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Desmopressin for treating nocturia in men (Review)

Han J, Jung JH, Bakker CJ, Ebell MH, Dahm P

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Desmopressin for treating nocturia in men (Review)

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[Intervention Review]

Desmopressin for treating nocturia in men

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ABSTRACT

Background

Nocturia is the bothersome symptom of awakening one or more times per night to void. Desmopressin is a commonly used medication for treating nocturia.

Objectives

To assess the effects of desmopressin as compared to other interventions in the treatment of nocturia in men.

Search methods

We performed a comprehensive search of the medical literature with no restrictions on the language of publication or publication status. The date of the latest search of all databases was August 2017.

Selection criteria

We included randomised or quasi-randomised trials. Inclusion criteria were men with nocturia defined as one or more voids per night. We excluded trials of children or adults with primary or secondary enuresis or underlying distinct disorders.

Data collection and analysis

Two review authors independently classified studies and abstracted data from the included studies. We performed statistical analyses using a random-effects model and interpreted data according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We compared desmopressin with placebo, behavioural modification, alpha-blockers, in combination with alpha-blockers against alpha-blockers alone, and in combination with alpha-blocker against alpha-blocker plus anticholinergic. Our outcomes were mean number of voids, quality of life, adverse events, and sleep disturbance.

Main results

We included 14 studies with 2966 randomised men across five comparisons. The studies recruited from urology outpatients clinics and defined nocturia as two or more voids per night. The average age of study participants ranged between 57 and 74 years.

Desmopressin versus placebo: based on short-term follow-up (up to three months), desmopressin may result in a small, possibly unimportant effect on the number of nocturnal voids (mean difference (MD) -0.61, 95% confidence interval (CI) -0.96 to -0.27; low-quality evidence). We are uncertain about the effect of desmopressin on major adverse events at short-term follow-up (risk ratio (RR) 0.97, 95% CI 0.10 to 9.03; very low-quality evidence). For intermediate-term follow-up (three to 12 months), desmopressin may reduce the number

of nocturnal voids in an appreciable number of men (MD -0.85, 95% CI -1.17 to -0.53; low-quality evidence). There was one major adverse event in the desmopressin group at intermediate-term follow-up in one trial of 115 men (RR 3.05, 95% CI 0.13 to 73.39 for both outcomes; low-quality evidence). We found no evidence on quality of life. Subgroup analyses suggest a larger effect on nocturnal voiding with oral, higher-dose formulations of desmopressin and in men with documented nocturnal polyuria.

Desmopressin versus behaviour modification: there were no data regarding the effect on the number of nocturnal voids, quality of life, or major adverse events.

Desmopressin versus alpha-blocker: based on short-term follow-up in one small trial, desmopressin likely has a similar effect on the number of nocturnal voids (MD 0.30, 95% CI -0.20 to 0.80; moderate-quality evidence) and quality of life measured on the International Prostate Symptom Score (IPSS) scale (MD 0.00, 95% CI -0.35 to 0.35; moderate-quality evidence). There were no major adverse events in either group.

Desmopressin plus alpha-blocker versus alpha-blocker alone: based on short-term follow-up, combination therapy likely results in a small, unimportant effect on the number of nocturnal voids (MD -0.47, 95% CI -0.73 to -0.21; moderate-quality evidence) and quality of life (MD -0.29, 95% CI -0.51 to -0.07; moderate-quality evidence). The risk of major adverse events may be similar (0.5% versus 0.3%; RR 0.30, 95% CI 0.01 to 7.32; low-quality evidence).

Desmopressin plus alpha-blocker versus alpha-blocker plus an anticholinergic: based on short-term follow-up, combination therapy likely results in little or no difference in the number of nocturnal voids (MD -0.43, 95% CI -0.97 to 0.11; moderate-quality evidence). We found no evidence on quality of life or sleep duration. There were no major adverse events in either study group.

Authors' conclusions

Desmopressin may reduce the number of nocturnal voids by a small amount compared to placebo in intermediate-term (three to 12 months) follow-up without increasing major adverse events. We found insufficient evidence to determine the effects of desmopressin when compared with behaviour modification. The effect on the number of nocturnal voids in the short term is likely to be similar to that of alpha-blockers, with very infrequent major adverse events. There appears to be little added benefit in the combined use of desmopressin with an alpha-blocker. The findings of this review were limited by short-term follow-up, study limitations, and imprecision.

PLAIN LANGUAGE SUMMARY

Desmopressin for treating nocturia in men with lower urinary tract symptoms

Review question

Is desmopressin effective for treating nocturia in men?

Background

Nocturia is the bothersome symptom of waking one or more times per night to pass urine. It is common in older men. More than half of men older than 70 years of age have nocturia, and there are many reasons for this. Desmopressin is a drug that regulates urine volume and concentration in the body. It is also used to treat nocturia.

Study characteristics

The search is up-to-date to 1 August 2017. We identified 14 clinical trials including 2966 men. We compared desmopressin alone or in combination with other medicines used for urinary problems (such as alpha-blockers or anticholinergics) against placebo (pretend treatment), behaviour changes, or medicines used for urinary problems alone or in combination. Most of the included studies enrolled only older men.

Key results

Treatment with desmopressin for three to 12 months may reduce how often men urinate at night in a small number of men compared to placebo. Serious side effects were not increased. We do not know how the use of desmopressin compares to changes in behaviour. The effect of desmopressin on how often men urinate at night is likely to be similar to that of alpha-blockers when given for up to three months (i.e. short-term treatment) without major side effects. Adding desmopressin to an alpha-blocker seems to work little better than an alpha-blocker alone or an alpha-blocker combined with an anticholinergic.

Quality of the evidence

We rated the quality of the evidence to be low in most cases, meaning that we cannot fully trust the results. The included studies were poorly designed, small, and only followed people for a short time (usually three months or less).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Desmopressin versus placebo for men with nocturia (short term)

Participants: men with nocturia

Setting: likely outpatient

Intervention: desmopressin

Control: placebo

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Assumed risk with placebo	Corresponding risk difference with desmopressin
Number of nocturnal voids assessed with: voiding diary follow-up: range 1 to 3 months	1982 (6 RCTs)	⊕⊕⊕⊕ Low ^{1 2}	-	The mean number of nocturnal voids ranged from 1.9 to 4.57.	MD 0.61 lower (0.96 lower to 0.27 lower)
Quality of life - not reported	-	-	-	-	-
Major adverse events follow-up: range 1 to 3 months	536 (2 RCTs)	⊕⊕⊕⊕ Very low ^{1 2 3}	RR 0.97 (0.10 to 9.03)	Study population 29 per 1000	 1 fewer per 1000 (26 fewer to 233 more)
Duration of first sleep episode assessed with: voiding diary follow-up: range 1 to 3 months	652 (4 RCTs)	⊕⊕⊕⊕ Very low ^{1 2 3}	-	The mean duration of first sleep episode ranged from 26.21 to 174 minutes.	MD 54.61 minutes higher (13.97 higher to 95.25 higher)
Time to first void	383 (1 RCT)	⊕⊕⊕⊕ Low ^{1 3}	-	The mean time to first void was 72.9 minutes.	MD 40.8 minutes higher (17.07 higher to 64.53 higher)
Minor adverse event follow-up: range 1 to 3 months	594 (3 RCTs)	⊕⊕⊕⊕ Low ^{1 3}	RR 0.87 (0.67 to 1.13)	Study population 257 per 1000	 33 fewer per 1000 (33 more to 85 more)
Treatment withdrawal due to adverse event follow-up: range 1 to 3 months	614 (4 RCTs)	⊕⊕⊕⊕ Low ^{1 3}	RR 1.10 (0.56 to 2.15)	Study population 49 per 1000	 5 more per 1000 (21 fewer to 56 more)

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded by one level for study limitations: unclear or high risk of bias for one or more domains in at least 50% of the studies.

²Downgraded by one level for inconsistency: substantial heterogeneity among studies.

³Downgraded by one level for imprecision: confidence interval was wide or crossed assumed threshold of clinically important difference (or both).

Summary of findings 2. Desmopressin versus placebo for men with nocturia (intermediate term)

Participants: men with nocturia

Setting: likely outpatient

Intervention: desmopressin

Control: placebo

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Assumed risk with placebo	Corresponding risk difference with desmopressin
Number of nocturnal voids assessed with: voiding diary follow-up: range 3 to 12 months	115 (1 RCT)	⊕⊕⊕⊕ Low ^{1,2}	-	Mean number of nocturnal voids was 4.14 voids.	MD 0.85 voids fewer (1.17 fewer to 0.53 fewer)
Quality of life - not reported	-	-	-	-	-
Major adverse events follow-up: range 3 to 12 months	115 (1 RCT)	⊕⊕⊕⊕ Low ^{1,2,3}	RR 3.05 (0.13 to 73.39)	Study population	
				-	-

Duration of first sleep episode assessed with: voiding diary follow-up: range 3 to 12 months	115 (1 RCT)	⊕⊕⊕⊖ Moderate ¹	-	Mean duration of first sleep episode was 101.6 minutes.	MD 18.4 minutes higher (11.6 higher to 25.2 higher)
Time to first void - not reported	-	-	-	-	-
Minor adverse events follow-up: range 3 to 12 months	115 (1 RCT)	⊕⊕⊕⊖ Low ^{1,2}	RR 0.86 (0.49 to 1.49)	Study population	
				328 per 1000	46 fewer per 1000 (167 fewer to 161 more)
Treatment withdrawal due to adverse event follow-up: range 3 to 12 months	115 (1 RCT)	⊕⊕⊕⊖ Low ^{1,2,3}	RR 3.05 (0.13 to 73.39)	Study population	
				-	-

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded by one level for study limitations: unclear risk of bias for one or more domains in the included study.

²Downgraded by one level for imprecision: confidence interval was wide or crossed assumed threshold of clinically important difference (or both).

³Only one event in desmopressin group.

Summary of findings 3. Desmopressin versus behaviour modifications for men with nocturia (short term)

Participants: men with nocturia

Setting: likely outpatient

Intervention: desmopressin

Control: fluid restriction during nighttime

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)
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			Assumed risk with behaviour modifica- tion	Corresponding risk difference with desmopressin
Number of nocturnal voids - not reported	-	-	-	-
Quality of life - not reported	-	-	-	-
Major adverse events - not reported	-	-	-	-
Duration of first sleep episode assessed with: not reported follow-up: mean 2 months	60 (1 RCT)	⊕⊕⊕⊕ Low ^{1,2}	-	Mean duration of first sleep episode was 150 minutes. MD 90 minutes higher (1.95 higher to 178.05 higher)
Time to first void - not reported	-	-	-	-
Minor adverse events - not reported	-	-	-	-
Treatment withdrawal due to adverse event - not reported	-	-	-	-

***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; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded by one level for study limitations: unclear risk of bias in almost all domains in the included study.

²Downgraded by one level for imprecision: confidence interval crossed assumed threshold of clinically important difference.

Summary of findings 4. Desmopressin versus alpha-blocker for men with nocturia (short term)

Participants: men with nocturia

Setting: likely outpatient

Intervention: desmopressin

Control: alpha-blocker

Outcomes	N° of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Assumed risk with alpha-blocker	Corresponding risk difference with desmopressin
Number of nocturnal voids assessed with: voiding diary follow-up: range 1 to 3 months	31 (1 RCT)	⊕⊕⊕⊖ Moderate ¹	-	Mean number of nocturnal voids was 1.2 voids.	MD 0.3 voids more (0.2 fewer to 0.8 more)
Quality of life assessed with: IPSS and N-QoL follow-up: range 1 to 3 months	31 (1 RCT)	⊕⊕⊕⊖ Moderate ¹	-	Mean quality of life was 1.8 bothersome.	MD 0 (0.35 lower to 0.35 higher)
Major adverse events follow-up: range 1 to 3 months	31 (1 RCT)	⊕⊕⊖⊖ Low ^{1,2}	Not estimable	Study population	
				-	-
Duration of first sleep episode - not reported	-	-	-	-	-
Time to first void - not reported	-	-	-	-	-
Minor adverse events follow-up: range 1 to 3 months	31 (1 RCT)	⊕⊖⊖⊖ Very low ^{1,3}	RR 1.07 (0.07 to 15.57)	Study population	
				63 per 1000	4 more per 1000 (58 fewer to 911 more)
Treatment withdrawal due to adverse event follow-up: range 1 to 3 months	31 (1 RCT)	⊕⊕⊖⊖ Low ^{1,2}	Not estimable	Study population	
				-	-

***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; **IPSS:** International Prostate Symptom Score; **MD:** mean difference; **N-QoL:** Nocturia-Quality of Life questionnaire; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

- ¹Downgraded by one level for study limitations: unclear or high risk of bias for one or more domains in the included study.
²Downgraded by one level for imprecision: no event in either group.
³Downgraded by two levels for imprecision: confidence interval was wide and crossed assumed threshold of clinically important difference.

Summary of findings 5. Desmopressin plus alpha-blocker versus alpha-blocker for men with nocturia (short term)

Participants: men with nocturia

Setting: likely outpatient

Intervention: desmopressin + alpha-blocker

Control: alpha-blocker alone

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Assumed risk with alpha-blocker	Corresponding risk difference with desmopressin + alpha-blocker
Number of nocturnal voids assessed with: voiding diary follow-up: range 1 to 3 months	341 (3 RCTs)	⊕⊕⊕⊖ Moderate ¹	-	Mean number of nocturnal voids ranged from 1.68 to 2.6.	MD 0.47 voids fewer (0.73 fewer to 0.21 fewer)
Quality of life assessed with: IPSS and N-QoL follow-up: range 1 to 3 months	341 (3 RCTs)	⊕⊕⊕⊖ Moderate ¹	-	Mean quality of life ranged from 1.53 to 4.4.	MD 0.29 lower (0.51 lower to 0.07 lower)
Major adverse events follow-up: range 1 to 3 months	402 (3 RCTs)	⊕⊕⊕⊖ Low ^{1,2}	RR 0.30 (0.01 to 7.32)	Study population	
				5 per 1000	3 fewer per 1000 (5 fewer to 32 more)
Duration of first sleep episode - not reported	-	-	-	-	-
Time to first void - not reported	-	-	-	-	-
Minor adverse events follow-up: range 1 to 3 months	402 (3 RCTs)	⊕⊕⊕⊖ Very low ^{1,3}	RR 1.60 (0.15 to 16.82)	Study population	
				80 per 1000	48 more per 1000 (68 fewer to 1000 more)

Treatment withdrawal due to adverse event follow-up: range 1 to 3 months	402 (3 RCTs)	⊕⊕⊕⊕ Low ^{1,2}	RR 2.84 (0.46 to 17.66)	Study population	
				5 per 1000	9 more per 1000 (3 fewer to 83 more)

***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; **IPSS:** International Prostate Symptom Score; **MD:** mean difference; **N-QoL:** Nocturia-Quality of Life questionnaire; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded by one level for study limitations: unclear or high risk of bias for one or more domains among the included studies.

²Downgraded by one level for imprecision: no event or very rare event resulting in wide confidence interval.

³Downgraded by two level for imprecision: confidence interval was wide and crossed assumed threshold of clinically important difference.

