What is the most effective treatment for nocturia or nocturnal incontinence in adult women?

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ABSTRACT

Context: Nocturia is a prevalent symptom with varied aetiology and no consensus on treatment options.

Objective: We systematically reviewed evidence comparing the benefits and harms of various treatment options for nocturia or nocturnal incontinence in women.

Evidence acquisition: Literature search was performed using Embase, Medline, Cochrane databases (from January 1, 1946 to September 26, 2017), following the methods detailed in the Cochrane Handbook. The protocol was registered with PROSPERO. Certainty of evidence was assessed with GRADE approach.

Evidence synthesis: The literature search identified 3573 citations, of which 11 full text articles were included. 3 studies on desmopressin and 4 on antimuscarinics provided evidence of improving nocturia symptoms. 4 studies on behavioural treatment provided limited evidence and controversial results. 1 study on oestrogen did not prove the benefit of any mode of administration, and one small study on functional magnetic stimulation provided some evidence of effectiveness in nocturia. One RCT (141 participants) reported a statistically significant difference between the desmopressin and placebo group (desmopressin patients experienced 0.75 (95% CI 0.47-1.03) nocturia episodes less than placebo; certainty of evidence = low). The only RCT on antimuscarinics in women with nocturia reported oxybutynin reduced the number of nocturia episodes by 0.3 (95% CI -0.02 to 0.62) versus placebo. In one RCT comparing tolterodine to the combination of tolterodine with behavioural therapy, there was significant change from baseline nocturnal incontinence episodes in both groups.

Conclusions There is some evidence that desmopressin and antimuscarinics are effective treatment options for nocturia, however there is very limited evidence for other treatment options. The findings should be interpreted with caution as there were some methodological flaws in the included studies, particularly outcome heterogeneity.

Patient summary This review identified several medical treatments for nocturia in women, such as desmopressin and antimuscarinics, that appear to improve the severity of the condition.

1. Introduction

Nocturia is defined by the International Continence Society (ICS) as "waking to pass urine during the main sleep period". Nocturnal incontinence is a complaint of intermittent incontinence that occurs during the main period of sleep after the age of 3-5 at which bladder control usually occurs [1]. Nocturnal polyuria (NP) is defined as passing large volumes of urine during the main sleep period that should be quantified using a bladder diary [2]; some of the definitions propose thresholds like nocturnal urine volume greater than 20% to 33% of total 24-hour urinary volume.

Nocturia is a prevalent symptom in men and women of all age groups. This paper will focus on women only. According to Bosch and Weiss, 1 in 5 or 6 younger people consistently wake to void at least twice each night. Up to 60% of older people void 2 or more times nightly [3]. Age is one of the most important risk factors. There is some controversial evidence about gender as a risk factor. There is some evidence about association with metabolic syndrome, obesity, diabetes, cardiac disease, other conditions and ethnicity (African-American race) [4, 5]. Although nocturia is not a life-threatening condition itself, there is a risk of increased mortality in some patients due to hip fractures caused by risk of falls when getting up to urinate [6]. Economic burden of nocturia is important, frequently leading to repeated consultations, diagnostic procedures, medications and therapies with costs adding up with every patient. Sleep disturbance/bother and impact on quality of life are the most important reasons for consultation[7].

Concerning the optimal treatment of nocturia in women there is no consensus due to the multifactorial pathophysiology (common symptom in different diseases). The underlying causes may be urologic, e.g. LUTS, neurogenic voiding dysfunction; or non-urological in origin, such as chronic heart failure, sleep apnea and hormonal . [8] The question of optimal treatment was studied previously but evidence was limited [9-13]. Currently available treatments include antidiuretics and antimuscarinics. Desmopressin is an antidiuretic, working at the level of the renal collecting duct, binding to the V2 receptors present in the distal collecting tubules. It is thought to work in patients with nocturnal polyuria by decreasing diuresis. Muscarinic receptor antagonists or antimuscarinics such as darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, trospium chloride, block the activity of muscarinic acetylcholine receptor. Some of them are more specific to the M3-receptor, which is most prevalent in detrusor muscle; some are less specific and act on all receptor sub-types (M1, M2 and M3) leading to more side effects.

There is no consensus on which treatment option is the most effective in women with nocturia or nocturnal incontinence. Furthermore, since the topic is not covered in the recent EAU Guidelines, the Urinary Incontinence Panel conducted a systematic review (SR) on female nocturia and female nocturnal incontinence to enable recommendations in a future version of the guidelines. In this study we systematically reviewed evidence for the most effective treatment of nocturia or nocturnal incontinence in terms of improving symptom severity and quality of life in adult women.

2. Evidence acquisition

This SR was undertaken under the auspices of the European Association of Urology (EAU). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance and the Cochrane Handbook for systematic reviews of interventions [14, 15]. The protocol was registered at PROSPERO (CRD42017058997).

The databases searched were the Embase, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), EBM

Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews from 1946 to September 2017. Studies were limited to full text articles published in English, French, Spanish, Russian and German language. The complete search strategy is provided in Supplementary Material Appendix 1. The detailed PICO search strategy is shown in Table 1.

Data collection and analysis

The study selection process is described in Figure 1 [16]. All stages of selection were done with Covidence (www.covidence.org).

Two review authors (DB and DA) independently assessed the risk of bias (RoB), using the Cochrane RoB assessment tool for RCTs [17]. Risk of bias in non-RCT was evaluated with an extra item to assess the risk of confounding [18, 19]. Study authors were contacted to provide missing information. Any disagreements were resolved by discussion or by consulting a third review author (IO).

