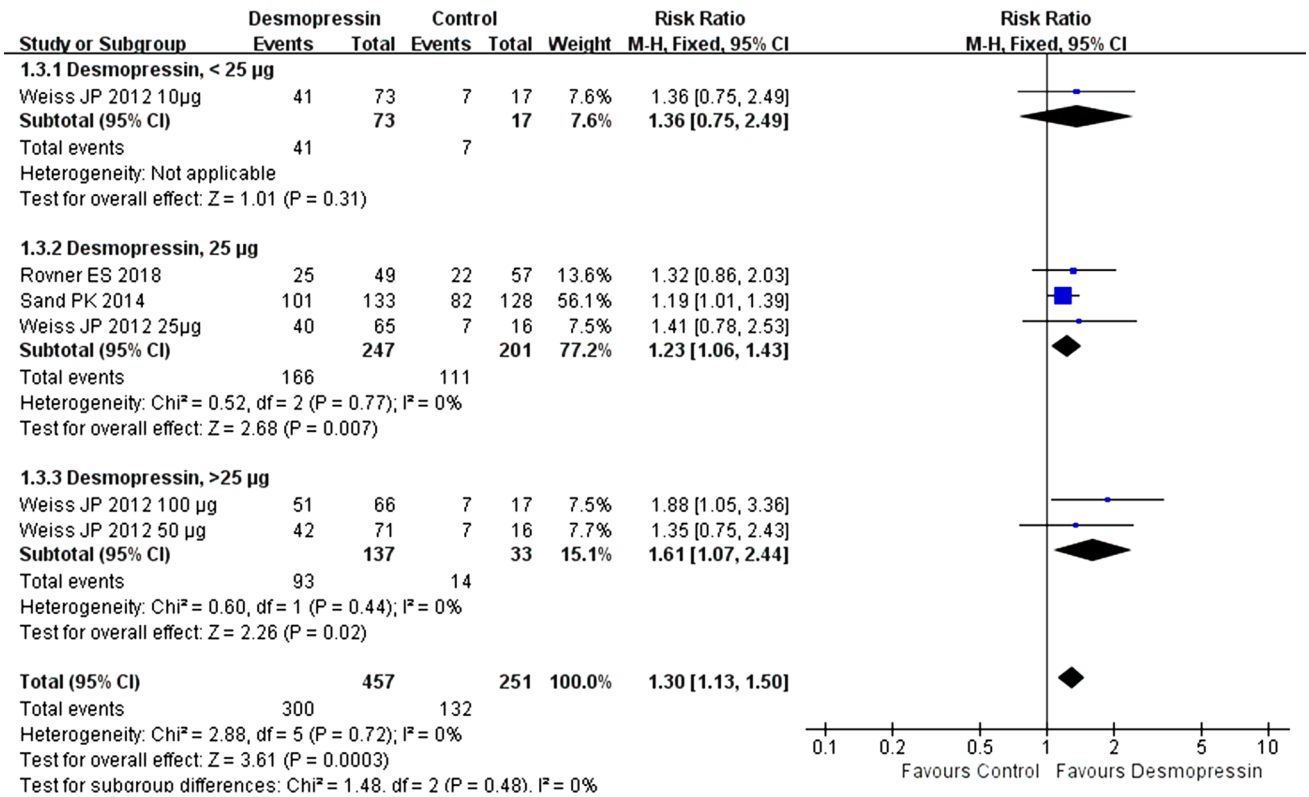

Fig. 7 Comparison of 33% responder rate

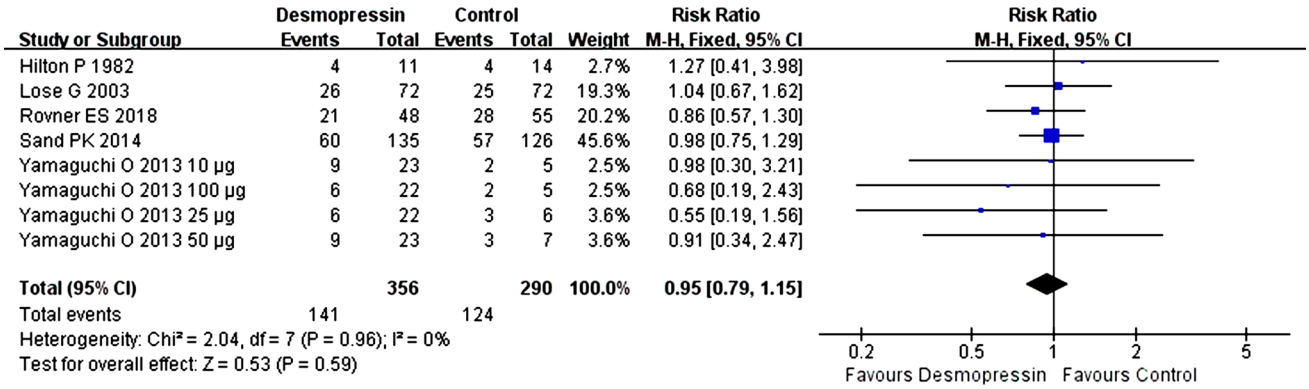

Fig. 8 Comparison of the incidence of reported AEs

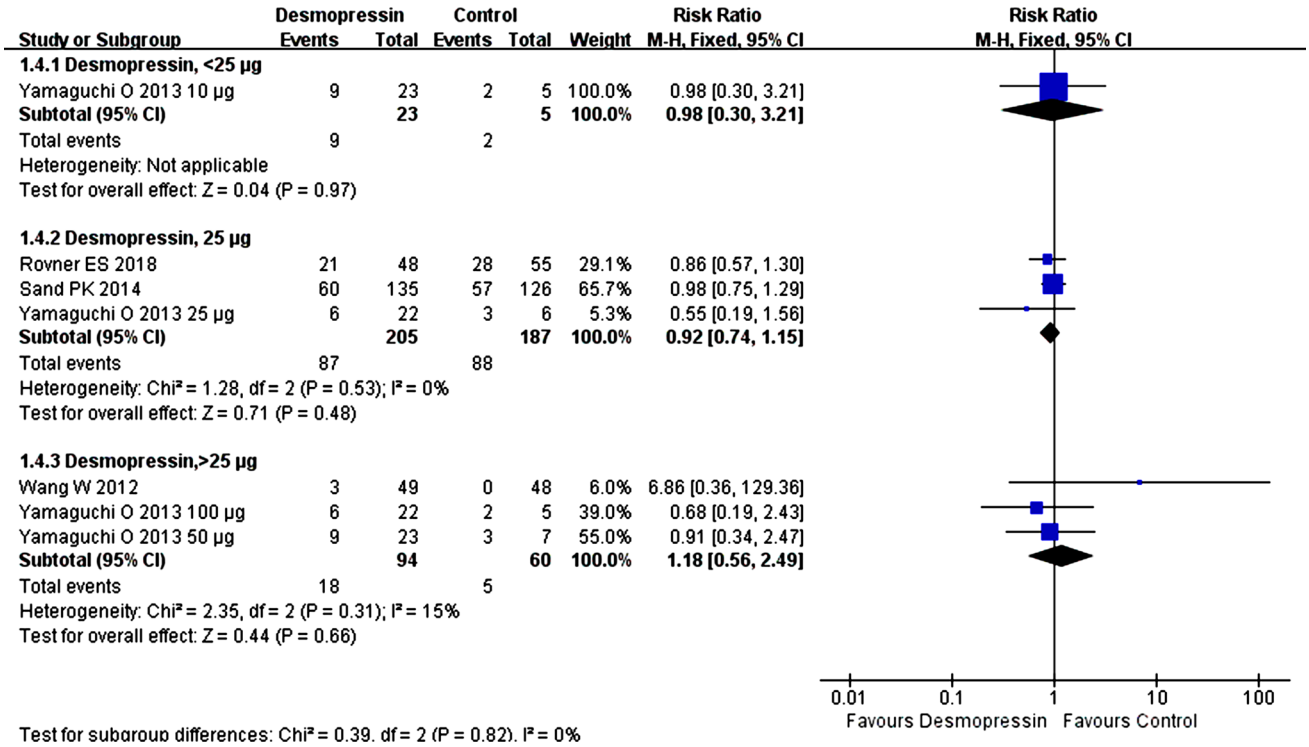

Fig. 9 Dose subgroup analysis of desmopressin ODT for the incidence of reported AEs

as only one trial reported hyponatremia separately from the AEs. Also, the data of serum sodium from three trials could not been pooled. What is more, the differences might be due to differences in age, and differences in baseline of different trials. Three trials only included old female participants, while the remaining included females aged females aged ≥ 65 years and higher desmopressin dose are predictors of clinically significant decrease in serum sodium [19]. The