Summary of findings 6. Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic for men with nocturia (short term)

Participants: men with nocturia

Setting: likely outpatient

Intervention: desmopressin + alpha-blocker

Control: anticholinergic + alpha-blocker

Outcomes	Nº of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Assumed risk with alpha-blocker + anticholinergic	Corresponding risk difference with desmopressin + alpha-blocker
Number of nocturnal voids assessed with: voiding diary follow-up: range 1 to 3 months	405 (1 RCT)	⊕⊕⊕⊕ Moderate ¹	-	Mean number of nocturnal voids was 6.97 voids.	MD 0.43 voids fewer (0.97 fewer to 0.11 more)
Quality of life - not reported	-	-	-	-	-

Major adverse events follow-up: range 1 to 3 months	427 (1 RCT)	⊕⊕⊕⊕ Low ^{1,2}	Not estimable	Study population	
				-	-
Duration of first sleep episode - not reported	-	-	-	-	-
Time to first void - not reported	-	-	-	-	-
Minor adverse events follow-up: range 1 to 3 months	427 (1 RCT)	⊕⊕⊕⊕ Low ^{1,3}	RR 0.22 (0.05 to 0.98)	Study population	
				45 per 1000	35 fewer per 1000 (43 fewer to 1 fewer)
Treatment withdrawal due to adverse event follow-up: range 1 to 3 months	427 (1 RCT)	⊕⊕⊕⊕ Low ^{1,3}	RR 0.22 (0.05 to 0.98)	Study population	
				45 per 1000	35 fewer per 1000 (43 fewer to 1 fewer)

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded by one level for study limitations: unclear risk of bias for one or more domains in the included study.

²Downgraded by one level for imprecision: no event in either group.

³Downgraded by one level for imprecision: confidence interval crossed assumed threshold of clinically important difference.

BACKGROUND

Description of the condition

Nocturia is defined as waking at night one or more times to pass urine with each void being preceded and followed by sleep. This is distinct from nocturnal enuresis, which is defined as voiding during sleep (Van Kerrebroeck 2002). Although somewhat controversial, clinically significant nocturia is defined as one or more voids per night (Abrams 2002). Nocturia is one of the most bothersome lower urinary tract symptoms (LUTS), with a correlation between degree of severity and increased bother (Bliwise 2009).

Pathophysiology

Nocturia occurs when nocturnal urine volume exceeds the maximal voiding volume, which is reflective of the functional bladder capacity (Bosch 2013; Cornu 2012). The maximal voiding volume may be different at night than it is during the day. Nocturia has both urologic and non-urologic causes that are behavioural, physiological, or pathologic in nature. Overall, the causes fall into four main categories: reduced bladder capacity secondary to anatomical or functional factors, which may or may not only occur at night; overall increase in urine production (24-hour polyuria); nocturnal polyuria; or any primary or secondary sleep disorder (Bosch 2013; Cornu 2012). Benign prostatic hyperplasia (BPH) contributes to, but is not the sole cause of, LUTS, including nocturia. Benign prostatic hyperplasia can cause bladder outlet obstruction, which may induce secondary bladder overactivity and reduction in functional bladder capacity, resulting in nocturia (Yoshimura 2003). Men may also experience nocturia with or without detrusor overactivity or postvoid residual urine (Berges 2014).

Epidemiology

Nocturia can affect any population at any age, however its incidence generally increases with age. Nocturia defined as one or more micturitions at night affects 20.4% to 43.9% of men aged 20 to 40 years and 68.9% to 93% in men older than 70 years (Bosch 2013).

Risk factors

Risk factors for nocturia are dependent upon the underlying causes, which can be overlapping. General risk factors include advancing age, higher body mass index, alcohol consumption, smoking, hypertension, cardiovascular disease, cerebrovascular disease, diabetes mellitus, and metabolic syndrome (Yoshimura 2003). Men with LUTS suggestive of BPH are more susceptible to nocturia than are men without LUTS. Advancing age, smaller functional bladder capacity, increased nocturnal urine volume, and severity of urgency are predictors of frequent nocturnal voiding (Yoshimura 2003). Overall, age is considered the most important risk factor (Yoshimura 2012).

Diagnosis

Initial assessment of nocturia includes patient history, review of current medications, physical exam including a digital rectal examination in men, urinalysis, measurement of postvoid residual volumes, and validated symptom questionnaires such as the Nocturia-Quality of Life questionnaire (N-QoL) and the International Prostate Symptom Score (IPSS) (Abraham 2004). Other tests that may be necessary include uroflowmetry, urodynamic evaluation of bladder function, cystoscopy, bladder biopsies, sleep laboratory evaluation, and advanced cardiology

tests (Oelke 2014a). A potential dilemma in diagnosing nocturia in men is that it is often not the only symptom mentioned during medical consultations, and it is rarely the symptom that prompted seeking medical evaluation. Its evaluation is therefore often limited to patient-reported numbers of voids per night as an item on the IPSS and subjective history. The International Continence Society encourages the use of the frequency volume chart, an important diagnostic tool that involves the person recording the time and volume of all voids as well as incontinence episodes and the number of incontinence pads used over a specific time, which is usually seven days (Van Kerrebroeck 2002).

Treatment

Treatment is dependent upon the cause of nocturia as well as the person's individual treatment goals. Goals that are cited as being important include decreasing the number of nocturnal voiding episodes, prolongation of undisturbed sleep to greater than four hours, and improvement of sleep quality (Oelke 2014a). Treatment for nocturia can be divided into behavioural modification, medical management, and surgical modalities.

Behavioural treatment

Although treatment should be centred on the cause of nocturia, behavioural modifications appear to be universally beneficial regardless of underlying aetiology. Lifestyle modification is therefore often used as first-line therapy (Van Kerrebroeck 2010). Behavioural treatments include restriction of fluids before going to sleep, avoiding caffeinated or alcoholic beverages in the evening, pre-emptive voiding immediately before going to bed, strategic medication timing, leg elevation in the case of lower extremity oedema, moderate physical exercise, and keeping warm in bed. Lifestyle modifications have been associated with up to 50% of people reporting improvement in nocturia (Soda 2010).

Medical management

Medical management includes therapy with a single drug or a combination of drugs from different classes. Nocturia has historically been considered a symptom secondary to underlying bladder or prostate dysfunction, therefore therapies have been targeted towards these conditions. Current therapies include antimuscarinics, alpha-1 adrenergic receptor blockers, 5-alpha-reductase inhibitors, phosphodiesterase type 5 inhibitors, anti-inflammatory drugs, and desmopressin.

The use of alpha-1 adrenergic receptor blockers and 5-alpha-reductase inhibitors are in the context of BPH management, with only a few studies focusing on nocturia as a primary outcome. Overall, the evidence supporting the efficacy of alpha-1 adrenergic receptor blockers and 5-alpha-reductase inhibitors in treating nocturia is low with inconsistent evidence that at best accounts for minor improvements (Schneider 2009). In one large study analysing 3047 men randomised to one of four groups (doxazosin, finasteride, doxazosin plus finasteride, and placebo), the doxazosin and doxazosin plus finasteride groups showed statistically significant mean reductions in the number of nocturia episodes by 0.77 for doxazosin and 0.80 for doxazosin plus finasteride at one year (Johnson 2007). The placebo group had a decrease in the mean number of nocturia episodes by 0.61 and the finasteride group had a decrease of 0.60 at one year. These results were modest, and whether they are clinically significant is highly questionable.

Tadalafil is a phosphodiesterase type 5 inhibitor that also has approval for treatment of LUTS/BPH. Integrated data from four randomised, placebo-controlled studies investigating the use of daily tadalafil for nocturia found a mean decrease in the number of episodes of 0.4 in the placebo group and 0.5 in the tadalafil group (Oelke 2014b). While the difference between groups was statistically significant, the difference was very small and unlikely to be indicative of a clinically meaningful improvement.

Most studies on antimuscarinics such as solifenacin and tolterodine are in the context of overactive bladder management, and evidence that they are effective for the specific management of nocturia is limited. The clinical impact of these agents is also questionable, as they result in a reduction of half a void or less per night (Smith 2011). The population that may benefit most from these agents are people with severe overactive bladder who have frequent nighttime awakenings associated with urgency.

Few studies have been done on anti-inflammatory drugs for nocturia. One study evaluating celecoxib in men with BPH with refractory nocturia showed promising results (Falahatkar 2008). Men in the active treatment group had a statistically significant decrease in nocturnal frequency from (mean $\pm$ standard deviation (SD)) 5.17 ± 2.1 episodes to 2.5 ± 1.9 episodes, a dramatic response that is better than any other treatment modality. However, this study included only 80 men and was for a period of only four weeks. Without more reports with longer follow-up and larger study populations, the evidence to support the use of anti-inflammatory drugs for nocturia in men remains unclear.

Surgical management

Surgical treatment may be appropriate for men with nocturia due to LUTS related to benign prostatic obstruction, although no surgical therapy is specifically indicated for nocturia (Cornu 2012). Surgical options to reduce prostatic obstruction include transurethral resection of the prostate, transurethral incision of the prostate, transurethral microwave therapy of the prostate, and prostatectomy. Transurethral resection of the prostate has been associated with a one-point reduction in nocturia, which correlates to one less nightly episode (Wada 2014; Yoshimura 2003). Prostatectomy has been associated with a decrease in nighttime voiding frequency of 0.8 (mean $\pm$ SD): from 3.4 ± 1.2 episodes to 2.6 ± 0.99 episodes (Margel 2007). Other interventions such as botulinum toxin detrusor injection, sacral neuromodulation, or tibial electric nerve stimulation are used in the context of overactive bladder where nocturia is regarded a secondary outcome (Cornu 2012).

Description of the intervention

Desmopressin is the synthetic analogue of the human hormone vasopressin, which has been used clinically in a variety of formulations since 1974. Vasopressin, also known as antidiuretic hormone, is produced by the posterior pituitary gland, and its role is to maintain serum osmolality and volume via modulation of free water excretion. Vasopressin is released in states of hyperosmolality and hypovolaemia, which is detected by chemoreceptors and baroreceptors located in the hypothalamus and carotid sinus, respectively. It acts on the V2 receptors in the distal collecting tubules, which subsequently results in translocation of aquaporin channels associated with cytosolic vesicles to the apical membrane of collecting duct cells. Free water is then passively reabsorbed from the nephron back into

the systemic circulation via basolateral membrane channels. Vasopressin also plays a minor role in increasing systemic vascular resistance and increasing urea reabsorption in the medullary collecting tubule (Shoskes 2011). It is the most frequently tested medication for the specific treatment of nocturia, but has traditionally been used to treat central diabetes insipidus, bleeding disorders such as Von Willebrand disease, and primary nocturnal enuresis. The US Food and Drug Administration (FDA) approved desmopressin acetate nasal spray with the trademark name of NOCTIVA in March 2017 for nocturia due to nocturnal polyuria in adults who awaken at least twice per night to void (Serenity Pharmaceuticals 2017).

Adverse events of the intervention

The most frequently encountered adverse events include headache, hyponatraemia, insomnia, dry mouth, hypertension, abdominal pain, peripheral oedema, and nausea (Friedman 2013).

How the intervention might work

Desmopressin is effective in the treatment of polyuric states, and nocturnal polyuria is very common in people with nocturia (as high as 82.9%) (Chang 2006). Desmopressin may help alleviate nocturnal voiding by inducing antidiuresis resulting in increased urine osmolality and decreased urine output.

Why it is important to do this review

Nocturia may decrease quality of life and is associated with a high degree of bother. Reduced sleep due to nocturia has been associated with diurnal fatigue, decreased concentration, lower performance at work, and accidents from cognitive and motor impairment (Asplund 2005; Chartier-Kastler 2006). In the elderly population, nocturia is associated with an increased risk of bone fractures due to nighttime falls (Nakagawa 2010). Although various treatment modalities have been used to treat LUTS successfully, nocturia remains one of the most elusive and problematic symptoms.

There are also inherent risks in recommending a medication to treat a symptom if the underlying disease process is not thoughtfully considered. Desmopressin can also cause hyponatraemia, which is often asymptomatic but in limited cases can have deleterious effects. With regard to assessing efficacy, a common outcome measure is the decrease in the number of nocturnal voids, however there is no existing consensus on its clinical significance. To better assess clinically meaningful efficacy it is therefore crucial to critically analyse and synthesise the symptoms, quality of life measures, and sleep parameters in existing clinical trials (Cornu 2012).

One systematic review on this topic exists (Ebell 2014). However, no review has used GRADE to assess the quality of evidence supporting the use of desmopressin for the treatment of nocturia in men. Given the modest efficacy and questionable clinical significance of the multiple medical and surgical treatments for nocturia in men, such an investigation into the effects of desmopressin based on the totality of available evidence as summarised in a rigorous systematic review is critically important. In an era of rising health costs and an increased emphasis on evidence-based medicine, the findings of this review will be especially relevant to policymakers and healthcare providers. Furthermore, as a drug can gain regulatory approval based on statistical significance, it is

important to know that this does not automatically mean that the drug has a clinically significant impact. This is of particular concern when the effect size is small or when the potential adverse events are considerable, or both ([Fralick 2017](#)).

OBJECTIVES

To assess the effects of desmopressin as compared to other interventions in the treatment of nocturia in men.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised or quasi-randomised trials regardless of their publication status or language of publication.

Types of participants

Men with nocturia defined as one or more voids per night ([Abrams 2002](#)). We excluded trials of children or adults with primary or secondary enuresis or underlying distinct disorders such as Cushing disease, multiple sclerosis, or autonomic dysfunction.

We mostly included studies focused on this specific population of participants. In addition, we included studies in which a subset of participants met our inclusion criteria, if relevant data were reported separately to permit data analysis.

Types of interventions

We planned to investigate the following comparisons of experimental intervention versus comparator intervention.

Experimental interventions

- Desmopressin.
- Desmopressin plus other drug treatment for LUTS.

Comparator interventions

- Placebo.
- Behavioural modifications.
- Drug treatments for LUTS.
- Surgery for LUTS.

Comparisons

- Desmopressin versus placebo.
- Desmopressin versus behavioural modification.
- Desmopressin versus drug treatment for LUTS.
- Desmopressin plus other drug treatment for LUTS versus drug treatment for LUTS alone.
- Desmopressin versus surgery for LUTS.

We required that concomitant interventions be the same in the experimental and comparator groups to establish fair comparisons.

Types of outcome measures

We did not use the measurement of the outcomes specified in this review as an eligibility criterion.

Primary outcomes

- Number of nocturnal voids.
- Quality of life.
- Major adverse events.

Secondary outcomes

- Duration of first sleep episode.
- Time to first void.
- Minor adverse events.
- Treatment withdrawal due to adverse event.

Method and timing of outcome measurement

We used clinically important differences (CID) for each outcome to rate the quality of the evidence in the 'Summary of findings' tables ([Johnston 2010](#)).

Number of nocturnal voids

- Measured by voiding diary (final value or change from baseline).
- Minimal clinically important differences (MCIDs) for outcomes when treating nocturia have not been defined. We considered improvement of nocturia of at least one episode per night as CID for nocturia ([Krader 2012](#)).

Quality of life

- Assessed using condition-specific, validated health measures (such as IPSS and N-QoL; final value or change from baseline).
- We used an MCID of one point for IPSS-QoL to assess efficacy and comparative effectiveness ([Brasure 2016](#)). While no thresholds were established for N-QoL and Impact of Nighttime Urination, we used a CID of eight points for both questionnaires to assess efficacy and comparative effectiveness ([Serenity Pharmaceuticals 2016](#)).

Major adverse events

- Such as symptomatic hyponatraemia, arrhythmia, need for hospital admission, respiratory insufficiency.

Duration of first sleep episode

- Measured by voiding diary (final value or change from baseline).

Time to first void

- Measured by voiding diary (final value or change from baseline).

Minor adverse events

- Such as asymptomatic hyponatraemia requiring treatment, headache, nausea, insomnia, dry mouth, hypertension, abdominal pain, and peripheral oedema.

Treatment withdrawal due to adverse event

- Defined as treatment discontinuation from any cause at any time after men were randomised to intervention/comparator groups.

The CID for the duration of first sleep episode, time to first void, major and minor adverse events, and treatment withdrawal due to adverse event have not been defined. We considered improvement of at least one hour per night as the CID for duration of first sleep episode and time to first void. We considered the CID for major and

minor adverse events, and treatment withdrawal due to adverse event as a relative risk reduction of at least 25% (Guyatt 2011a).

We separately considered outcomes measured up to three months (short term), more than three months up to 12 months (intermediate term), and more than 12 months (long term).