Meta-analysis, funnel plots interpretation or assessment of heterogeneity and sensitivity analyses were planned, but not feasible due to paucity of data. Furthermore, the studies used different dosages and modes of administration of drugs. Quantitative synthesis was not undertaken for non-randomized studies. Instead, we used the narrative synthesis [14, 20] approach to summarize the results.

The GRADE approach was used for assessing the certainty of evidence. The following outcomes were selected for the "Summary of Findings" table:

- Number/frequency of nocturia episodes;
- NPI (NP index; nocturnal urine volume/24-h urine volume [%]);
- nocturnal urinary volume
- nocturnal urinary incontinence episodes

3. Evidence synthesis

3.1. Description of the included studies

3573 references were identified for screening and 195 selected for full-text screening. The authors of 41 articles with mixed populations were contacted to get separate female data, but after 12 months with 2 reminders, data from only one study had been received, so it was decided to exclude these articles. The characteristics of 11 included studies are reported in Supplementary table.

Risk of bias (RoB) in included studies

The domains of RoB for the 11 included studies are summarized in Figure 2. All except one study showed high risk of bias in at least one of the seven domains that apply to RCT's as well as non-RCT's.

Desmopressin:

This is a synthetic analogue of the hormone vasopressin. It is most often used for management of nocturia due to nocturnal polyuria. We found 3 trials specifically conducted in women [21-23], but more additional data could be extracted from mixed populations [9-11, 13].

In the oldest study, by Hilton in 1982 [21], there were statistically significant differences in the main nocturia outcomes. Further studies in a mixed population supported that finding [9-11, 13].

Lose [22] used desmopressin in doses 0.1, 0.2, 0.4 mg orally at bedtime after a dose-titration period, in participants that responded to the dose-titration phase. Of the 80 withdrawals after the dose-titration phase, only 8 patients lacked a pharmacological response. The authors randomized 144 women to desmopressin (N=72) or placebo (N=72) and after follow-up of 3 weeks showed a benefit of desmopressin for all measured outcomes for nocturia (Table2). There was a difference in the number of nocturnal voids in favour of desmopressin, as well as for nocturnal diuresis.

Yamaguchi [23] reported results of different doses of desmopressin separately for men and women (aged 55-75). A total of 58 women in 5 groups (12 in placebo, 12 in 10 µg, 11 in 25 µg, 11 in 50 µg, 12 in 100 µg group, respectively) were followed for 4 weeks. The authors observed a dose-response relationship. In the gender comparison they found that female patients were more sensitive to desmopressin, so they propose to minimize the risk of hyponatraemia in women by using lower doses. There were statistically significant differences in the change in nocturnal urinary volumes in the following comparisons in favour of the higher desmopressin dose: 10µg vs 25µg and 10µg vs 100 µg. Also, there were differences in the NPI (nocturnal polyuria index) in following comparisons in favour of desmopressin over placebo or in favour of the higher desmopressin dose: placebo vs 25µg; placebo vs 100µg; 10µg vs 25µg; 10µg vs 100µg.

Unfortunately, we could not combine the three studies above in a meta-analysis because of different dosages and modes of administration. However, we generated a forest plot combining the main findings cited above for comparisons of desmopressin vs. placebo (Fig. 3).

Desmopressin can be safely combined with antimuscarinics with a significant benefit in women with nocturnal polyuria, as shown by Rovner [24] in a post-hoc analysis of an RCT comparing 3-month once-daily combination (desmopressin 25 µg/tolterodine 4mg; n=49) or monotherapy (tolterodine 4 mg/placebo; n=57).

3.2. Antimuscarinics

We found 4 RCTs of antimuscarinics such as oxybutynin 2.5 mg/day [25], tolterodine 4mg/day [24, 26, 27].

Johnson reported results of a secondary analysis from a prospective RCT [25]. In 131 women (aged 55-92) with nocturia followed up for 8 weeks they found that 46 women on 2.5 mg once a day immediate-release, with possibility to self-titrate oxybutynin, had less nocturia episodes than the 38 in the placebo group, but more episodes than the 47 patients in the behavioural treatment group. There was no statistically significant difference in nocturia episodes between oxybutynin and placebo group, but there was one in favour of behavioural treatment.

Three selected studies on tolterodine in a female population did not include a placebo group but compared tolterodine monotherapy to some type of combination treatment. All 3 studies showed a significant change from baseline. Various other studies in mixed populations [9-11, 13] showed comparable results.

FitzGerald followed-up 305 women for 8 weeks in 2 groups: with tolterodine tartrate extended-release capsules 4mg alone or in combination with behavioural training [26]. The authors observed small (in absolute numbers of episodes) but statistically significant differences ($p < 0.001$) in mean nocturia frequency and nocturnal incontinence frequency as compared to baseline in both groups, but no difference between study treatment groups.

Rovner performed a RCT in 97 women randomized to a 3-month once-daily combination (desmopressin 25 µg/tolterodine 4mg; n=49) or monotherapy (tolterodine 4mg/placebo; n=57) [24]. The significant changes in mean number of nocturnal voids from baseline was comparable between groups. In a post-hoc analysis in subgroups with/without nocturnal polyuria, the

authors probed the benefit of combination therapy, and there was no difference in the reduction of mean number of nocturnal voids.