exploration of appropriate dose in female patients should be conducted, and other influential factors, such as age, should also be considered in future studies.

Limitations of this review

Our study was limited by clinical heterogeneity due to different doses, study designs, inclusion criteria, and study populations of different ages. The trials included in this meta-analysis were relatively short term, and had small sample sizes. Future studies with adequate duration are needed to provide information regarding long-term benefits and harms of desmopressin. Due to different study designs, different inclusion criteria, and different duration of medication, the analysis of dose–response could not been conducted in this study. The subgroups investigated

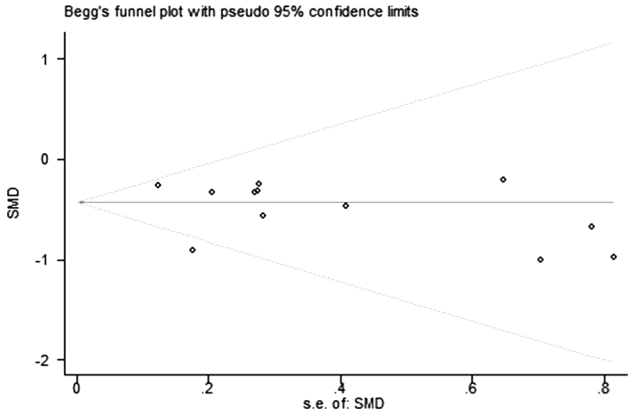