Main outcomes for 'Summary of findings' tables

We presented 'Summary of findings' tables for the following outcomes.

- Number of nocturnal voids.
- Quality of life.
- Major adverse events.
- Duration of first sleep episode.
- Time to first void.
- Minor adverse events.
- Treatment withdrawal due to adverse event.

Search methods for identification of studies

We performed a comprehensive search with no restrictions on the language of publication or publication status.

Electronic searches

We searched the following sources from inception of each database. We initially searched the following sources from inception to 22 June 2015. The date of last search of all databases was 1 August 2017.

- The Cochrane Library (from 1991 via Wiley for the search strategy, see Appendix 2);
 - * Cochrane Database of Systematic Reviews (CDSR);
 - * Cochrane Central Register of Controlled Trials (CENTRAL);
 - * Database of Abstracts of Reviews of Effects (DARE);
 - * Health Technology Assessment (HTA) Database.
- MEDLINE (from 1946 via Ovid; Appendix 3).
- EMBASE (from 1974 via Ovid; Appendix 4).
- Scopus (from 1966; Appendix 5).
- Google Scholar (Appendix 6).
- Web of Science (from 1900; Appendix 7).
- Western Pacific Region Index Medicus (from 1950; Appendix 8).

We also searched the following clinical trial registries. The date of last search of all clinical trial registries was 1 August 2017.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; Appendix 9).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/; Appendix 10).

Searching other resources

We attempted to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports. We also contacted study authors of included trials to identify any further studies that we may have missed.

We contacted Ferring Pharmaceuticals, the sponsor of several trials, for ongoing or unpublished trials. We also searched for

unpublished studies by handsearching the abstract proceedings of the annual meetings of the American Urological Association, European Association of Urology, International Continence Society, and the British Association of Urological Surgeons from 2012 to 2017.

Data collection and analysis

Selection of studies

We used reference management software to identify and remove potential duplicate records (EndNote). Two review authors (JH, JHJ) independently scanned the abstract, title, or both, of the remaining records to determine which studies should be assessed further in Covidence. In the second stage, two review authors (JH, JHJ) investigated all potentially relevant records as full text; mapped records to studies; and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Any discrepancies were resolved through consensus or recourse to a third review author (PD). We documented reasons for exclusion of studies that may have reasonably been expected to have been included in the review in the *Characteristics of excluded studies* table. We presented an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We developed a dedicated data abstraction form that we pilot tested ahead of time.

Two review authors (JH, JHJ) independently abstracted the following information for studies that fulfilled our inclusion criteria, which we summarised in the *Characteristics of included studies* table.

- Study design.
- Study dates (if dates were not available, we reported this as such).
- Study settings and country.
- Participant inclusion and exclusion criteria.
- Participant details, baseline demographics.
- Number of participants by study and study arm.
- Details of relevant experimental and comparator interventions such as desmopressin dose, route, frequency, and duration.
- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups.
- Study funding sources.
- Declarations of interest by primary investigators.

We extracted outcomes data relevant to this review as needed for the calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals for completion of a two-by-two table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we attempted to obtain means and SDs or data needed to calculate this information.

Any disagreements were resolved by discussion or by consulting a third review author (PD).

We attempted to contact authors of included studies to obtain key missing data as needed and documented these communications.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximised the yield of information by mapping all publications to unique studies and collating all available data using the most complete data set aggregated across all known publications.

Assessment of risk of bias in included studies

Two review authors (JHJ, PD) independently assessed the risk of bias of each included study on a per-outcome basis. We resolved all disagreements by discussion and consensus.

We assessed risk of bias using the Cochrane 'Risk of bias' assessment tool employing the following domains ([Higgins 2011b](#)).

- 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 sources of bias.

We judged 'Risk of bias' domains as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We presented a 'Risk of bias' summary figure to illustrate these findings.

For selection bias (random sequence generation and allocation concealment) and reporting bias (selective reporting), we evaluated risk of bias at the level of the trial.

For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we evaluated the risk of bias separately for each outcome. We considered all outcomes similarly susceptible to bias and assessed them as one group.

We assessed attrition bias (incomplete outcome data) on an outcome-specific basis. Since judgements were identical across some outcomes, we collapsed these ratings into groups when reporting our findings in the 'Risk of bias' tables.

We further summarised the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)).

Measures of treatment effect

We expressed dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MD) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant. We identified no cluster-randomised trials. For cross-over trials, we only considered

data up to the time point that cross-over occurred in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011c](#)).

Dealing with missing data

We sought to obtain missing data from study authors and to perform intention-to-treat analyses if data were available; we otherwise performed available-case analyses, which we identified as such. We investigated attrition rates, for example dropouts, losses to follow-up, and withdrawals, and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity unexplained by subgroup analyses, we planned not to report outcome results as the pooled effect estimate in a meta-analysis but to provide a narrative description of the results of each study only.

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis ([Higgins 2002](#); [Higgins 2003](#)). We interpreted the I^2 statistic as follows.

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

In the setting of heterogeneity, we planned to determine the possible reasons for the heterogeneity by examining individual study and subgroup characteristics. However, due to a paucity of studies for each comparison, this was not feasible.

Assessment of reporting biases

We attempted to obtain study protocols to assess selective outcome reporting.

For 10 or more studies investigating a particular outcome, we planned to use funnel plots to assess small-study effects. However, the number of included studies was consistently too low to permit this type of analysis.

Data synthesis

We summarised data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We used the Mantel-Haenszel method for dichotomous outcomes, and the inverse variance method for continuous outcomes. We performed all analyses in Review Manager 5 software ([RevMan 2014](#)).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and planned to carry out subgroup analyses with investigation of interactions limited to the primary outcomes.

- Routes of administration of desmopressin (intranasal versus sublingual versus oral) to evaluate whether the treatment effects depended on the routes of administration. The differences in the systemic absorption of the three administration routes are reflected in the bioavailability (Fransén 2009).
- Desmopressin dose (less than 10 µg versus 10 µg or greater to less than 100 µg versus 100 µg or greater) to evaluate whether the efficacy of desmopressin depends on the dose. Statistically significant benefits have been seen with doses as low as 25 µg, however a greater magnitude of benefit has been shown with doses of 100 µg or higher with no associated statistically significant increase in adverse events (Ebell 2014).
- In men with or without nocturnal polyuria to evaluate whether desmopressin has more benefit in men with nocturnal polyuria (Berges 2014).

We used the test for subgroup differences in Review Manager 5 to compare subgroup analyses if there were sufficient studies (RevMan 2014).

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes limited to the primary outcomes.

- Restricting the analysis by considering risk of bias, excluding studies at 'high risk' or 'unclear risk'.
- Restricting the analysis by considering risk of bias, excluding studies with run-in periods.
- Restricting the analysis by considering the clinically recommended dosage of desmopressin, excluding lower dose levels.

'Summary of findings' tables

We presented the overall quality of the evidence for each outcome according to the GRADE approach, which considers five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such

as directness of results (Guyatt 2008). For each comparison, two review authors (JH, JHJ) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT (GRADEpro GDT), resolving any discrepancies by consensus, or, if needed, by recourse to a third review author (PD). For each comparison, we presented a summary of the evidence for the main outcomes in 'Summary of findings' tables, which provided key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences, for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011b; Schünemann 2011).

RESULTS

Description of studies

Results of the search

Our comprehensive literature search identified 1524 records that included six records found through the trial registries and the New Drug Applications submitted to the FDA. After removal of duplicates, we screened the titles and abstracts of 1355 records and excluded 1298. We screened 57 full-text articles and excluded 22 studies (23 articles). Seventeen studies did not meet the inclusion criteria or were not relevant to our review question (Ahmed 2015b; Asplund 1999; Cho 2015; Cho 2016; Fu 2011; Gilbert 2011; Holm-Larsen 2013a; Kaminetsky 2016; Lam 2017; Malli 2014; Moon 2002; Moon 2003; Shin 2014b; van Kerrebroeck 2007; Wang 2011b; Weiss 2012b; Yassin 2010). We identified four studies awaiting classification (Holm-Larsen 2013b; NCT01694498; Salvatore 1996; Weiss 2001), and one ongoing trial (NCT02904759). Fourteen studies (34 articles) ultimately met the inclusion criteria and were included in the qualitative synthesis of this review (Ahmed 2015a; Cannon 1999; Ceylan 2013; Kim 2017; Koca 2012; Mattiasson 2002; Rezakhaniha 2011; Serenity Pharmaceuticals 2016; Shin 2014a; Wang 2011a; Wang 2012; Weiss 2012a; Weiss 2013; Yamaguchi 2013). The flow of literature through this assessment process is shown in the PRISMA flowchart (Figure 1).

Figure 1. PRISMA flow diagram.

Figure 1. (Continued)

Included studies

A detailed description of the characteristics of included studies is presented elsewhere (see [Characteristics of included studies](#) table; [Table 1](#); [Table 2](#)).

Source of data

The literature search identified all 14 trials included in the review. Of the 14 included studies, we found one study by the New Drug Application submitted to the FDA ([Serenity Pharmaceuticals 2016](#)), and the remaining studies were published trials. We contacted all trial authors of the included trials except two studies supported by pharmaceutical companies ([Serenity Pharmaceuticals 2016](#); [Yamaguchi 2013](#)). We received a reply from six trial authors ([Kim 2017](#); [Mattiasson 2002](#); [Rezakhaniha 2011](#); [Shin 2014a](#); [Weiss 2012a](#); [Weiss 2013](#)).

Study design and settings

Two trials were cross-over randomised controlled trials ([Cannon 1999](#); [Shin 2014a](#)). The remaining studies were parallel-group randomised controlled trials ([Ahmed 2015a](#); [Ceylan 2013](#); [Kim 2017](#); [Koca 2012](#); [Mattiasson 2002](#); [Rezakhaniha 2011](#); [Serenity Pharmaceuticals 2016](#); [Wang 2011a](#); [Wang 2012](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)). One trial was single-blinded ([Ahmed 2015a](#)). Four trials were reported as double-blinded, and stated that participants and investigators were blinded ([Serenity Pharmaceuticals 2016](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)). Three trials were reported to be double-blinded, but it was unclear which groups were actually blinded ([Cannon 1999](#); [Mattiasson 2002](#); [Wang 2011a](#)). The lead author of [Kim 2017](#) confirmed that participants and personnel were blinded. Five trials provided no information regarding blinding ([Ceylan 2013](#); [Koca 2012](#); [Rezakhaniha 2011](#); [Shin 2014a](#); [Wang 2012](#)). Four trials had run-in periods ([Cannon 1999](#); [Mattiasson 2002](#); [Serenity Pharmaceuticals 2016](#); [Shin 2014a](#)). None of the trials were terminated early (for benefit).

All studies were likely conducted in an outpatient urology clinic setting. Five of 14 trials explicitly stated that the trial was conducted in an outpatient urology clinic setting ([Ahmed 2015a](#); [Ceylan 2013](#); [Koca 2012](#); [Rezakhaniha 2011](#); [Wang 2012](#)). Six trials were multicentre studies ([Kim 2017](#); [Mattiasson 2002](#); [Serenity Pharmaceuticals 2016](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)).

Seven trials were performed in Asia ([Ahmed 2015a](#); [Kim 2017](#); [Rezakhaniha 2011](#); [Shin 2014a](#); [Wang 2011a](#); [Wang 2012](#); [Yamaguchi 2013](#)), and the remaining studies were conducted in Europe and the USA. Trials were performed during the time frame of 1999 to 2016. Thirteen trials were published in English, and one was published in Turkish ([Koca 2012](#)), which was translated into English using Google Translate.

Participants

This review included a total of 4195 randomised participants (range 20 to 1556), of which a total of 4011 were subsequently accounted for in the analysis. Of the 4011 participants, 1045 were women (26.0%), as three trials included women ([Serenity Pharmaceuticals 2016](#); [Weiss 2012a](#); [Yamaguchi 2013](#)). The ethnic group representation was clearly reported in only one trial ([Serenity Pharmaceuticals 2016](#): 78.4% white; 12.1% African-American; 2% Asian; 6.6% Hispanic and others). The mean age of the men ranged from 57 to 74 years; four studies did not report age ([Cannon 1999](#); [Wang 2012](#); [Weiss 2012a](#); [Yamaguchi 2013](#)). One trial reported the mean prostate volume, which was 45.7 mL for the treatment group and 47.0 mL for the comparator group ([Ahmed 2015a](#)). Two trials reported mean prostate specific antigen, which ranged from 1.8 ng/mL to 2.6 ng/mL ([Ahmed 2015a](#); [Ceylan 2013](#)). Five studies reported mean baseline IPSS score, peak urinary flow rate, and postvoid residual ([Ahmed 2015a](#); [Ceylan 2013](#); [Kim 2017](#); [Koca 2012](#); [Shin 2014a](#)). Mean baseline IPSS score ranged from 12.1 to 24.9. Mean baseline maximum flow rate (Q_{max}) ranged from 10.3 mL/second to 17.8 mL/second. The mean baseline postvoid residual ranged from 32.9 mL to 61.8 mL. The mean IPSS score after intervention ranged from 6.5 to 23.2. The mean Q_{max} after intervention ranged from 13.3 mL/second to 22.7 mL/second. The mean postvoid residual after intervention ranged from 14.0 mL to 41.4 mL.

Eleven of 14 studies included participants aged over 40 years, [Ahmed 2015a](#); [Cannon 1999](#); [Kim 2017](#); [Koca 2012](#); [Serenity Pharmaceuticals 2016](#); [Shin 2014a](#); [Wang 2011a](#); [Yamaguchi 2013](#), or with old age (not defined; [Ceylan 2013](#); [Rezakhaniha 2011](#); [Wang 2012](#)). Three trials included participants aged over 18 years ([Mattiasson 2002](#); [Weiss 2012a](#); [Weiss 2013](#)). Three trials included men and women and reported the men's data separately ([Serenity Pharmaceuticals 2016](#); [Weiss 2012a](#); [Yamaguchi 2013](#)).

Major exclusion criteria from trials included prior treatment with desmopressin or other BPH medical therapy within three months, evidence of severe daytime voiding dysfunction, suspicion of bladder outlet obstruction or a urine flow less than 5 mL/second, prior genitourinary surgeries, urinary retention or elevated postvoid residual greater than 250 mL (or both), history of genitourinary malignancies, positive urine cultures, hyponatraemia, uncontrolled diabetes, uncontrolled hypertension, diuretic use, voiding dysfunctions arising from well-defined causes other than BPH, or polydipsia. For the two of three trials that included women ([Serenity Pharmaceuticals 2016](#); [Weiss 2012a](#)), potential for pregnancy, use of a pessary or pelvic prolapse, and presence of an unexplained pelvic mass were exclusion criteria.

Diagnosis

Most studies defined nocturia as two or more voids per night ([Ahmed 2015a](#); [Ceylan 2013](#); [Kim 2017](#); [Koca 2012](#); [Mattiasson 2002](#); [Rezakhaniha 2011](#); [Serenity Pharmaceuticals 2016](#); [Wang 2011a](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)), and only one study used one or more voids per night as an inclusion criterion ([Shin 2014a](#)). Two trials did not report a definition of nocturia ([Cannon 1999](#); [Wang 2012](#)). Four trials only included participants with nocturnal polyuria defined as the overproduction of urine at night (i.e. excess of a third or 30% of total daily urine volume; [Ahmed 2015a](#); [Cannon 1999](#); [Kim 2017](#); [Wang 2011a](#)).