The study by Yuan was not an RCT, but a well-designed large comparative study[27]. They followed 407 women with OAB and nocturia for 4 weeks. The patients were given tolterodine 2 mg twice a day as monotherapy in one group, and tolterodine 2 mg twice a day combined with estazolam 1 mg at night in the other group for 4 weeks, respectively. There were significant changes from baseline in both groups for the main outcomes, such as number of nocturia episodes. The tested combination included an agent to promote sleep (estazolam); the combination showed a significant benefit for women with OAB and nocturia compared to monotherapy: there were differences in number of nocturia episodes per night, urgency episodes in 24 hours, urgency incontinence episodes in 24 hours, voided volume per micturition.

3.3. Oestrogen

We only found one RCT investigating oestrogen for nocturia. Lose compared oestradiol-releasing vaginal ring and oestriol vaginal pessary in 251 women (follow-up = 24 weeks) [28]. The authors estimated the subjective score of urgency, frequency, nocturia, dysuria, stress and urge incontinence. There was no difference between the treatment groups in the number of women reporting nocturia though they reported significant change from baseline in both treatment arms (for nocturia 51% and 54% responded to treatment respectively).

3.4. Behavioural treatment

Analyzing studies on behavioural treatment we found more heterogeneity in the results. While the studies by Johnson, Aslan and Lo [27, 32, 33] were favourable for behavioural treatment, FitzGerald [28] did not show a benefit of the addition of behavioural therapy to drug treatment. The heterogeneous character of behavioural therapy itself can explain these results, while the treatment also differed from site to site.

Aslan studied 50 women aged 70-89, who were randomized to the treatment group (bladder training and Kegel exercises) or the control group, in equal proportion. Follow-up at a single site in Turkey was 6 months [32]. There was a significant decrease of the nocturia complaints in the treatment group compared to the control group between the 8-week and 6-month evaluations ($p < 0.05$, reported binary; certainty of evidence = very low).

Lo conducted an RCT in only 24 women (aged ≥ 20 years), 12 in each group. A group with pelvic floor exercise was compared to a group receiving interferential therapy (transcutaneous electrical nerve stimulation) in addition to pelvic floor exercise. The treatment was given 3 times a week for 4 weeks [29]. The authors did not reach planned recruitment due to limitation of resources, and there was no difference in the number of nocturia episodes as indicated in their results. Although they did not find significant changes between the groups (probably because of small number of participants), the differences before and after treatment were statistically significant in both groups.

The study of Johnson was described above[25]. The authors found that the group with behavioural training (4 visits, anorectal and pelvic muscle biofeedback, teaching skills and strategies for dealing with incontinence and urgency) showed better results than the groups receiving placebo. There was a difference in number of nocturia episodes in favour of behavioural treatment, and also in favour of the behavioural treatment group over the oxybutynin group.

FitzGerald reported the number of nocturia episodes and nocturnal incontinence episodes as a change from baseline [26]. The result of the change in number of nocturia episodes from baseline appears to favour the tolterodine plus behavioural therapy group, however 95%CI

touched the line of no difference. There was also no difference in the change in number of nocturnal incontinence episodes. In contrast to the Johnson study, FitzGerald, who added behavioural therapy to tolterodine 4 mg, did not show a significant benefit of behavioural treatment. The difference in outcome between these two studies can be explained by difference in age (Johnson studied older women, mean age 68, and in FitzGerald study mean age 56 years); also the patients in the FitzGerald study were less symptomatic (1.7 voids/night vs. 1.9 voids/night in Johnson), and there were pharmacological differences between the drugs: immediate release of oxybutynin and sustained release formulation of tolterodine.

3.5. Functional magnetic stimulation

We identified one small, single-centre RCT in which functional magnetic stimulation (FMS) was compared with placebo (But 2005 [30]). But and colleagues recruited 39 women (aged 28-70), who were randomly assigned to the FMS group (N=23) or placebo (16). They followed these patients for 2 months and reported a significant decrease in voiding frequency (from 9.0 to 6.7, p = 0.0002), nocturia (from 2.6 to 1.4, p = 0.0007) and pad use (from 3.9 to 2.2, p = 0.007) in the treatment group compared to the placebo group.

3.6. Results on nocturnal incontinence

We have found only one study that reported on the number of nocturnal incontinence episodes as change from baseline [27]. There was no statistically significant difference in the mean difference.

3.7. DISCUSSION

3.7.1. Principal findings

Our systematic review confirms that desmopressin and antimuscarinics are effective treatment options for nocturia in women, whereas other options, such as behavioural treatment, hormonal therapy or functional magnetic stimulation, are controversial. Many of the studies had methodological flaws and provided conflicting results when evaluating the same treatment. Risk of bias in random sequence generation was judged to be high in 2 and unclear in 4 studies. Allocation concealment was judged unclear in 4 studies. This was considered while assessing the overall certainty of evidence. As a result, majority of the outcomes were either rated as “low” or “very low” when assessing the certainty using the GRADE approach. Therefore, the findings of this SR should be interpreted with caution.

Although 3 reported studies on desmopressin [21-23] showed that this drug is more effective than placebo in women in terms of decreasing the number of nocturia episodes, there are two main issues to consider. First is a necessity of screening for hyponatremia at baseline, since this is a contraindication for antidiuretic therapy. A second issue that we observed in the largest study identified is a dose-titration phase before the full trial. This increases the likelihood of a positive outcome because non-responders were excluded at this stage. Furthermore, we may suppose that desmopressin is more effective in patients with nocturnal polyuria as the predominant cause of nocturia, although we did not find studies that had distinguished these patient sub-categories.