Fig. 10 The Begg's funnel plot

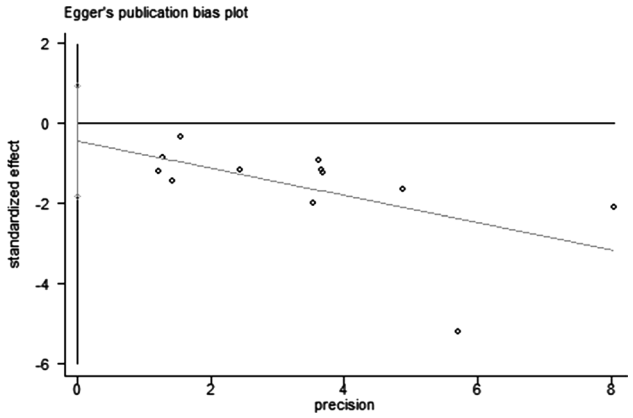

Fig. 11 The Egger's publication bias plot

in nocturia and overactive bladder, versus nocturia with nocturia could not been conducted, as only one trial enrolled patients with nocturia and overactive bladder.

Conclusions

In summary, desmopressin offered a modest benefit in nocturia women with adequate safety. The dosage of > 25 μg showed better efficacy than 25-μg dose, with similar safety. The exploration of appropriate dose for female patients should be conducted, and other influential factors, such as age, should also be considered in future.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

Informed consent Not applicable.

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