Interventions and comparators

Three included studies administered desmopressin as a nasal spray ([Cannon 1999](#); [Ceylan 2013](#); [Serenity Pharmaceuticals 2016](#)), while the remaining 11 studies administered an oral or sublingual formulation. Two studies used desmopressin 20 µg nasal spray ([Cannon 1999](#); [Ceylan 2013](#)), and one trial used a new formulation of nasal spray submitted for FDA approval with a desmopressin dose ranging from 0.75 µg to 1.5 µg ([Serenity Pharmaceuticals 2016](#)). Four trials administered desmopressin as a sublingual agent (orally disintegrating tablet), with a dose range from 10 µg to 100 µg ([Ahmed 2015a](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)). The remaining studies administered desmopressin as an oral agent (dose range from 0.1 mg to 0.4 mg). Three studies included participants given sublingual desmopressin less than the clinical dosage (60 µg) as an experimental group ([Weiss 2012a](#): 10/25/50 µg, [Weiss 2013](#): 50 µg, [Yamaguchi 2013](#): 10/25/50 µg). Ten of 14 studies used desmopressin as monotherapy ([Cannon 1999](#); [Ceylan 2013](#); [Mattiasson 2002](#); [Rezakhaniha 2011](#); [Serenity Pharmaceuticals 2016](#); [Wang 2011a](#); [Wang 2012](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)). Four trials investigated the combination of desmopressin with alpha-blocker therapy ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#); [Shin 2014a](#)). One study had dose titration of desmopressin prior to randomisation, and only participants who obtained a 20% reduction in nocturnal diuresis were enrolled in the study (active run-in; [Mattiasson 2002](#)).

Comparators were behaviour modification and four agents, namely placebo, alpha-blocker, desmopressin plus alpha-blocker, and desmopressin plus anticholinergic. Placebo was administered in accordance with the frequencies of desmopressin administration ([Cannon 1999](#); [Mattiasson 2002](#); [Rezakhaniha 2011](#); [Serenity Pharmaceuticals 2016](#); [Wang 2011a](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)). [Wang 2012](#) encouraged liquid restriction during nighttime for participants in the control group. A variety of alpha-blockers (alfuzosin, doxazosin, and tamsulosin) were administered

orally as monotherapy, [Ahmed 2015a](#); [Ceylan 2013](#); [Koca 2012](#), and combination therapy with placebo, [Kim 2017](#), or anticholinergic, [Shin 2014a](#). Alfuzosin (10 mg; [Koca 2012](#)), doxazosin (2 mg or 4 mg; [Ceylan 2013](#)), and tamsulosin (0.2 mg or 0.4 mg; [Ahmed 2015a](#); [Shin 2014a](#)) were used as comparator drug agents. Solifenacin (5 mg; [Shin 2014a](#)) was used as a comparator in combination therapy with an alpha-blocker.

The duration of interventions ranged from three weeks to 12 months. All included studies reported short-term outcomes across five comparisons. Only one study reported intermediate-term outcomes for the comparison of desmopressin versus placebo ([Wang 2011a](#)). No studies reported long-term follow-up.

Comparisons

We included five comparisons in this review, of which eight studies compared desmopressin to placebo ([Cannon 1999](#); [Mattiasson 2002](#); [Rezakhaniha 2011](#); [Serenity Pharmaceuticals 2016](#); [Wang 2011a](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)). One study compared desmopressin to behavioural modifications ([Wang 2012](#)). One study compared desmopressin to an alpha-blocker ([Ceylan 2013](#)). Three studies compared the addition of desmopressin to alpha-blocker therapy versus an alpha-blocker alone ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#)). One study compared desmopressin with an alpha-blocker to an alpha-blocker with an anticholinergic ([Shin 2014a](#)). No trials compared desmopressin to surgery.

Outcomes

We identified all primary outcomes in each of the included studies for four comparisons. The number of nocturnal voids and major adverse events were reported in all comparisons except desmopressin versus behaviour modification. Quality of life outcomes were reported in the comparisons of desmopressin versus alpha-blocker and desmopressin plus alpha-blocker versus alpha-blocker. Eight trials reported health-related quality of life using the IPSS ([Ahmed 2015a](#); [Ceylan 2013](#); [Kim 2017](#); [Koca 2012](#); [Shin 2014a](#); [Wang 2011a](#); [Weiss 2012a](#); [Weiss 2013](#)). We were able to use the information regarding quality of life outcomes for the comparisons of desmopressin versus alpha-blocker and desmopressin plus alpha-blocker versus alpha-blocker. The authors of included studies did not use validated score systems such as Common Terminology Criteria for Adverse Events to assess adverse events ([National Cancer Institute](#)), therefore we judged the severity of adverse events using the available information described in the studies.

For secondary outcomes, the duration of the first sleep episode was reported in the comparisons of desmopressin versus placebo and desmopressin versus behaviour modification. None of the studies reported time to first void. The outcomes of minor adverse events and treatment withdrawal due to adverse event were reported in all comparisons except desmopressin versus behaviour modification.

Funding source and conflicts of interest

Seven studies specified funding sources ([Kim 2017](#); [Rezakhaniha 2011](#); [Serenity Pharmaceuticals 2016](#); [Shin 2014a](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)): five were supported by pharmaceutical companies; one was funded by government; and one reported no funding source. Six studies reported no conflicts of interest ([Ahmed 2015a](#); [Ceylan 2013](#); [Koca 2012](#);

Mattiasson 2002; Rezakhaniha 2011; Shin 2014a), and five reported having relationships with pharmaceutical companies (Cannon 1999; Serenity Pharmaceuticals 2016; Weiss 2012a; Weiss 2013; Yamaguchi 2013).

Excluded studies

We excluded 17 studies (18 articles) after evaluation of the full publication (see [Characteristics of excluded studies](#) table). Six studies were duplicates (Ahmed 2015b; Cho 2016; Kaminetsky 2016; Shin 2014b; Wang 2011b; Weiss 2012b). Four studies had the wrong study design (Gilbert 2011; Holm-Larsen 2013a; Moon 2002; Moon 2003). Four studies had the wrong study population (Asplund 1999; Lam 2017; van Kerrebroeck 2007; Yassin 2010). Of the remaining studies, one had the wrong intervention (Fu 2011); one had the wrong comparator (Cho 2015); and one had the wrong outcome (Malli 2014).

Studies awaiting classification

There are four studies awaiting classification (see [Characteristics of studies awaiting classification](#) table) (Holm-Larsen 2013b; NCT01694498; Salvatore 1996; Weiss 2001).

Ongoing studies

We found one ongoing study (see [Characteristics of ongoing studies](#) table) (NCT02904759).

Risk of bias in included studies

Detailed results of the 'Risk of bias' assessment are provided in [Figure 2](#) and [Figure 3](#), and judgements for individual domains are provided in the [Characteristics of included studies](#) table.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

	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): Number of nocturnal voids	Incomplete outcome data (attrition bias): QoL	Incomplete outcome data (attrition bias): Duration of first sleep episode	Incomplete outcome data (attrition bias): Time to first void	Incomplete outcome data (attrition bias): Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Selective reporting (reporting bias)	Other bias
Ahmed 2015a	+	?	-	?	+	+	+	?	+	?	+
Cannon 1999	?	?	?	?	?	?	?	?	?	?	?
Ceylan 2013	?	?	?	?	-	-	-	-	-	?	+
Kim 2017	+	+	+	+	-	-	-	?	-	+	+
Koca 2012	?	?	?	?	+	+	?	?	+	?	+
Mattiasson 2002	?	?	?	?	+	?	+	?	+	?	-
Rezakhaniha 2011	?	?	?	?	+	?	+	?	+	?	+

Figure 2. (Continued)

Rezakhaniha 2011	?	?	?	?	+	?	+	?	+	?	+
Serenity Pharmaceuticals 2016	?	?	+	+	+	?	?	+	+	-	?
Shin 2014a	?	?	?	?	+	?	?	?	+	+	+
Wang 2011a	+	?	?	?	+	+	+	?	+	?	+
Wang 2012	?	?	?	?	+	+	+	?	?	?	?
Weiss 2012a	+	+	+	+	?	?	?	?	?	+	?
Weiss 2013	+	?	+	+	+	?	?	+	+	+	+
Yamaguchi 2013	+	?	+	+	-	-	-	?	?	+	?

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Allocation

Random sequence generation

The sequence generation for participation allocation was adequate in six trials and rated at low risk of bias (Ahmed 2015a; Kim 2017; Wang 2011a; Weiss 2012a; Weiss 2013; Yamaguchi 2013). In the remaining trials, the method of sequence generation was unclear or not specified.

Allocation concealment

Two trials had adequate allocation concealment and were at low risk of bias (Kim 2017; Weiss 2012a). In the remaining trials, treatment allocation was unclear.

Blinding

Blinding of participants and personnel

Five trials were at low risk of bias (Kim 2017; Serenity Pharmaceuticals 2016; Weiss 2012a; Weiss 2013; Yamaguchi 2013), and one study was at high risk of bias (Ahmed 2015a). The remaining studies were at unclear risk of bias.

Blinding of outcome assessment

Five studies were at low risk of bias (Kim 2017; Serenity Pharmaceuticals 2016; Weiss 2012a; Weiss 2013; Yamaguchi 2013). The remaining studies were at unclear risk of bias.

Incomplete outcome data

Number of nocturnal voids

Nine trials were at low risk of bias for number of nocturnal voids (Ahmed 2015a; Koca 2012; Mattiasson 2002; Rezakhaniha 2011; Serenity Pharmaceuticals 2016; Shin 2014a; Wang 2011a; Wang 2012; Weiss 2013). Three studies were at high risk of bias (Ceylan 2013; Kim 2017; Yamaguchi 2013). The remaining studies were at unclear risk of bias.

Quality of life

Four trials were at low risk of bias (Ahmed 2015a; Koca 2012; Wang 2011a; Wang 2012). Three studies were at high risk of bias (Ceylan 2013; Kim 2017; Yamaguchi 2013). The remaining studies were at unclear risk of bias.

Duration of first sleep episode

Five trials were at low risk of bias (Ahmed 2015a; Mattiasson 2002; Rezakhaniha 2011; Wang 2011a; Wang 2012). Three studies were at high risk of bias (Ceylan 2013; Kim 2017; Yamaguchi 2013). The remaining studies were at unclear risk of bias.

Time to first void

Two studies were at low risk of bias (Serenity Pharmaceuticals 2016; Weiss 2013). One study was at high risk of bias (Ceylan 2013). The remaining (11 of 14) studies were at unclear risk of bias.

Major adverse events, minor adverse events, and treatment withdrawal due to adverse event

Most studies (eight of 14) were at low risk of bias (Ahmed 2015a; Koca 2012; Mattiasson 2002; Rezakhaniha 2011; Serenity Pharmaceuticals 2016; Shin 2014a; Wang 2011a; Weiss 2013). Two studies were at high risk of bias (Ceylan 2013; Kim 2017). The remaining studies were at unclear risk of bias.

Selective reporting

We identified published protocols for four included studies and rated the risk of reporting bias for these studies as low (Kim 2017; Weiss 2012a; Weiss 2013; Yamaguchi 2013). Although there was a published protocol for a fifth study, we rated this study as at high risk of reporting bias due to important deficits in outcome reporting (Serenity Pharmaceuticals 2016). One study did not have a published protocol, but we rated it at low risk of bias due to its comprehensive outcome reporting (Shin 2014a). We judged the risk of selective reporting bias as unclear for the remaining studies.

Other potential sources of bias

We rated eight trials as at low risk of bias (Ahmed 2015a; Ceylan 2013; Kim 2017; Koca 2012; Rezakhaniha 2011; Shin 2014a; Wang 2011a; Weiss 2013). We rated one study as at high risk of bias due to the exclusion of participants who did not respond in the active run-in period (Mattiasson 2002). The remaining five trials were at unclear risk of bias: two trials had placebo or active run-in periods (Cannon 1999; Serenity Pharmaceuticals 2016); three trials had a participant population that consisted of almost 50% women (which we were able to selectively exclude from the analysis); we noted that the investigators did not stratify randomisation based on gender, which may have resulted in prognostic imbalances (Serenity Pharmaceuticals 2016; Weiss 2012a; Yamaguchi 2013); and one trial, reported as abstract only, had insufficient information to assess for other biases and was rated as at unclear risk of bias (Wang 2012).

Effects of interventions

See: [Summary of findings for the main comparison](#) Desmopressin versus placebo for men with nocturia (short term); [Summary of findings 2](#) Desmopressin versus placebo for men with nocturia (intermediate term); [Summary of findings 3](#) Desmopressin versus behaviour modifications for men with nocturia (short term); [Summary of findings 4](#) Desmopressin versus alpha-blocker for men with nocturia (short term); [Summary of findings 5](#) Desmopressin plus alpha-blocker versus alpha-blocker for men with nocturia (short term); [Summary of findings 6](#) Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic for men with nocturia (short term)

Desmopressin versus placebo

We included eight studies comparing desmopressin versus placebo with short-term follow-up (Cannon 1999; Mattiasson 2002; Rezakhaniha 2011; Serenity Pharmaceuticals 2016; Wang 2011a; Weiss 2012a; Weiss 2013; Yamaguchi 2013; [Summary of findings for the main comparison](#)), and one study with intermediate-term follow-up in this comparison (Wang 2011a; [Summary of findings 2](#)). There were no studies with long-term follow-up.

Primary outcomes

1. Number of nocturnal voids

We included six studies with 1982 men (intervention 1360, control 622) for short-term follow-up (Mattiasson 2002; Serenity Pharmaceuticals 2016; Wang 2011a; Weiss 2012a; Weiss 2013; Yamaguchi 2013). Desmopressin may result in a small, possibly unimportant effect on the number of nocturnal voids (mean difference (MD) -0.61, 95% confidence interval (CI) -0.96 to -0.27) ([Analysis 1.1](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and inconsistency.

We included one study with 115 men (intervention 57, control 58) for intermediate-term follow-up (Wang 2011a). Desmopressin may reduce the number of nocturnal voids in an appreciable number of men (MD -0.85, 95% CI -1.17 to -0.53) ([Analysis 1.2](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

2. Quality of life

None of the included studies reported quality of life.

3. Major adverse events

We included two studies with 536 men (intervention 329, control 207) for short-term follow-up (Mattiasson 2002; Weiss 2013). We are uncertain about the effect of desmopressin on major adverse events (risk ratio (RR) 0.97, 95% CI 0.10 to 9.03) ([Analysis 1.3](#)). We rated the quality of evidence as very low according to GRADE, downgrading for study limitations, inconsistency, and imprecision.

We included one study with 115 men (intervention 57, control 58) for intermediate-term follow-up (Wang 2011a). Desmopressin may result in little or no difference in major adverse events (RR 3.05, 95% CI 0.13 to 73.39) ([Analysis 1.4](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

Secondary outcomes

1. Duration of first sleep episode

We included four studies with 652 men (intervention 443, control 209) for short-term follow-up (Mattiasson 2002; Wang 2011a; Weiss 2012a; Yamaguchi 2013). Desmopressin may improve the duration of first sleep episode, but we are very uncertain of this finding (MD 54.61 minutes, 95% CI 13.97 to 95.25) ([Analysis 1.5](#)). We rated the quality of evidence as very low according to GRADE, downgrading for study limitations, inconsistency, and imprecision.

We included one study with 115 men (intervention 57, control 58) for intermediate-term follow-up (Wang 2011a). Desmopressin likely results in a small effect, but this may not represent a clinically important improvement in the duration of first sleep episode (MD 18.4 minutes, 95% CI 11.6 to 25.2) ([Analysis 1.6](#)). We rated the

quality of evidence as moderate according to GRADE, downgrading for study limitations.