Antimuscarinics showed some benefit in OAB-related nocturia. However, most studies in our search reported on a mixed but female-predominant (about 80%) population. For this reason, we did not include these studies in the final SR. We found only one study with comparison of antimuscarinics as monotherapy versus placebo in women only [25]. Other studies [24, 26, 27] reported comparison of antimuscarinics to some form of combination therapy but without a placebo group. We suggest considering subcategorizing OAB-related nocturia in trials with OAB medications, to study the possible benefit of antimuscarinics.

The above-mentioned studies show that the underlying pathophysiological mechanisms of nocturia that may vary from patient to patient are often not well addressed when recruiting patients to trials. Important etiologic factors to consider are sleep apnoea, cardiovascular disease, and diabetes mellitus. Ideally, nocturia should be treated with a cause-specific strategy. The question of subcategories of nocturia should be considered when designing new trials; the use of questionnaires only to select patients tends to lump these heterogeneous patient categories together. Therefore, conclusions derived from the studies in this systematic review should be regarded with caution. Furthermore, the issue of objective markers for nocturia, such as voiding diaries, versus subjective patient perception (questionnaires) might have an impact on the results. This issue could not be further addressed in this review because of lack of data.

3.7.2. Recommendations for future research

Additional research is needed to examine other options for the treatment of nocturia and nocturnal incontinence in women. Many studies were undertaken in a mixed population and we suggest that authors report their results for men and women separately because the underlying pathophysiology varies significantly between the two genders. We also highly recommend classifying the underlying symptomatology as nocturia or nocturnal polyuria, using standard ICS definitions.

We would like to emphasize the lack of long-term outcomes and large studies in female patients. Some outcomes are statistically significant, but it is unclear whether they are clinically relevant. We recommend the professional community to discuss and to determine minimally important difference (the smallest change in a treatment outcome that an individual patient would identify as important and which would indicate a change in the patient's management) in the number of nocturia episodes per night. Furthermore, no core outcome set for nocturia can be found in the COMET database; therefore, we recommend its development.

Many identified studies reported combination treatments; this causes a problem of detecting what type of treatment is primarily responsible for the outcome; therefore, we recommend designing trials with monotherapies for comparison. This issue is particularly relevant in case of behavioural treatment, usually combined with lifestyle changes: protocols are often heterogeneous from site to site, which complicates generalisation of the outcomes.

Strength and limitations of the review

The main strength of this SR is that it is the first comprehensive literature search for all treatment options for nocturia in adult women specifically, using a robust and transparent methodological approach based on the Cochrane handbook.

During the full-text screening we realized that the inclusion of studies with nocturia as a secondary outcome led to a high level of heterogeneity among the studies and the impossibility to derive conclusions from this selection. We had to make an amendment in the protocol: after discussion in the EAU UI Guidelines Panel, studies with nocturia as a secondary outcome were excluded because they did not focus on the treatment of nocturia patients.

We did not include studies with mixed populations, even if the female population was more than 80-90% of the total, because randomization was done in the whole population, leading to imbalanced groups. During full-text screening 60 articles with mixed population were retrieved. In order to maximize the possibility to include as many female patients as possible in the review, the decision was made to contact authors for separate female data. The first letters were sent on the 28th of June 2018; unfortunately, only one author responded and since we had decided to analyse this type of data separately, we finally decided not to use the data of this author in the review.

Major limitations of the review include significant heterogeneity among the studies identified. Many of the evaluated studies on desmopressin used a dose titration phase, which may represent another source of bias.

Whilst we identified only one study that reported treatment of nocturnal incontinence in women, we could not make any recommendations on this subject. There is no consensus about definition of nocturnal incontinence; the last ICS report on standardization of terminology did not include this term; instead, the term "enuresis" was proposed (included in our search strategy as well). It may be possible that patients with nocturia do not have nocturnal incontinence, because they wake up before leakage occurs; therefore, nocturia, which is getting up to void at night, may protect against nocturnal incontinence because the critical bladder volume is not reached.

4. Conclusions

Nocturia is a common symptom that can be associated with various diseases. Treatment choice should be made after thorough clinical evaluation of all possible causes. RCT evidence supports of the use of desmopressin in the management of nocturia associated with nocturnal polyuria, with careful serum sodium monitoring. RCT evidence also supports the use of antimuscarinic drugs for nocturia associated with symptoms of overactive bladder. Behavioural treatments may be considered as a non-invasive conservative measure for nocturia management, but the evidence is of low quality, weak and controversial. Other treatment options cannot be recommended due to lack of evidence or very low quality of evidence. We cannot provide any recommendations for treatment of nocturnal incontinence due to total absence of evidence.

Table 1. PICO search strategy

P	Population	*Inclusion criteria:*
		• Adult women (≥18 years old) categorised within the following symptom groups:
		  o Nocturia as the primary presentation (i.e. nocturia as the predominant bothersome symptom)
		  o Nocturia as a secondary component of lower urinary tract symptoms (LUTS) i.e. LUTS including nocturia
		  o Nocturnal incontinence as a secondary component of incontinence
		  o Nocturnal polyuria (following International Continence Society definition, or as defined by trialist)
		Exclusion criteria:
		• Neuro-urology patients such as spinal cord injury patients, multiple sclerosis, myelomeningocele and nerve tube defects, Parkinson's disease, Alzheimer's disease (according to EAU Guidelines [13])
		• Children