2. Time to first void

We included one study with 383 men (intervention 241, control 142) for short-term follow-up (Weiss 2013). Desmopressin may result in a small, possibly unimportant effect on time to first void (MD 40.80, 95% CI 17.07 to 64.53) (Analysis 1.7). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

3. Minor adverse events

We included three studies with 594 men (intervention 357, control 237) for short-term follow-up (Mattiasson 2002; Rezakhaniha 2011; Weiss 2013). Desmopressin may result in little or no difference in minor adverse events (RR 0.87, 95% CI 0.67 to 1.13) (Analysis 1.8). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

We included one study with 115 men (intervention 57, control 58) for intermediate-term follow-up (Wang 2011a). Desmopressin may result in little or no difference in minor adverse events (RR 0.86, 95% CI 0.49 to 1.49) (Analysis 1.9). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

4. Treatment withdrawal due to adverse event

We included four studies with 614 men (intervention 367, control 247) for short-term follow-up (Cannon 1999; Mattiasson 2002; Rezakhaniha 2011; Weiss 2013). Desmopressin may result in little or no difference in treatment withdrawal due to adverse events (RR 1.10, 95% CI 0.56 to 2.15) (Analysis 1.10). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

We included one study with 115 men (intervention 57, control 58) for intermediate-term follow-up (Wang 2011a). Desmopressin may result in little or no difference in treatment withdrawal due to adverse events (RR 3.05, 95% CI 0.13 to 73.39) (Analysis 1.11). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

Subgroup analysis

We were able to perform preplanned subgroups for short-term outcomes only.

1. Routes of administration (intranasal, sublingual, or oral)

Number of nocturnal voids

The mean change in the number of nocturnal voids for intranasal was MD -0.20 (95% CI -0.34 to -0.06), for sublingual was MD -0.37 (95% CI -0.71 to -0.03), and for oral was MD -1.14 (95% CI -1.41 to -0.86). The test for interaction was significant ($P < 0.001$, $I^2 = 94.4\%$) (Analysis 1.1).

Major adverse events

The test for interaction was non-significant for major adverse events (sublingual: RR 2.53, 95% CI 0.73 to 8.73; oral: RR 0.25, 95% CI 0.03 to 2.37) ($P = 0.08$, $I^2 = 68.0\%$) (Analysis 1.3).

2. Desmopressin dose (very low, low, or high dose)

Number of nocturnal voids

The mean change in the number of nocturnal voids for the very low dose was MD -0.20 (95% CI -0.34 to -0.06), for low dose was MD -0.33 (95% CI -0.72 to 0.06), and for high dose was MD -1.03 (95% CI -1.41 to -0.66). The test for interaction was significant ($P < 0.001$, $I^2 = 88.1\%$) (Analysis 1.12).

Major adverse events

The test for interaction was non-significant for major adverse events (low dose: RR 2.53, 95% CI 0.73 to 8.73; high dose: RR 0.25, 95% CI 0.03 to 2.37) ($P = 0.08$, $I^2 = 68.0\%$) (Analysis 1.3).

3. Presence of nocturnal polyuria (with or without)

Two studies defined men with nocturia and nocturnal polyuria as inclusion criteria (Cannon 1999; Wang 2011a). The remaining studies included men with nocturia without any description of nocturnal polyuria.

Number of nocturnal voids

When comparing men with nocturnal polyuria versus without nocturnal polyuria, we found an MD of -1.28 (95% CI -1.64 to -0.92) with nocturnal polyuria versus an MD of -0.45 (95% CI -0.73 to -0.17) without nocturnal polyuria. The test for interaction was significant ($P < 0.001$, $I^2 = 92.1\%$) (Analysis 1.13).

Major adverse events

As eligible studies in this analysis did not include men with nocturia and nocturnal polyuria, we were unable to perform a subgroup analysis.

Sensitivity analysis

1. Restricting the analysis by considering risk of bias, excluding studies at 'high risk' or 'unclear risk'

We rated all included studies as at high or unclear risk of bias and were therefore unable to perform a sensitivity analysis.

2. Restricting the analysis by considering risk of bias, excluding studies with run-in periods

Number of nocturnal voids

We included four studies with 966 men (intervention 665, control 301) for short-term follow-up (Wang 2011a; Weiss 2012a; Weiss 2013; Yamaguchi 2013). The MD for this sensitivity analysis was -0.66 (95% CI -1.17 to -0.14) compared to an MD of -0.61 (95% CI -0.96 to -0.27) for the main analysis (Analysis 1.14).

The results of the main and sensitivity analyses were the same for intermediate-term follow-up.

Major adverse events

We included one study with 385 men (intervention 243, control 142) for short-term follow-up (Weiss 2013). Sensitivity analyses (RR 2.53, 95% CI 0.73 to 8.73) did not alter the treatment effect compared to the main analysis (RR 0.97, 95% CI 0.10 to 9.03) (Analysis 1.15).

3. Restricting the analysis by considering clinically recommended dosage of desmopressin, excluding lower dose levels

Number of nocturnal voids

We included six studies with 1586 men (intervention 964, control 622) for short-term follow-up ([Mattiasson 2002](#); [Serenity Pharmaceuticals 2016](#); [Wang 2011a](#); [Weiss 2012a](#); [Weiss 2013](#); [Yamaguchi 2013](#)). The MD for this sensitivity analysis was -0.76 (95% CI -1.15 to -0.38) compared to an MD of -0.61 (95% CI -0.96 to -0.27) for the main analysis ([Analysis 1.16](#)).

The results of the main and sensitivity analyses were the same for intermediate-term follow-up.

Major adverse events

We included two studies with 417 men (intervention 210, control 207) for short-term follow-up ([Mattiasson 2002](#); [Weiss 2013](#)). Sensitivity analyses (RR 0.98, 95% CI 0.10 to 9.71) did not alter the treatment effect substantially compared to the main analysis (RR 0.97, 95% CI 0.10 to 9.03) ([Analysis 1.17](#)).

Desmopressin versus behaviour modification

We found one study with 60 men (intervention 30, control 30) comparing desmopressin versus behaviour modification for short-term follow-up ([Wang 2012](#); [Summary of findings 3](#)).

Primary outcomes

1. Number of nocturnal voids

The study did not report number of nocturnal voids.

2. Quality of life

The study did not report quality of life.

3. Major adverse events

The study did not report major adverse events.

Secondary outcomes

1. Duration of first sleep episode

Desmopressin may result in a small, possibly unimportant effect on duration of first sleep episode (MD 90.00 minutes, 95% CI 1.95 to 178.05) ([Analysis 2.1](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

2. Time to first void

The study did not report time to first void.

3. Minor adverse events

The study did not report minor adverse events.

4. Treatment withdrawal due to adverse event

The study did not report treatment withdrawal due to adverse event.

Subgroup and sensitivity analysis

We were unable to perform any of the planned secondary analyses due to a paucity of included studies or lack of relevant data in the included studies.

Desmopressin versus alpha-blocker

We included one study with 31 men (intervention 15, control 16) comparing desmopressin versus alpha-blocker for all review outcomes in short-term follow-up ([Ceylan 2013](#); [Summary of findings 4](#)). There were no studies with intermediate- or long-term follow-up.

Primary outcomes

1. Number of nocturnal voids

Desmopressin likely results in little or no difference in the number of nocturnal voids (MD 0.30, 95% CI -0.20 to 0.80) ([Analysis 3.1](#)). We rated the quality of evidence as moderate according to GRADE, downgrading for study limitations.

2. Quality of life

Desmopressin likely results in little or no difference in quality of life (MD 0.00, 95% CI -0.35 to 0.35) ([Analysis 3.2](#)). We rated the quality of evidence as moderate according to GRADE, downgrading for study limitations.

3. Major adverse events

No major adverse events were reported in either study group.

Secondary outcomes

1. Duration of first sleep episode

The study did not report duration of first sleep episode.

2. Time to first void

The study did not report time to first void.

3. Minor adverse events

We are uncertain about the effect on minor adverse events (RR 1.07, 95% CI 0.07 to 15.57) ([Analysis 3.4](#)). We rated the quality of evidence as very low according to GRADE, downgrading for study limitations and twice for imprecision.

4. Treatment withdrawal due to adverse event

No treatment withdrawals due to adverse events were reported in either study group.

Subgroup and sensitivity analysis

We were unable to perform any of the planned secondary analyses due to a paucity of included studies or lack of relevant data in the included studies.

Desmopressin plus alpha-blocker versus alpha-blocker

We included three studies comparing desmopressin plus alpha-blocker versus alpha-blocker with short-term follow-up ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#); [Summary of findings 5](#)). There were no studies with intermediate- or long-term follow-up.

Primary outcomes

1. Number of nocturnal voids

We included three studies with 341 men (intervention 176, control 165) ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#)). Desmopressin combined with an alpha-blocker likely results in a small, possibly unimportant effect on the number of nocturnal voids (MD -0.47, 95% CI -0.73 to

-0.21) ([Analysis 4.1](#)). We rated the quality of evidence as moderate according to GRADE, downgrading for study limitations.

2. Quality of life

We included three studies with 341 men (intervention 176, control 165) ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#)). Desmopressin combined with an alpha-blocker likely results in a small, possibly unimportant effect on quality of life (MD -0.29, 95% CI -0.51 to -0.07) ([Analysis 4.3](#)). We rated the quality of evidence as moderate according to GRADE, downgrading for study limitations.

3. Major adverse events

We included three studies with 402 men (intervention 202, control 200) ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#)). Desmopressin combined with an alpha-blocker may result in little to no difference in major adverse events (RR 0.30, 95% CI 0.01 to 7.32) ([Analysis 4.5](#)). There was only one adverse event in the control group in one study ([Kim 2017](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

Secondary outcomes

1. Duration of first sleep episode

No study reported duration of first sleep episode.

2. Time to first void

No study reported time to first void.

3. Minor adverse events

We included three studies with 402 men (intervention 202, control 200) ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#)). We are uncertain about the effect on minor adverse events (RR 1.60, 95% CI 0.15 to 16.82) ([Analysis 4.7](#)). We rated the quality of evidence as very low according to GRADE, downgrading for study limitations and twice for imprecision.

4. Treatment withdrawal due to adverse event

We included three studies with 402 men (intervention 202, control 200) ([Ahmed 2015a](#); [Kim 2017](#); [Koca 2012](#)). Desmopressin combined with an alpha-blocker may result in little to no difference in treatment withdrawal due to adverse events (RR 2.84, 95% CI 0.46 to 17.66) ([Analysis 4.8](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

Subgroup analysis

1. Desmopressin route of administration and dose (intranasal/very low, sublingual/low, or oral/high)

Number of nocturnal voids

The mean change in the number of nocturnal voids for sublingual/low dose was MD -0.66 (95% CI -0.90 to -0.42) and for oral/high dose was MD -0.31 (95% CI -0.60 to -0.02). The test for interaction was non-significant ($P = 0.06$, $I^2 = 70.8\%$) ([Analysis 4.1](#)).

Quality of life

The mean change in quality of life score for sublingual/low dose was MD -0.23 (95% CI -0.49 to 0.03) and for oral/high dose was MD -0.44 (95% CI -0.85 to -0.03). The test for interaction was non-significant ($P = 0.41$, $I^2 = 0.0\%$) ([Analysis 4.3](#)).

Major adverse events

We were unable to estimate the subgroup difference due to no events in the sublingual/low-dose group ([Analysis 4.5](#)).

2. Presence of nocturnal polyuria (with or without)

Number of nocturnal voids

When comparing men with nocturnal polyuria versus without nocturnal polyuria, we found an MD of -0.30 (95% CI -0.74 to 0.14) with nocturnal polyuria versus an MD of -0.52 (95% CI -0.86 to -0.18) without nocturnal polyuria. The test for interaction was non-significant ($P = 0.44$, $I^2 = 0.0\%$) ([Analysis 4.2](#)).

Quality of life

We found an MD of -0.20 (95% CI -0.84 to 0.44) for men with nocturnal polyuria versus an MD of -0.34 (95% CI -0.67 to -0.01) for men without nocturnal polyuria. The test for interaction was non-significant ($P = 0.71$, $I^2 = 0.0\%$) ([Analysis 4.4](#)).

Major adverse events

We were unable to estimate the subgroup difference due to no events in men with nocturia ([Analysis 4.6](#)).

Sensitivity analysis

The results of the main and sensitivity analyses were the same.

Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic

We included one study with short-term follow-up in this comparison ([Shin 2014a](#); [Summary of findings 6](#)). There were no studies with intermediate- or long-term follow-up.

Primary outcomes

1. Number of nocturnal voids

We included 405 men (intervention 196, control 209). Desmopressin combined with alpha-blocker likely results in little or no difference in the number of nocturnal voids (MD -0.43, 95% CI -0.97 to 0.11) ([Analysis 5.1](#)). We rated the quality of evidence as moderate according to GRADE, downgrading for study limitations.

2. Quality of life

The study did not report quality of life.

3. Major adverse events

We included 427 men (intervention 205, control 222). No major adverse events were reported in either study group.

Secondary outcomes

1. Duration of first sleep episode

The study did not report duration of first sleep episode.

2. Time to first void

The study did not report time to first void.

3. Minor adverse events

We included 427 men (intervention 205, control 222). Desmopressin combined with alpha-blocker may result in a small, possibly unimportant effect on minor adverse events (RR 0.22, 95% CI

0.05 to 0.98) ([Analysis 5.3](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

4. Treatment withdrawal due to adverse event

We included 427 men (intervention 205, control 222). Desmopressin combined with alpha-blocker may result in a small, possibly unimportant effect on treatment withdrawal due to adverse events (RR 0.22, 95% CI 0.05 to 0.98) ([Analysis 5.4](#)). We rated the quality of evidence as low according to GRADE, downgrading for study limitations and imprecision.

Subgroup and sensitivity analysis

We were unable to perform any of the planned secondary analyses due to a paucity of included studies or lack of relevant data in the included studies.

Desmopressin versus surgery

We found no trials comparing desmopressin versus surgery.

DISCUSSION

Summary of main results

We included 14 unique studies with 2966 male participants with nocturia across five comparisons. We included all comparisons with short-term follow-up and one comparison (desmopressin versus placebo) with intermediate-term follow-up. The mean age of the male participants ranged from 57 to 74 years.

Desmopressin versus placebo

Based on short-term follow-up, desmopressin may reduce the number of nocturnal voids, but this may not represent a clinically important reduction to patients. We are uncertain about the effect of desmopressin on major adverse events.

For intermediate-term follow-up, desmopressin may reduce number of nocturnal voids in comparison to placebo in an appreciable number of men. Desmopressin may result in little or no difference in major adverse events.

None of the studies reported quality of life.

Subgroup analyses suggest a larger effect with oral, higher-dose formulations of desmopressin and in men with documented nocturnal polyuria. Sensitivity analyses based on risk of bias, run-in periods, and clinical dosage of desmopressin did not alter the treatment effect substantially.

Desmopressin versus behaviour modification

We found no evidence on primary outcomes for the comparison of desmopressin versus behaviour modification.

Desmopressin versus alpha-blocker

Based on short-term follow-up, desmopressin likely has a similar effect to alpha-blocker on the number of nocturnal voids and quality of life. No major adverse events were reported in either study group.

Desmopressin plus alpha-blocker versus alpha-blocker

Based on short-term follow-up, combination therapy likely results in a small, possibly unimportant effect compared with desmopressin alone on the number of nocturnal voids and quality of life. Combination therapy was not associated with a meaningful impact on major adverse events.

Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic

Based on short-term follow-up, desmopressin plus alpha-blocker likely results in little or no difference compared with an alpha-blocker plus anticholinergic in the number of nocturnal voids. We found no evidence on quality of life. No major adverse events were reported in either study group.

Desmopressin versus surgery

We found no studies comparing desmopressin to surgical interventions.

Overall completeness and applicability of evidence

- The focus of this systematic review was male participants with nocturia irrespective of aetiology but excluding men with known metabolic disorders potentially associated with a secondary nocturnal diuresis, such as Cushing disease. We included men with and without nocturnal polyuria, since desmopressin has been used in both patient populations.
- This review included three different formulations of desmopressin with different bioavailability. While we labelled the dosage as high, low, and very low in this review, actual bioavailability may be different.
- The existing body of evidence was largely limited to short-term outcomes, with 13 of 14 studies reporting outcomes of three months' duration or less. Given the usually chronic nature of men's nocturia complaints, such short-term outcomes appear to be insufficient to provide assurance of long-term effectiveness and safety.
- Desmopressin is known to lower serum sodium levels. We made a conscious decision not to include serum sodium levels as an outcome of this review given that their levels per se are not patient important. Instead, we focused on both major and minor adverse events, expecting that clinically important serum sodium level reductions would have been reflected in the event rates for these outcomes. The findings of this review did not suggest increased rates for either outcomes, although the quality of evidence was only low or very low. However, participants in clinical trials are commonly monitored more closely than in routine clinical practice, thereby potentially reducing the risk of adverse events and limiting the applicability of our findings. In addition, as previously mentioned, the time-horizon of most included studies was short, thereby negating the opportunity for us to document any long-term effects of desmopressin on serum sodium levels. Large observational studies may therefore provide additional insight into the 'real-life' safety profile of this drug when used longer term.
- We identified trials that appeared to be eligible for inclusion but did not provide data in such a way as to allow analyses, for example results reporting by gender group. Our efforts to obtain additional information from the manufacturers and trial sponsors were largely unsuccessful. This raises concerns about

selective reporting and potential publication bias, although we found insufficient indication to downgrade the quality of evidence for publication bias.

- Given that one-third of trials had active run-in periods, study findings may have been biased in favour of the intervention, since people with adverse events or limited compliance may have been excluded up-front.
- We performed subgroup analyses based on the presence or absence of nocturnal polyuria. Four trials included men with documented nocturnal polyuria, defined as more than 30% or one-third of a person's 24-hour urine output excreted during their sleeping time. However, the other trials did not describe whether the men had nocturnal polyuria or not. Given that this analysis did not exactly match our intended analysis, we are less confident in its findings. These analyses may also have been underpowered to detect a difference.
- There were small differences in the pooled effect estimates among subgroups, which may represent true differences or spurious findings due to prognostic imbalances in the absence of stratified randomisation.

Quality of the evidence

We rated the quality of evidence as low or moderate for most outcomes and comparisons. Our confidence in the estimates of effect were lowered for the following reasons.

- Study limitation: issues surrounding allocation concealment and blinding.
- Inconsistency: high I^2 values, which we were unable to explain through secondary analyses.
- Imprecision: few events resulting in wide CIs.

Potential biases in the review process

- In order to reduce the potential for publication bias, we followed a published protocol (Han 2016), and performed a comprehensive and updated literature search without publication or language restriction. In addition, we searched trial registries for unpublished, planned, or ongoing studies. We found a few abstract proceedings of the annual meetings of the American Urological Association, European Association of Urology, International Continence Society, and the British Association of Urological Surgeons from 2012 to 2017 and one ongoing trial. Should any results of such studies become available, we will include them in updates of this review.
- We contacted study authors on several occasions, who provided feedback to some of our queries. However, we received additional information from only two out of six study authors. This may represent a source of bias with potential under-reporting of the true treatment burden.
- We included only randomised controlled trials in this review, which were all relatively small and had a short time-horizon. To understand infrequent and long-term adverse events better, additional non-randomised studies are likely necessary but were outside the scope of this review.

Agreements and disagreements with other studies or reviews

A systematic review assessing the efficacy and safety of desmopressin for nocturia in adults was published in 2014 (Ebell

2014). The review included 10 studies with 2191 participants, of which several studies included a significant portion of women. We excluded studies with only women from our review, as we focused on the use of desmopressin to treat nocturia in men. One study comparing desmopressin in addition to alpha-blocker therapy versus alpha-blocker therapy alone was published after the systematic review by Ebell and colleagues (Ahmed 2015a). Similar to our review, Ebell 2014 found a small improvement in nocturia mainly based on a small decrease in the number of nocturnal voids and increase in duration of first sleep episode (Ebell 2014). The authors viewed desmopressin as generally safe with an overall favourable adverse effect profile and very rare major adverse events. In congruence with our review, their results were limited to the short term, and they acknowledged the need for additional, well-designed studies of longer duration. These reviews did not use GRADE or assess the quality of evidence on a per-outcome basis.

Another review discussing the medical treatment of nocturia in men with LUTS found that desmopressin was more effective than placebo in decreasing nocturnal voiding frequency and increasing duration of undisturbed sleep (Sakalis 2017). However, of the included studies, three trials had mixed populations of men and women. Given the review's clearly defined focus on men and the unique pathophysiology of men, we believe these studies introduced meaningful heterogeneity and should have been excluded. Furthermore, another included study compared furosemide (a diuretic) with desmopressin to placebo, and the contribution of each drug could not be isolated. This review provided no quality of evidence ratings and did not use an explicit CID (Jung 2017). They found an MD of -0.87 (95% CI -1.15 to -0.60) comparing desmopressin to placebo; the proposed CID is a reduction of at least one episode per night (Krader 2012).

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this Cochrane Review showed that desmopressin was associated with similar or small, unimportant effects on the number of nocturnal voids, quality of life, and major adverse events across the included comparisons.

Implications for research

Given the low-quality evidence for most of the reported analyses, there is a need for additional research with regard to drug effectiveness and safety.

- Future trials should be conducted according to higher methodological standards with regard to allocation concealment and blinding in order to minimise concerns about selection, performance, and detection bias.
- Trials should focus on long-term, patient-important outcomes and include quality of life as an outcome.
- Study data, especially for adverse events, need to be fully available to the research community.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ahmed 2015a

Methods	<p>Design: RCT, parallel, single-blind.</p> <p>Randomisation ratio: 1:1.</p> <p>Setting: outpatient/Egypt.</p> <p>Dates when study was conducted: November 2011 to February 2014.</p>
Participants	<p>Inclusion criteria: men with LUTS/BPH, ages ≥ 50 years (nocturia ≥ 2 voids/night), nocturnal polyuria (nocturnal urine volume $> 30\%$ of 24-hour urine volume) on voiding diary.</p> <p>Exclusion criteria: men on, or previously treated (within 3 months prior to enrolment) with, desmopressin or BPH medical therapy; uncontrolled diabetes mellitus or hypertension; previous surgery for bladder neck obstruction or BPH; renal, cardiovascular, and neurologic diseases; diuretic use; voiding dysfunctions; BPH; IPSS ≤ 8, $Q_{\max} < 5$ mL/s; abnormal digital rectal examination; elevated PSA (≥ 10 ng/dL); urinary tract infection; hyponatraemia (serum sodium < 135 mEq/L); lower urinary tract lithiasis, urothelial malignancy, and significant high PVR (≥ 250 mL).</p> <p>Total number of participants randomly assigned: 248.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> number of participants randomly assigned: 123 age (years; mean $\pm$ SD): 70.14 ± 9.27 prostate volume (mL; mean $\pm$ SD): 45.71 ± 15.34

Ahmed 2015a (Continued)

- PSA (ng/mL; mean $\pm$ SD): 2.39 ± 0.82
- IPSS (mean $\pm$ SD): 16.78 ± 2.26
- $Q_{\max}$ (mL/s; mean $\pm$ SD): 10.28 ± 1.10
- PVR (mL; mean $\pm$ SD): 36.10 ± 27.7

Control group:

- number of participants randomly assigned: 125
- age (years; mean $\pm$ SD): 68.58 ± 10.51
- prostate volume (mL; mean $\pm$ SD): 47.01 ± 15.45
- PSA (ng/mL; mean $\pm$ SD): 2.51 ± 0.84
- IPSS (mean $\pm$ SD): 17.01 ± 1.99
- $Q_{\max}$ (mL/s; mean $\pm$ SD): 9.99 ± 1.5
- PVR (mL; mean $\pm$ SD): 34.46 ± 31.84

Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin (Melt: 60 μg) with tamsulosin (oral controlled absorption system: 0.4 mg) daily.</p> <p>Control: tamsulosin (oral controlled absorption system: 0.4 mg) tablet daily.</p> <p>Duration: 3 months.</p>
Outcomes	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • number of nocturnal voids <p>Secondary endpoints:</p> <ul style="list-style-type: none"> • first sleep period • IPSS and QoL scores • % of nocturnal urine volume • $Q_{\max}$ • adverse effects (reported side effect, blood pressure, body weight, and serum electrolytes)
Funding sources	Not reported.
Declarations of interest	No conflict of interest.
Notes	Language of article: English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized into two groups using computer randomization program (http://random-allocation-software.software.informer.com/2.0/). Randomization in blocks of two was used, and each center had its own list to keep the groups closely balanced."
Allocation concealment (selection bias)	Unclear risk	Comment: not described/unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Group I, received daily oral dose of tamsulosin OCAS 0.4-mg tablet and desmopressin (MELT) 60 mcg, and Group II, received only tamsulosin (OCAS) 0.4-mg tablet daily." "prospective, randomized, single-blind, comparative study."

Desmopressin for treating nocturia in men (Review)

Ahmed 2015a (Continued)

		Comment: "single blinding" undertaken.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "prospective, randomized, single-blind, comparative study." Comment: "single blinding" undertaken, but it was unclear who was blinded and how this was achieved.
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Comment: 16/139 (11.5%) participants in desmopressin group and 9/134 (6.7%) participants in tamsulosin group not included in analysis.
Incomplete outcome data (attrition bias) QoL	Low risk	Comment: 16/139 (11.5%) participants in desmopressin group and 9/134 (6.7%) participants in tamsulosin group not included in analysis.
Incomplete outcome data (attrition bias) Duration of first sleep episode	Low risk	Comment: 16/139 (11.5%) participants in desmopressin group and 9/134 (6.7%) participants in tamsulosin group not included in analysis.
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	Comment: 16/139 (11.5%) participants in desmopressin group and 9/134 (6.7%) participants in tamsulosin group not included in analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: "time to first void" not described, and protocol not published.
Other bias	Low risk	Comment: not detected

Cannon 1999

Methods	Design: RCT, cross-over. Setting: Bristol, UK. Dates when study was conducted: not reported.
Participants	Inclusion criteria: men aged > 50 years with nocturnal polyuria (using 48 h of inpatient monitoring or 1-week frequency volume chart). Exclusion criteria: men with nocturnal enuresis or incontinence; significant cardiovascular, renal, or hepatic disease; diabetes; urinary tract infection; or concomitant medication active on the lower urinary tract. Total number of participants randomly assigned: cross-over study. <ul style="list-style-type: none"> number of participants: 20 (20 participants initially entered into the study, 18 participants complete study at the end of cross-over) age (years): not reported prostate volume (mL): not reported

Cannon 1999 (Continued)

- PSA (ng/mL): not reported
- IPSS: not reported
- $Q_{\max}$ (mL/s): not reported
- PVR (mL): not reported

Interventions	<p>Run-in period: 1-week placebo run-in.</p> <p>Extension period: desmopressin 40 µg for all participants for final 2 weeks after 4 weeks' cross-over.</p> <p>Experimental: desmopressin (nasal spray: 20 µg) before going to bed each evening.</p> <p>Control: placebo (nasal spray) before going to bed each evening.</p> <p>Duration: 4 weeks (8 weeks (cross-over study design)).</p>
Outcomes	<ul style="list-style-type: none"> • Nocturnal frequency • Nocturnal volume • % of urine passed at night (nocturnal volume/24-hour urine) • Adverse events
Funding sources	Not reported.
Declarations of interest	Acknowledgements: support of Ferring Pharmaceuticals Ltd.
Notes	<p>Review authors used data before cross-over due to unit of analysis error.</p> <p>Language of article: English.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo-controlled study, double-blind but not clear who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo-controlled study, double-blind but not clear who was blinded.
Incomplete outcome data (attrition bias) Number of nocturnal voids	Unclear risk	Comment: 2/20 (10.0%) participants excluded from analysis, and insufficient data were given for analysis due to cross-over design.
Incomplete outcome data (attrition bias) QoL	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias)	Unclear risk	Comment: not described

Cannon 1999 (Continued)

Duration of first sleep episode

Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Unclear risk	Comment: 2/20 (10.0%) participants excluded from analysis, and insufficient data were given for analysis due to cross-over design.
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes insufficiently described, and protocol not published.
Other bias	Unclear risk	Comment: active run-in period

Ceylan 2013

Methods	<p>Design: RCT, parallel, preliminary (pilot) study.</p> <p>Randomisation ratio: 1:1.</p> <p>Setting: outpatient/Ankara, Turkey.</p> <p>Dates when study was conducted: January 2011 to June 2011.</p>
Participants	<p>Inclusion criteria: men with advanced age, BPH with complaints of LUTS and nocturia ≥ 3 times/night.</p> <p>Exclusion criteria: men with pathologically diagnosed prostate cancer; positive urine culture; prior surgery of the bladder, prostate, urethra; and additional urological pathology.</p> <p>Total number of participants randomly assigned: 31.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 15 • age (years; mean $\pm$ SD): 57.7 ± 9.8 • prostate volume (mL): not reported • PSA (ng/mL; mean $\pm$ SD): 2.6 ± 3.9 • IPSS (mean $\pm$ SD): 12.1 ± 4.9 • $Q_{\max}$ (mL/s; mean $\pm$ SD): 17.6 ± 7.7 • PVR (mL; mean $\pm$ SD): 36.6 ± 32.4 <p>Control group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 16 • age (years; mean $\pm$ SD): 58.1 ± 7.8 • prostate volume (mL): not reported • PSA (ng/mL; mean $\pm$ SD): 1.8 ± 1.4 • IPSS (mean $\pm$ SD): 14.6 ± 4.3 • $Q_{\max}$ (mL/s; mean $\pm$ SD): 13.3 ± 5.5 • PVR (mL; mean $\pm$ SD): 44.3 ± 35.9
Interventions	Run-in period: no

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Ceylan 2013 (Continued)

Experimental: desmopressin 20 µg intranasal before bedtime.

Control: doxazosin orally 2 mg orally for 2 weeks followed by 4 mg for 6 weeks before bedtime.

Duration: 2 months.

Outcomes	<ul style="list-style-type: none"> • Number of nocturia • IPSS and QoL score • Q_{max} • Residual urine • Adverse events
Funding sources	Not reported.
Declarations of interest	No conflict of interest.
Notes	Language of article: English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Number of nocturnal voids	High risk	Comment: appearance of large proportion of participants (51/80) excluded postrandomisation
Incomplete outcome data (attrition bias) QoL	High risk	Comment: appearance of large proportion of participants (51/80) excluded postrandomisation
Incomplete outcome data (attrition bias) Duration of first sleep episode	High risk	Comment: appearance of large proportion of participants (51/80) excluded postrandomisation
Incomplete outcome data (attrition bias) Time to first void	High risk	Comment: appearance of large proportion of participants (51/80) excluded postrandomisation
Incomplete outcome data (attrition bias)	High risk	Comment: appearance of large proportion of participants (51/80) excluded postrandomisation

Ceylan 2013 (Continued)

Major adverse events/minor adverse events/treatment withdrawal due to adverse event

Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes insufficiently described, and protocol not published.
Other bias	Low risk	Comment: not detected

Kim 2017

Methods	<p>Design: randomised, double-blind, placebo-controlled study.</p> <p>Randomization ratio: 1:1.</p> <p>Setting: multicentre (8)/South Korea.</p> <p>Dates when study was conducted: not reported.</p>
Participants	<p>Inclusion criteria: men aged 40 to 65 years with LUTS, IPSS ≥ 13, persistent nocturia (≥ 2 episodes/night), nocturia index score ≥ 1 despite use of alpha-blocker treatment for ≥ 8 weeks, and nocturnal polyuria defined as nocturnal polyuria index $> 33\%$.</p> <p>Exclusion criteria: men with total daily urine volume of ≥ 3000 mL, diabetes insipidus, history of prostate surgery in the past 6 months, cardiac failure, serum sodium < 135 mmol/L, clinically significant abnormalities of serum potassium or creatinine, current treatment for insomnia, desmopressin treatment in previous month, uncontrolled hypertension, urgency urinary incontinence, significant anatomical abnormalities in the urinary tract, use of other drugs that could influence desmopressin (diuretics, tricyclic antidepressants, indomethacin, carbamazepine, chlorpropamide, or a combination), or use of anticholinergics or 5-alpha reductase inhibitor in the past 3 months excluded from analysis.</p> <p>Total number of participants randomly assigned: 109.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 57 • age (years; mean $\pm$ SD): 59.2 ± 5.1 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS (mean $\pm$ SD): 24.9 ± 8.2 • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported <p>Control group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 52 • age (years; mean $\pm$ SD): 60.3 ± 4.5 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS (mean $\pm$ SD): 23.2 ± 6.4 • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported
Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin 0.2 mg oral + alpha-blocker at bedtime.</p>

Desmopressin for treating nocturia in men (Review)

Kim 2017 (Continued)

Control: placebo + alpha-blocker at bedtime.