I	Intervention	• Medical treatment (we included all published doses and schedules): anticholinergic drug, mirabegron, desmopressin, diuretics (all types), sleep promoting agents (e.g. hypnotics – diazepam, nitrazepam), oestrogen (topical or hormone replacement therapy), treatment for pain (e.g. sodium hyaluronate bladder instillations), phytotherapy (e.g. herbal treatment) • Surgical treatment: botulinum toxin Type A, neuromodulation (sacral nerve stimulation, etc.), neurostimulation (e.g. Parasacral Transcutaneous Electrical Neural Stimulation (PTENS)), surgery to relieve bladder outlet obstruction in women • Lifestyle modification (e.g. moderating fluid intake at night, leg elevation, avoiding caffeine, etc.) • Any other treatment (e.g. acupuncture, Continuous Positive Airway Pressure machine (CPAP), etc.), compression stockings, psychotherapy, hypnotherapy
C	Comparator	• Placebo • No treatment • Other experimental treatment as listed above under intervention

O	Outcomes	*No core outcome set for nocturia was found in the COMET database* The primary benefit outcome was • improvement in symptom severity/number of voids*/ for nocturia (outcome measure as defined by trialist). The primary harm outcomes were: • Adverse events* of treatment (ad hoc listing of events, e.g. dry eyes, blurring of vision, constipation, etc.), and events leading to potential harm (e.g. hyponatremia, voiding difficulties) • Any other outcomes judged relevant by the review author team. Secondary outcomes: • Night-time incontinence episodes* • Quality of life* (measured by validated questionnaire (such as IPSS, ICIQ-SF), at any time point) • Sleep quality (measured by validated questionnaire, at any time point) • Global improvement scales (not specific to incontinence, pain or sexual function) (measured by validated questionnaire (SF-Qualiveen), at any time point) • Healthcare resource use (QALY) • Bladder function (measured by validated questionnaire or by urodynamic, or by voiding diary, at any time point) • Sexual function (measured by validated questionnaire, at any time point)

Table 2. Summary of findings; Desmopressin versus placebo

Desmopressin compared to Placebo for nocturia or nocturnal incontinence in terms of improving symptom severity and quality of life in adult women?

Patient or population: nocturia or nocturnal incontinence in terms of improving symptom severity and quality of life in women?

Setting: outpatient department (multicenter study)

Intervention: Desmopressin

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Desmopressin**				
No. of nocturnal voids - 3 weeks	The mean no. of nocturnal voids - 3 weeks was **0**	The mean no. of nocturnal voids - 3 weeks in the intervention group was 0,75 lower (1,03 lower to 0,47 lower)	-	141 (1 RCT)	⨁⨁◯◯ LOW [a]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded two levels due to following reasons: random sequence generation was done by pharmaceutical company, outcome assessors were not blinded, supported by a grant from pharmaceutical company, and "patients with no pharmacological response during dose titration were excluded before randomization"