Duration: 8 weeks.

Alpha-blocker: type and dose were not reported.

Outcomes	<p>Primary endpoint:</p> <ul style="list-style-type: none">• number of nocturia <p>Secondary endpoints:</p> <ul style="list-style-type: none">• proportion of participants with ≥ 50% decrease in number of nocturia episodes• changes in nocturnal urine volume• nocturnal polyuria index• IPSS• nocturnal hesitancy score• QoL: International Consultation on Incontinence Questionnaire Nocturia and IPSS-QoL <p>Safety assessment:</p> <ul style="list-style-type: none">• adverse events• vital signs• laboratory data	
Funding sources	None.	
Declarations of interest	Not reported.	
Notes	Short-term primary and secondary outcome, information related to risk of bias obtained from author. Protocol: KCT0000271. Language of article: English.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author reply: computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	Author reply: sequentially numbered, opaque, sealed envelopes used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Enrolled patients received oral desmopressin 0.2 mg or matching placebo at bedtime for 8 weeks." Comment: participants and investigator blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: placebo-controlled study, participants and investigator blinded.
Incomplete outcome data (attrition bias) Number of nocturnal voids	High risk	Comment: 10/57 (17.6%) participants in intervention group and 13/52 (25.0%) participants in control group not included in analysis.

Kim 2017 (Continued)

Incomplete outcome data (attrition bias) QoL	High risk	Comment: 10/57 (17.6%) participants in intervention group and 13/52 (25.0%) participants in control group not included in analysis. Information on QoL obtained from author.
Incomplete outcome data (attrition bias) Duration of first sleep episode	High risk	Comment: 10/57 (17.6%) participants in intervention group and 13/52 (25.0%) participants in control group not included in analysis. Information on QoL obtained from author.
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	High risk	Comment: 10/57 (17.6%) participants in intervention group and 13/52 (25.0%) participants in control group not included in analysis.
Selective reporting (reporting bias)	Low risk	Comment: protocol (KCT0000271) published, and data obtained through contact with author.
Other bias	Low risk	Comment: not detected

Koca 2012

Methods	<p>Design: RCT, parallel.</p> <p>Randomisation ratio: 1:1.</p> <p>Setting: outpatient/Istanbul, Turkey.</p> <p>Dates when study was conducted: not reported.</p>
Participants	<p>Inclusion criteria: men with LUTS and nocturia (≥ 2/night) aged between 50 and 70 years.</p> <p>Exclusion criteria: history of congestive heart failure, neurological diseases, and diabetes mellitus who are taking diuretics; BPH because of medical treatments; prostate cancer; and urethral strictures.</p> <p>Total number of participants randomly assigned: 49 (data from only 45 participants who completed the study were shown).</p> <p>Experimental group:</p> <ul style="list-style-type: none"> number of participants who completed the study: 22 age (years; mean $\pm$ SD): 58.9 ± 7.9 prostate volume (mL): not reported PSA (ng/mL): not reported IPSS (mean $\pm$ SD): 17.5 ± 3.9 $Q_{\max}$ (mL/s; mean $\pm$ SD): 10.8 ± 4.1 PVR (mL; mean $\pm$ SD): 61.8 ± 31.4 <p>Control group:</p> <ul style="list-style-type: none"> number of participants who completed the study: 23 age (years; mean $\pm$ SD): 61.7 ± 9.1

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Koca 2012 (Continued)

- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS (mean $\pm$ SD): 17.8 ± 3.6
- $Q_{\max}$ (mL/s; mean $\pm$ SD): 10.6 ± 3.4
- PVR (mL; mean $\pm$ SD): 54.1 ± 28.2

Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin (Minirin) 0.2 mg with alfuzosin 10 mg tablets.</p> <p>Control: alfuzosin 10 mg tablets.</p> <p>Duration: 3 months.</p>
Outcomes	<ul style="list-style-type: none"> • IPSS and QoL score • $Q_{\max}$ • Residual urine • Adverse events
Funding sources	Not reported.
Declarations of interest	No conflict of interest.
Notes	Language of article: Turkish.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Comment: 4/49 (8.1%) participants not included in analysis.
Incomplete outcome data (attrition bias) QoL	Low risk	Comment: 4/49 (8.1%) participants not included in analysis.
Incomplete outcome data (attrition bias) Duration of first sleep episode	Unclear risk	Comment: not described

Koca 2012 (Continued)

Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	Comment: 4/49 (8.1%) participants not included in analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes insufficiently described, and protocol not published.
Other bias	Low risk	Comment: not detected

Mattiasson 2002

Methods	<p>Design: RCT, double-blind, placebo-controlled, parallel-group, phase III study.</p> <p>Randomisation ratio: 1:1.</p> <p>Setting: multicentre/UK, Sweden, the Netherlands, and the USA.</p> <p>Dates when study was conducted: not reported.</p>
Participants	<p>Inclusion criteria: men aged 18 years with nocturia (mean of ≥ 2 voids/night) and nocturnal urine production greater than their maximum functional bladder capacity (nocturia index scores of > 1).</p> <p>Exclusion criteria: men with nocturia arising from other well-defined causes of increased urinary frequency, e.g. diagnosed or suspected diabetes insipidus, primary polydipsia (40 mL/kg/24 h) or multiple sclerosis, urge incontinence or recently commenced medical or surgical treatment for benign prostatic obstruction; conditions characterised by fluid or electrolyte imbalance (or both) where antidiuresis was inappropriate (e.g. cardiac failure, use of diuretics); serum sodium levels below normal range, and uncontrolled hypertension.</p> <p>Total number of participants randomly assigned: 151.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 86 • age (years; mean $\pm$ SD): 64.5 ± 10.7 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported <p>Control group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 65 • age (years; mean $\pm$ SD): 65.6 ± 10.2 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported

Mattiasson 2002 (Continued)

- PVR (mL): not reported

Interventions	<p>Run-in period: desmopressin dose titration (1 to 3 weeks, followed by a 1-week 'washout').</p> <p>Experimental: desmopressin oral: from 0.1 mg to 0.4 mg after dose titration 1 h before bedtime.</p> <p>Control: placebo 1 h before bedtime.</p> <p>Duration: 3-week double-blind treatment period.</p>
Outcomes	<p>Primary efficacy endpoint:</p> <ul style="list-style-type: none"> • proportion of participants who had reduction by more than half in the mean number of nocturnal voids after treatment compared with baseline <p>Secondary efficacy endpoints:</p> <ul style="list-style-type: none"> • number of nightly voids • duration of sleep period until first void • nocturnal diuresis • nighttime/24-hour and nighttime/day urine volume • effect on QoL • safety of desmopressin treatment (adverse events and serum sodium levels)
Funding sources	Not reported.
Declarations of interest	No conflict of interest.
Notes	<p>Only participants who obtained $\geq 20\%$ reduction in nocturnal diuresis during dose titration period were randomised to either placebo or active treatment. Participants who experienced $< 20\%$ decrease in nocturnal diuresis at all doses during dose titration were classified as not responding and did not continue in study. If treatment-related adverse events were experienced during dose titration, participants were allocated to maximum tolerated dose that showed the best pharmacodynamic response.</p> <p>Language of article: English.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "randomized, double-blind, placebo-controlled, parallel-group, multi-national, phase III study evaluated."</p> <p>Comment: not described</p>
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo-controlled study, double-blind but not clear who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo-controlled study, double-blind but not clear who was blinded.
Incomplete outcome data (attrition bias)	Low risk	Comment: 5/85 (5.8%) participants in desmopressin group and 3/65 (4.6%) participants in placebo group not included in analysis.

Mattiasson 2002 (Continued)

Number of nocturnal voids

Incomplete outcome data (attrition bias) QoL	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Duration of first sleep episode	Low risk	Comment: 5/85 (5.8%) participants in desmopressin group and 3/65 (4.6%) participants in placebo group not included in analysis.
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	Comment: 5/85 (5.8%) participants in desmopressin group and 3/65 (4.6%) participants in placebo group not included in analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes insufficiently described, and protocol not published.
Other bias	High risk	Comment: active run-in period with exclusion of participants who did not respond

Rezakhaniha 2011

Methods	<p>Design: RCT, parallel, double-blind, placebo controlled.</p> <p>Randomisation ratio: 1:1.</p> <p>Setting: outpatient/single centre/Tehran, Iran.</p> <p>Dates when study was conducted: 2008 to 2009.</p>
Participants	<p>Inclusion criteria: men with voiding ≥ 2/night.</p> <p>Exclusion criteria: uncontrolled disease such as diabetes and cardiac disease, use of diuretics, hypertension, diabetes insipidus, diseases that influence medulla of kidney such as medullary cystic of kidney diseases, multiple sclerosis, urge incontinence and recent surgical treatment for BPH, known functional disease in urinary system, e.g. neurogenic bladder.</p> <p>Total number of participants randomly assigned: 60.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 30 • age (years; mean $\pm$ SD): 63.33 $\pm$ 13.21 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported

Rezakhaniha 2011 (Continued)

Control group:

- number of participants randomly assigned: 30
- age (years; mean $\pm$ SD): 64.26 $\pm$ 10.46
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Q_{max} (mL/s): not reported
- PVR (mL): not reported

Interventions	Run-in period: no. Experimental: desmopressin 0.1 mg 1 h before bedtime. Control: placebo 1 h before bedtime. Duration: 8 weeks.
Outcomes	<ul style="list-style-type: none"> • Number of voids (categorical: < 2, 2, and > 2 episodes) • Mean number of nocturia • Mean duration of first sleep period • Sleep quality (QoL questionnaire administered by urological societies/categorical: improved and non-improved) • Safety (adverse events)
Funding sources	Acknowledgement: thanks to Ferring drug company.
Declarations of interest	No conflict of interest.
Notes	Language of article: English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided into 2 study groups." Comment: method not described.
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind placebo-controlled study." Comment: placebo-controlled study, described as double-blind but unclear who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo-controlled study, described as double-blind but unclear who was blinded.
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Comment: all 60 participants included in final analysis.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: not described

Desmopressin for treating nocturia in men (Review)

Rezakhaniha 2011 (Continued)

QoL

Incomplete outcome data (attrition bias) Duration of first sleep episode	Low risk	Comment: all 60 participants included in final analysis.
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	Comment: all 60 participants included in final analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes insufficiently described, and protocol not published.
Other bias	Low risk	Comment: not detected

Serenity Pharmaceuticals 2016

Methods	<p>Design: incorporated report of 4 randomised, double-blind, placebo-controlled, parallel-arm, phase III trials.</p> <p>Randomisation ratio: 1:1:1:1 (placebo, 0.75 µg, 1.0 µg, or 1.5 µg desmopressin).</p> <p>Setting: multicentre/USA and Canada.</p> <p>Dates when study was conducted: not reported.</p>
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> men or women age ≥ 50 years documented nocturia by history (≥ 2 nocturic episodes/night for at least 6 months) documented nocturia by diary administered for 3 days during each week of the 2-week screening period: <ul style="list-style-type: none"> * mean ≥ 2.16 nocturic episodes/night or * ≥ 13 total nocturic episodes 24-hour urine output ≤ 57 mL/kg or up to 4500 mL/24 h normal serum sodium concentration serum triglycerides < 400 mg/dL <p>Exclusion criteria: nocturnal enuresis, diabetes insipidus, unstable diabetes mellitus, congestive heart failure (New York Heart Association Class II-IV), polydipsia or thirst disorders, uncontrolled hypertension, unstable angina, urinary retention (PVR > 150 mL) by medical history, hepatic or renal impairment, syndrome of inappropriate secretion of antidiuretic hormone, nephrotic syndrome, > 2+ pretibial oedema on physical exam, urinary bladder surgery or radiation therapy within the last 24 months prior to enrolment, severe daytime LUTS secondary to BPH, overactive bladder or severe stress urinary incontinence, daytime urinary frequency > 8 episodes/day by medical history or by 24-hour urine frequency/volume chart during screening, women with unexplained pelvic masses or > stage II pelvic prolapse, current or past malignancy (except cured basal cell carcinoma or squamous cell carcinoma of the skin) unless in remission for ≥ 5 years and with approval of the medical monitor, urinary bladder dysfunction of neurologic aetiology that in the judgement of the investigator would interfere with</p>

Serenity Pharmaceuticals 2016 (Continued)

study assessments, neurogenic detrusor overactivity, obstructive sleep apnoea, hyperkinetic limb disorders, work or lifestyle activities that interfere with nighttime sleep, alcohol or substance abuse within 12 months of enrolment.

Total number of participants randomly assigned: 1556 (latest 2 phase III trials).

Experimental group:

- number of all participants randomly assigned: 458/188/452 (desmopressin 0.75 µg/1.0 µg/1.5 µg)
- age (years): 66/66/66
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Q_{max} (mL/s): not reported
- PVR (mL): not reported

Control group:

- number of all participants randomly assigned: 458
- age (years): 66
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Q_{max} (mL/s): not reported
- PVR (mL): not reported

Interventions	<p>Run-in period: double-blind, 2-week, placebo lead-in period.</p> <p>Experimental: desmopressin 0.75 µg, 1.0 µg, or 1.5 µg in nasal spray at nighttime.</p> <p>Control: placebo at nighttime.</p> <p>Duration: 12 weeks.</p>
Outcomes	<p>Coprimary efficacy endpoints:</p> <ul style="list-style-type: none"> • change from baseline in the mean number of nocturic episodes per night • % participants with ≥ 50% reduction in mean number of nocturic voids per night <p>Secondary efficacy endpoints:</p> <ul style="list-style-type: none"> • time from when participant went to bed with the intention of falling asleep to first nocturic void (or first morning void in the absence of a nocturic void) • % nights without nocturic episodes • % nights with ≤ 1 nocturic episode • nocturnal urine volume <p>Safety:</p> <ul style="list-style-type: none"> • adverse events
Funding sources	Serenity Pharmaceuticals.
Declarations of interest	Serenity Pharmaceuticals.
Notes	<p>FDA briefing document based on 4 phase III studies (efficacy analysis: latest 2 trials, safety analysis: all 4 phase III trials).</p> <p>Protocol: NCT00937859, NCT00937378, NCT01357356, NCT01900704.</p>

Serenity Pharmaceuticals 2016 (Continued)

Language of article: English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind placebo-controlled study." Comment: participants and investigator were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind placebo-controlled study." Comment: placebo-controlled study, participants and investigator were blinded.
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Comment: 1080/1098 (98.3%) participants in desmopressin group and 446/458 (97.3%) participants in placebo group were included in analysis.
Incomplete outcome data (attrition bias) QoL	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Duration of first sleep episode	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Time to first void	Low risk	Comment: 1080/1098 (98.3%) participants in desmopressin group and 446/458 (97.3%) participants in placebo group were included in analysis.
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	High risk	Comment: published protocols included a part of reported outcomes in FDA document.
Other bias	Unclear risk	Quote: "double blind placebo lead-in." Comment: no stratification based on gender

Shin 2014a
Methods **Design:** RCT, cross-over.

Desmopressin for treating nocturia in men (Review)

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Shin 2014a (Continued)

Randomisation ratio: 1:1.

Setting: South Korea.

Dates when study was conducted: July 2010 to April 2013.