FIGURES

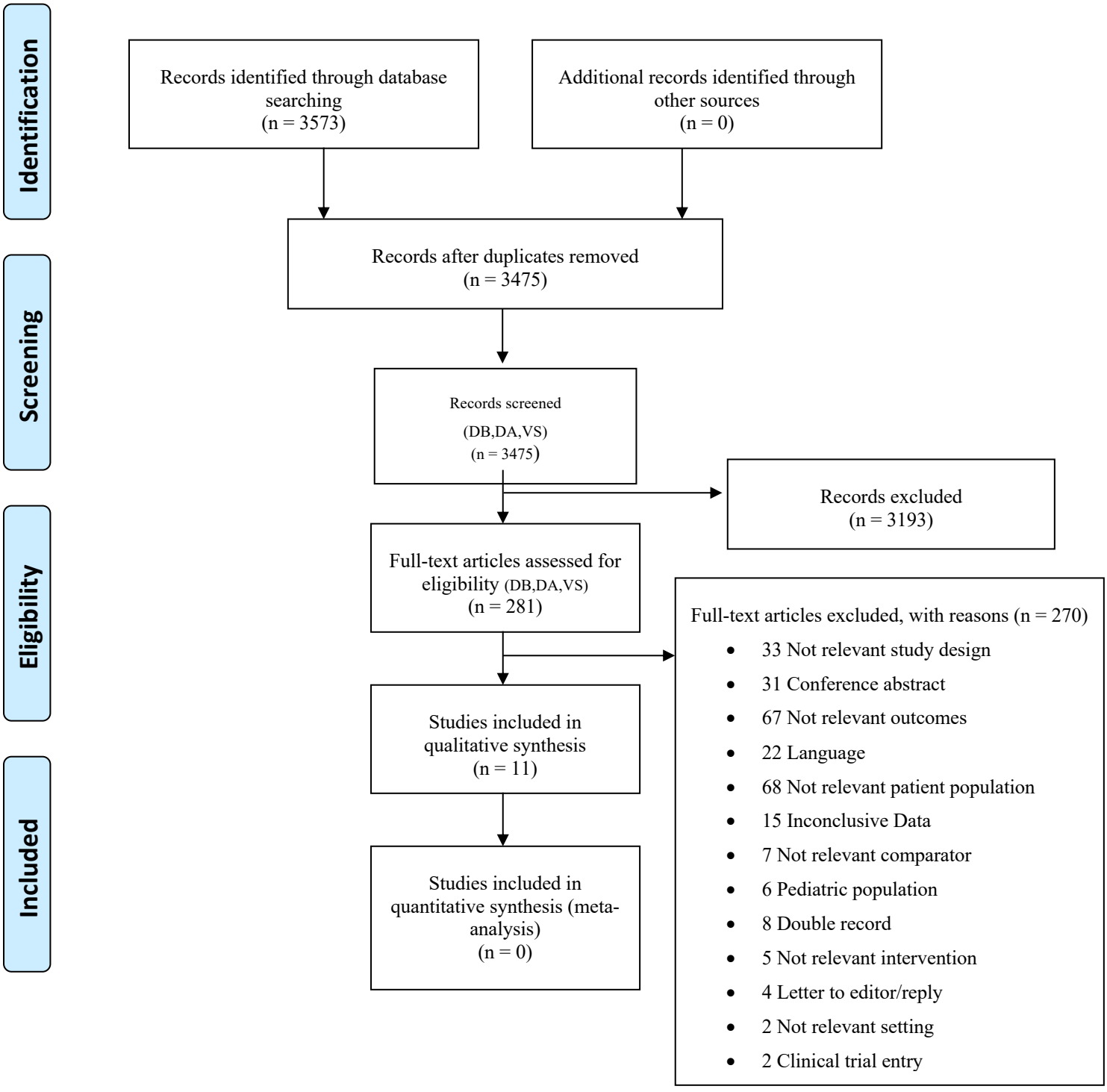
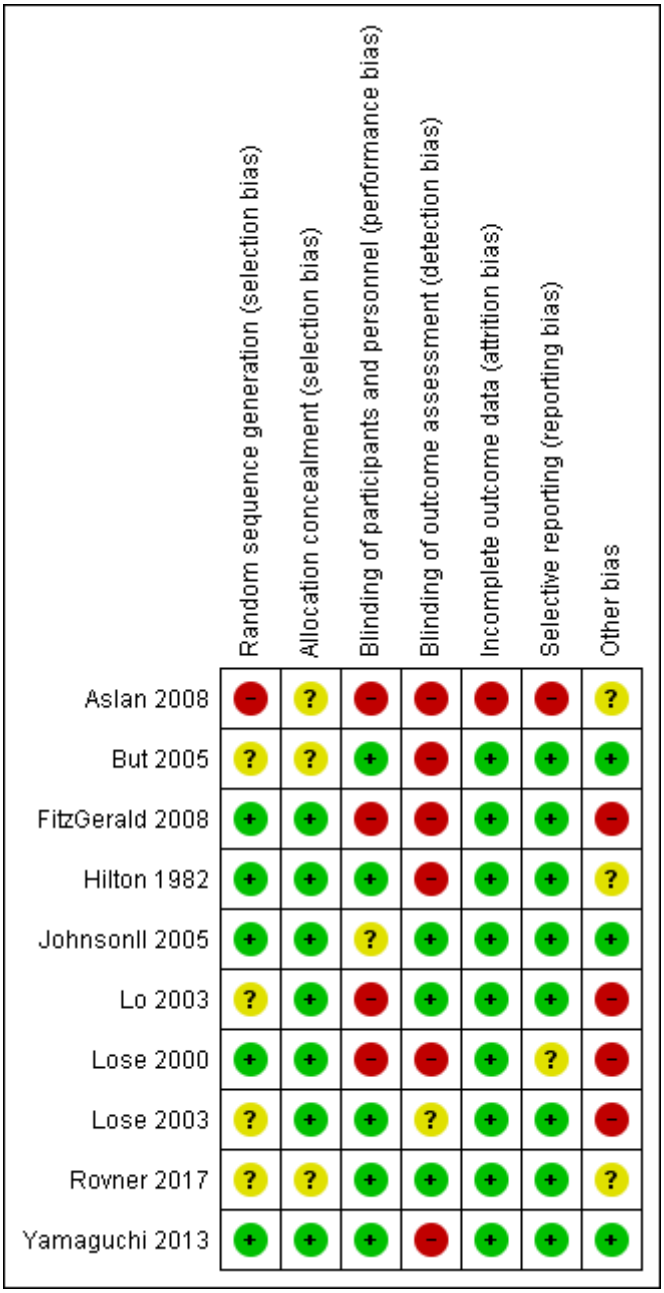
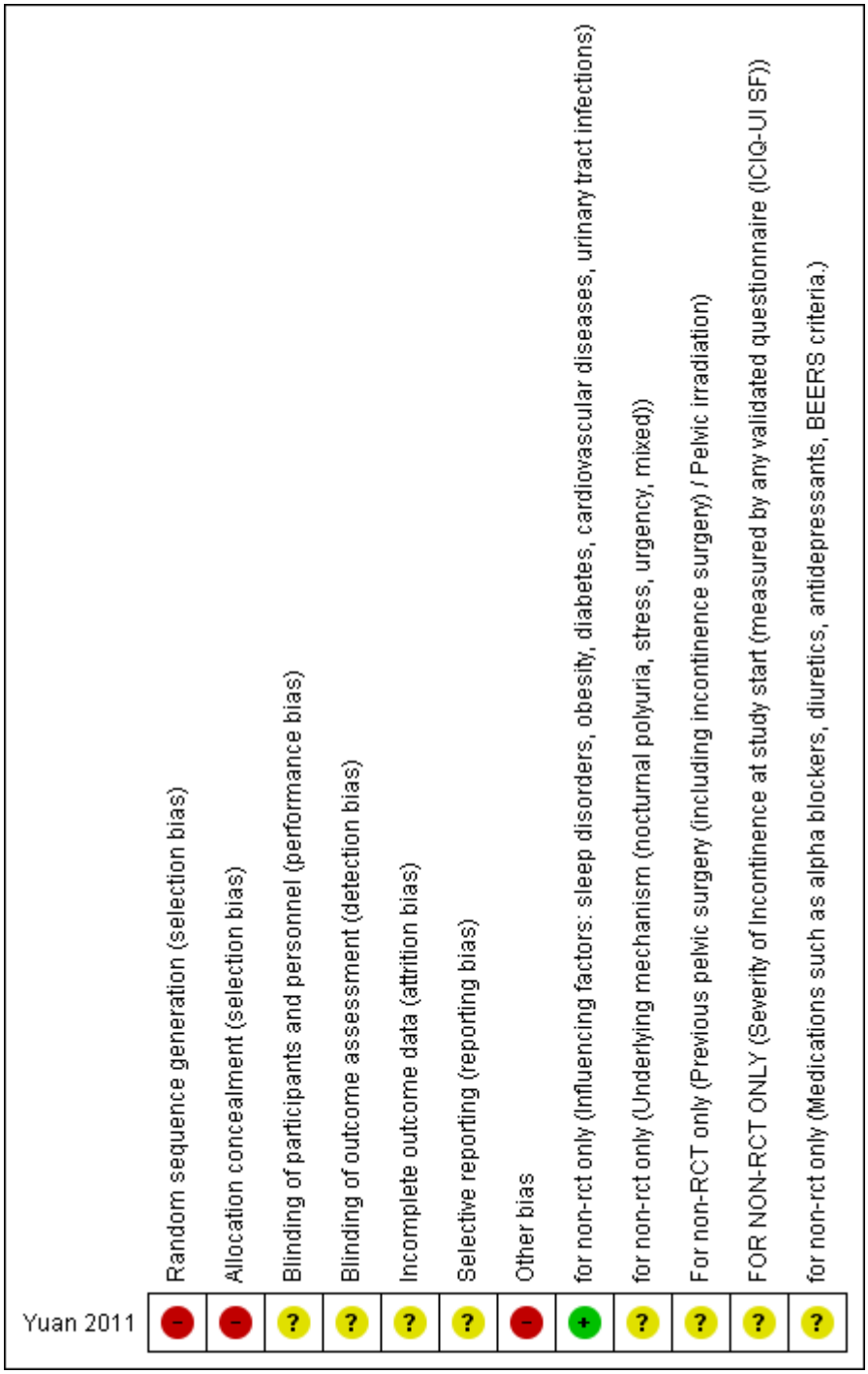


Figure 1. PRISMA flow diagram

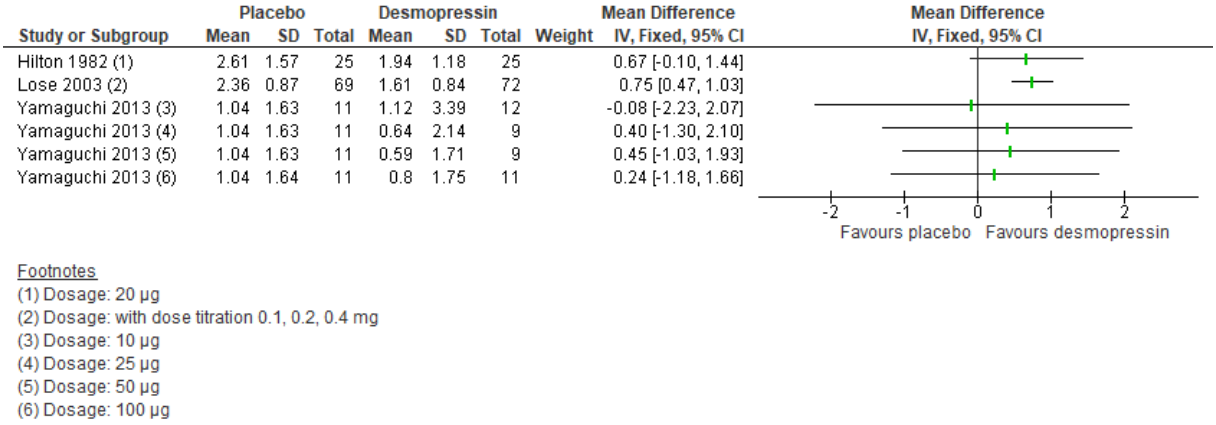

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Aslan 2008
But 2005
FitzGerald 2008
Hilton 1982
JohnsonII 2005
Lo 2003
Lose 2000
Lose 2003
Rovner 2017
Yamaguchi 2013

(a) RCT



(b) Non-RCT

Figure 2. Risk of bias summary according to the judgment of the review authors on each risk of bias item for each study included: (a) – for RCT studies, (b) – is for NRS. Key : red "-" is for high risk of bias, yellow "?" is for unclear risk of bias, green "+" is for low risk of bias



Footnotes
(1) Dosage: 20 µg
(2) Dosage: with dose titration 0.1, 0.2, 0.4 mg
(3) Dosage: 10 µg
(4) Dosage: 25 µg
(5) Dosage: 50 µg
(6) Dosage: 100 µg

Figure 3. Forest plot combining the main findings cited above for comparisons of desmopressin vs. placebo

Table 3. Key characteristics of included studies assessing outcomes

Authors	Year	Ref	Group 1	Comparator	Study	N of participants	Age (Mean, Range)	Follow-up	Outcome	Mean difference	I^2	Certainty of evidence
Desmopressin												
Hilton et al	1982	17	Desmopressin (DDAVP) 20 µg	Placebo	Single site, cross-over	25	56 (41-76)	6 weeks	Nocturnal urine output, ml	124ml lower, 95% CI 204.53 to 43.47 ml lower	100%	Low
									Nocturnal urinary frequency	0.67 times lower, 95% CI 1.44 lower to 0.10 higher	100%	Low
Lose et al	2003	18	Desmopressin (0.1, 0.2, 0.4 mg orally at bedtime after dose-titration period	Placebo	multicentre, multinational double-blind RCT	141	57 (21-89)	3 weeks	Nocturnal urinary frequency	0.75 lower, 95% CI 1.03 lower to 0.47 lower	100%	Low
									Nocturnal diuresis (mL/min)	0.62 ml/min lower, 95% CI 0.76 lower to 0.48 lower	100%	Low
Yamaguchi et al	2013	19	Desmopressin 10 µg	desmopressin 25 µg	multicentre double-blind RCT	21	NA (55-75)	4 weeks	Change on nocturnal urinary volume, mL	206.02 ml higher, 95% CI 11.27 higher to 400.77 higher	100%	Low

			desmopressin 10 µg	desmopressin 100 µg		23		4 weeks		MD 143.26 ml higher, 95% CI 20.52 higher to 266 higher	100%	Low
			placebo	desmopressin 25 µg		20			Change in NPI (NP index; nocturnal urine volume/24-h urine volume [%]	MD 7.75 higher, 95% CI 1.41 higher to 14.09 higher	100%	Low
			placebo	desmopressin 100 µg		22				MD 6.78 higher, 95% CI 1.02 higher to 12.54 higher	100%	Low
			desmopressin 10 µg	desmopressin 25 µg		21				8.54 higher, 95% CI 2.66 higher to 14.42 higher	100%	Low
			desmopressin 10 µg	desmopressin 100 µg		23				7.57 higher, 95% CI 2.31 higher to 12.83 higher	100%	Low
Antimuscarinics												
Johnson et al	2005	21	2.5 mg once a day immediate-release, with possibility to self-titrate	placebo	single site secondary analysis from prospective RCT	84	68 (55-92)	8 weeks	number of nocturia episodes	MD 0.30 lower, 95% CI 0.62 lower to 0.02 higher	100%	high

			Behavioural Treatment	2.5 mg once a day immediate-release oxybutynin		93			number of nocturia episodes	0.30 lower, 95% CI 0.59 lower to 0.01 lower	100%	high
FitzGerald et al	2008	22	Tolterodine tartrate extended-release capsules 4mg alone	Tolterodine 4 mg + behavioural treatment	multicentre RCT	271	only per group, mean(SD): 55.8 (14.2) 58.0 (13.5)	8 weeks	number of nocturia episodes reported as change from baseline	0.26 higher, 95% CI 0.00 to 0.52 higher	100%	moderate
						218			number of nocturnal incontinence episodes	0.06 higher, 95% CI 0.08 lower to 0.20 higher	100%	moderate
Rovner et al	2018	20	Desmopressin 25 µg + Tolterodine 4 mg	Tolterodine 4 mg:	multicentre RCT	97	55 (24–84)	3 months	mean number of nocturnal voids	0.34 lower, 95% CI 0.80 lower to 0.12 higher	100%	moderate
Yuan et al	2011	23	Tolterodine 4 mg + Estazolam 1mg	Tolterodine 4 mg	well-designed large comparative study	407	Onle per group, mean (SD): 56.5(9.2) 57(8.9)	4 weeks	Number of nocturnal voids	MD 1.20 lower, 95% CI 1.28 lower to 1.12 lower	100%	Very low
Oestrogens												
Lose et al	2000	24	Oestradiol-releasing vaginal ring	Oestriol vaginal pessary	RCT	251	66 (47-87)	24 weeks	number of women reporting nocturia	RR 0.94, 95% CI 0.74 to 1.19	100%	low

Behavioural treatment												
Aslan et al	2008	32	Bladder training + Kegel exercises	Control	Single site RCT	50	Only per group, mean (SD) 78.88 (4.80) 79.44 (5.32)	6 months	the nocturia complaints	significant decrease in the treatment group compared to the control group between the 8-week and 6-month evaluations		Very low
Lo et al	2003	25	Pelvic floor exercise	Pelvic floor exercise + Interferential therapy (transcutaneous electrical nerve stimulation)	prospective blinded single site RCT	24	Only per group, mean (SD): 52.1 (17.5) 55.1 (15.1)	4 weeks	number of nocturia episodes	MD 0.54 lower, 95% CI 1.3 lower to 0.22 higher; participants = 24	100%	Very low
Johnson et al	2005	21	Behavioural Treatment	placebo	single site secondary analysis from prospective RCT	84	68 (55-92)	8 weeks	number of nocturia episodes	MD 0.60 lower, 95% CI 0.88 lower to 0.32 lower	100%	moderate
			Behavioural Treatment	2.5 mg once a day immediate-release oxybutynin						0.30 lower, 95% CI 0.59 lower to 0.01 lower	100%	moderate
FitzGerald et al	2008	22	Tolterodine tartrate extended-release capsules 4mg alone	Tolterodine 4 mg + behavioural treatment	multicentre RCT	271	only per group, mean(SD): 55.8 (14.2) 58.0 (13.5)	8 weeks	number of nocturia episodes	0.26 higher, 95% CI 0.00 to 0.52 higher	100%	low
						218			number of nocturnal	MD 0.06 higher, 95% CI	100%	low

									incontinence episodes	0.08 lower to 0.20 higher		
Functional magnetic stimulation												
But et al	2005	26	functional magnetic stimulation (FMS)	placebo	single-centre RCT	39	54 (28-70)	2 months	Nocturia episodes	from 2.6 to 1.4, p = 0.0007		

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