Participants	<p>Inclusion criteria: men age ≥ 50 years diagnosed with LUTS due to bladder outlet obstruction, with a maximum urinary flow rate ≤ 15 mL/s, nocturia (≥ 1 void/night), and total IPSS ≥ 14 (voiding subscore ≥ 8 and storage subscore ≥ 6).</p> <p>Exclusion criteria: neurogenic bladder dysfunction, hyponatraemia, uncontrolled hypertension, congestive heart failure, history of prostate surgery, interstitial cystitis, elevated PSA, or previously treated with anticholinergic drugs or diuretics.</p> <p>Total number of participants randomly assigned: 427.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 205 • age (years; mean $\pm$ SD): 64.6 ± 4.4 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS (mean $\pm$ SD): 16.5 ± 4.5 • $Q_{\max}$ (mL/s; mean $\pm$ SD): 14.9 ± 5.9 • PVR (mL; mean $\pm$ SD): 32.9 ± 20.2 <p>Control group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 222 • age (years; mean $\pm$ SD): 66.6 ± 5.4 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS (mean $\pm$ SD): 18.0 ± 5.3 • $Q_{\max}$ (mL/s; mean $\pm$ SD): 13.5 ± 4.7 • PVR (mL; mean $\pm$ SD): 33.6 ± 22.7
Interventions	<p>Run-in period: 4 weeks of alpha-blocker treatment.</p> <p>Experimental: desmopressin 0.2 mg oral with tamsulosin 0.2 mg oral at bedtime.</p> <p>Control: solifenacin 5 mg oral with tamsulosin 0.2 mg oral at bedtime.</p> <p>Duration: 4 weeks (8 weeks (cross-over study design)).</p>
Outcomes	<ul style="list-style-type: none"> • 3-day voiding diary: <ul style="list-style-type: none"> * nocturia episodes * nocturnal urine volume * nocturnal index * urgency episodes * nocturnal bladder capacity index • IPSS (total and subscore) • Overactive Bladder Symptom Score • $Q_{\max}$ • PVR • Adverse events

Shin 2014a (Continued)

Funding sources	Acknowledgements: supported by grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea.
Declarations of interest	No conflicts of interest.
Notes	<ul style="list-style-type: none"> Participants' data in both groups subdivided into 3 subgroups: <ul style="list-style-type: none"> nocturnal polyuria (voided urine volume during sleep > 33% of the 24-hour output); decreased nocturnal bladder capacity (nocturnal bladder capacity index > 0; corresponded to actual number of voids subtracted by predicted number of voids; predict number of voids, nocturia index -1; nocturia index = nocturnal urine volume divided by functional bladder capacity; and functional bladder capacity is the single largest volume voided and recorded in voiding diary); and nocturia due to both causes. Review authors used data before cross-over due to unit of analysis error. Short-term primary and secondary outcome obtained from author. <p>Language of article: English.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly divided into two groups at the time of enrollment." Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Comment: all participants included in analysis.
Incomplete outcome data (attrition bias) QoL	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Duration of first sleep episode	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described

Shin 2014a (Continued)

Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	Comment: all participants included in analysis.
Selective reporting (reporting bias)	Low risk	Comment: protocol not published, but data obtained through contact with author.
Other bias	Low risk	Comment: not detected

Wang 2011a

Methods	<p>Design: RCT, parallel, double-blind, placebo controlled.</p> <p>Randomisation ratio: 1:1.</p> <p>Setting: single centre/Taiwan.</p> <p>Dates when study was conducted: October 2007 to December 2009.</p>
Participants	<p>Inclusion criteria: men with BPH age > 65 years, nocturia (mean ≥ 2), nocturnal polyuria (nocturnal urine volume > 30% of total daily urine volume).</p> <p>Exclusion criteria: men with urge incontinence, another voiding dysfunction, or urinary tract infection; received treatment with drugs known or suspected to interact with desmopressin (e.g. diuretics, tricyclic antidepressants, indomethacin, carbamazepine, or chlorpropamide); uncontrolled hypertension and diabetes mellitus; or had evidence of clinically relevant cardiac failure.</p> <p>Total number of participants randomly assigned: 115.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 57 • age (years; mean $\pm$ SD): 73.56 ± 7.71 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported <p>Control group:</p> <ul style="list-style-type: none"> • number of participants randomly assigned: 58 • age (years; mean $\pm$ SD): 74.52 ± 5.99 • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported
Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin 0.1 mg oral at bedtime.</p> <p>Control: placebo oral at bedtime.</p>

Wang 2011a (Continued)

Duration: 12 months.

Outcomes	Primary efficacy endpoint: <ul style="list-style-type: none"> proportion of participants with reduction by 2 in the mean number of nocturnal voids after long-term treatment vs baseline Secondary efficacy endpoints: <ul style="list-style-type: none"> number of nightly voids duration of sleep until the first void (increase of > 30 minutes) nocturnal volume and nighttime: 24-hour urine volume ratio ($\leq 30\%$) effect on QoL safety of long-term desmopressin treatment (adverse events and serum sodium levels)
Funding sources	Not reported.
Declarations of interest	Not reported.
Notes	Language of article: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were prospectively randomized into placebo and desmopressin groups using random numbers tables."
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo-controlled study, double-blind but unclear who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo-controlled study, double-blind but unclear who was blinded.
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Quote: "A total of 126 patients were enrolled into the treatment and randomized to both groups. In the placebo group 1 patient and in the desmopressin group 2 withdrew consent. During treatment 2 patients in the placebo group and 1 in the desmopressin group did not comply with followup protocol. In addition, 1 patient in the placebo group had a stroke and 1 had consciousness disturbance due to hyponatremia (116 mmol/l) so they could not complete the protocol. Thus, a total of 115 patients were enrolled into the study." Comment: 9/126 (7.1%) participants not included in analysis.
Incomplete outcome data (attrition bias) QoL	Low risk	Comment: 9/126 (7.1%) participants not included in analysis.
Incomplete outcome data (attrition bias) Duration of first sleep episode	Low risk	Comment: 9/126 (7.1%) participants not included in analysis.

Wang 2011a (Continued)

Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	Comment: 9/126 (7.1%) participants not included in analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: review outcomes insufficiently described, and protocol not published.
Other bias	Low risk	Comment: not detected

Wang 2012

Methods	<p>Design: RCT.</p> <p>Randomisation ratio: 1:1.</p> <p>Setting: outpatient/single centre/China.</p> <p>Dates when study was conducted: 2009 to 2010.</p>
Participants	<p>Inclusion criteria: older men with ≥ 2 voids/night.</p> <p>Exclusion criteria: not reported.</p> <p>Total number of participants randomly assigned: 60.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 30 • age (years): not reported • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported <p>Control group:</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 30 • age (years): not reported • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported
Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin 0.1 mg at bedtime.</p> <p>Control: liquid restriction during nighttime.</p>

Desmopressin for treating nocturia in men (Review)

Wang 2012 (Continued)

Duration: 8 weeks.

Outcomes	<ul style="list-style-type: none"> Nocturia cure rate Mean number of nocturia Mean duration of the first period Sleep quality
Funding sources	Not reported.
Declarations of interest	Not reported.
Notes	Abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Quote: "All patients were evaluated by nocturia cure rate, mean number of nocturia, mean duration of the first period and sleep quality."
Incomplete outcome data (attrition bias) QoL	Low risk	Quote: "All patients were evaluated by nocturia cure rate, mean number of nocturia, mean duration of the first period and sleep quality."
Incomplete outcome data (attrition bias) Duration of first sleep episode	Low risk	Quote: "All patients were evaluated by nocturia cure rate, mean number of nocturia, mean duration of the first period and sleep quality."
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Unclear risk	Comment: not described

Wang 2012 (Continued)

Selective reporting (reporting bias)	Unclear risk	Comment: protocol not published.
Other bias	Unclear risk	Comment: abstract only

Weiss 2012a

Methods	<p>Design: RCT, parallel, double-blind, placebo controlled.</p> <p>Randomisation ratio: 1:1:1:1:1 (placebo, desmopressin 10 µg, 25 µg, 50 µg, or 100 µg).</p> <p>Setting: multicentre/Canada and the USA.</p> <p>Dates when study was conducted: June 2007 to February 2008.</p>
Participants	<p>Inclusion criteria: men and women aged > 18 years, mean ≥ 2 voids/night determined via a 3-day frequency volume chart (serum sodium ≥ 135 mmol/L, serum creatinine within normal limits, and estimated glomerular filtration rate ≥ 60 mL/minutes), people on stable doses of medication for overactive bladder or BPH (or both) for 3 months could be included.</p> <p>Exclusion criteria: all individuals with urinary retention or PVR volume > 150 mL (or both); or history of urologic malignancies, neurogenic detrusor activity, or current genitourinary tract pathology that could interfere with voiding in addition to men with evidence of bladder outflow obstruction or urine flow < 5 mL/s (or both); or if surgery for bladder outflow obstruction/BPH had been performed within 6 months and women with potential for pregnancy, use of a pessary for pelvic prolapse, or presence of unexplained pelvic mass.</p> <p>Total number of participants randomly assigned: 799 (757 intention-to-treat population).</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 160/158/158/160 (10 µg/25 µg/50 µg/100 µg) • age (years): not reported • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported <p>Control group</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 160 • age (years): not reported • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported
Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin 10 µg, 25 µg, 50 µg, and 100 µg ODT once daily, 1 h before bedtime.</p> <p>Control: placebo (ODT) once daily, 1 h before bedtime.</p> <p>Duration: 4 weeks.</p>

Weiss 2012a (Continued)

Outcomes	Coprimary efficacy endpoints: <ul style="list-style-type: none">• change from baseline in mean number of nocturnal voids• proportion of participants with > 33% reduction in mean number of nocturnal voids from baseline Secondary efficacy endpoints: <ul style="list-style-type: none">• change in diuresis (total and nocturnal volumes)• change in initial period of undisturbed sleep• change in nocturia QoL score Safety: <ul style="list-style-type: none">• adverse events• serum sodium values	
Funding sources	Ferring Pharmaceuticals.	
Declarations of interest	JP Weiss has been working with Ferring Pharmascience for more than 10 years acting in the capacity of paid consultant and scientific advisor. NR Zinner has been involved in clinical trials and has received speaker honoraria and consultancy fees from Ferring Pharmaceuticals and Astellas. BM Klein and JP Nørgaard are employees of Ferring Pharmaceuticals.	
Notes	<ul style="list-style-type: none">• Baseline characteristics were only shown in all participants.• Nocturnal voids, 33% responder rate, initial period of undisturbed sleep, urinary volume (nocturnal and total) were shown in men and women independently. Protocol: NCT00477490. Language of article: English.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: central randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Treatments were packaged according to the computer generated randomization code to ensure that patients, investigators, and the sponsor remained fully blinded." Comment: remote central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Desmopressin and placebo were supplied by Ferring Pharmaceutical A/S and were indistinguishable with respect to appearance, smell, taste, and packaging. Treatments were packaged according to the computer generated randomization code to ensure that patients, investigators, and the sponsor remained fully blinded." Comment: blinding of participants and personnel described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Treatments were packaged according to the computer generated randomization code to ensure that patients, investigators, and the sponsor remained fully blinded." Comment: outcome assessors blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "The ITT [intention-to-treat] population included 757 subjects and 710 (89%) completed the study. Across treatment groups, 6-16% of subjects dis-

Weiss 2012a (Continued)

Number of nocturnal voids		continued prematurely. The most common reasons for discontinuation were withdrawal of consent (4%), AEs [adverse events] (2%), and lost to follow-up (2%)."
		Comment: 42 of 799 (5.2%) randomised participants not included in analysis, but data for men were not reported separately.
Incomplete outcome data (attrition bias) QoL	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Duration of first sleep episode	Unclear risk	Comment: 42/799 (5.2%) randomised participants not included in analysis, but data for men not reported separately.
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Unclear risk	Comment: not described
Selective reporting (reporting bias)	Low risk	Comment: protocol (NCT01262456) published, and all predefined review outcomes were well described.
Other bias	Unclear risk	Comment: no stratification based on gender

Weiss 2013

Methods	<p>Design: RCT, parallel, double-blind, placebo controlled.</p> <p>Randomisation ratio: 1:1:1 (placebo, desmopressin 50 µg or 75 µg).</p> <p>Setting: multicentre/Canada and the USA.</p> <p>Dates when study was conducted: February 2011 to January 2012.</p>
Participants	<p>Inclusion criteria: men aged ≥ 18 years with nocturia (≥ 2 voids/night determined via a 3-day frequency volume chart).</p> <p>Exclusion criteria: severe daytime voiding dysfunction (> 1 urge incontinence or urgency episode daily or > 8 daytime voids/day in the 3-day diary); suspicion of bladder outlet obstruction or a urine flow < 5 mL/s; surgery for bladder outlet obstruction or BPH within 6 months of screening; urinary retention or PVR volume > 250 mL (confirmed by ultrasound if investigator suspected retention) (or both); history of urologic malignancies, neurogenic detrusor activity, or current genitourinary tract pathology that could interfere with voiding, polydipsia, and hyponatraemia (serum sodium < 135 mmol/L).</p> <p>Total number of participants randomly assigned: 395.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> number of all participants randomly assigned: 119/124 (50 µg/75 µg) age (years; mean ± SD): 60.8 ± 13.2/60.1 ± 11.6 (50 µg/75 µg) prostate volume (mL): not reported

Desmopressin for treating nocturia in men (Review)

Weiss 2013 (Continued)

- PSA (ng/mL): not reported
- IPSS: not reported
- Q_{max} (mL/s): not reported
- PVR (mL): not reported

Control group:

- number of all participants randomly assigned: 142
- age (years; mean ± SD): 60.8 ± 14.2
- prostate volume (mL): not reported
- PSA (ng/mL): not reported
- IPSS: not reported
- Q_{max} (mL/s): not reported
- PVR (mL): not reported

Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin 50 µg and 75 µg (ODT) once daily.</p> <p>Control: placebo (ODT) once daily.</p> <p>Duration: 3 months.</p>
Outcomes	<p>Coprimary efficacy endpoints:</p> <ul style="list-style-type: none"> • change from baseline in mean number of nocturnal voids • proportion of 33% responders (participants with a decrease of ≥ 33% in mean number of nocturnal voids at each visit compared to baseline) <p>Secondary efficacy endpoints:</p> <ul style="list-style-type: none"> • change from baseline at 3 months in mean number of nocturnal voids • proportion of 33% responders • mean time to first void and mean nocturnal urine volume <p>Exploratory endpoints:</p> <ul style="list-style-type: none"> • mean self rated sleep quality • nocturia QoL • work productivity and activity impairment percentages <p>Safety and tolerability:</p> <ul style="list-style-type: none"> • adverse events • serum sodium values
Funding sources	Supported by Ferring Pharmaceuticals.
Declarations of interest	Jeffrey P Weiss: financial interest or other relationship (or both) with Ferring, Pfizer, Allergan, Astellas, and Lilly; Sender Herschorn: financial interest or other relationship (or both) with Ferring, Astellas, Pfizer, Allergan, Watson, American Medical Systems, Eli Lilly, Cook, and Gynecare; Egbert A van der Meulen and Cerasela D Albei: financial interest or other relationship (or both) with Ferring.
Notes	<p>Protocol: NCT01262456.</p> <p>Language of article: English.</p>
Risk of bias	

Weiss 2013 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using a computer generated list prepared before study enrollment. Randomization was stratified by age." Comment: method of sequence generation described.
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Desmopressin and placebo ODT were supplied by Ferring Pharmaceuticals, and were indistinguishable with respect to appearance, smell, taste and packaging." Comment: participant and investigator blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: placebo-controlled study, participants and investigator blinded.
Incomplete outcome data (attrition bias) Number of nocturnal voids	Low risk	Comment: 2/243 (0.9%) participants in desmopressin group and 0/142 (0.0%) participants in placebo group not included in analysis.
Incomplete outcome data (attrition bias) QoL	Unclear risk	Comment: 33/243 (13.5%) participants in desmopressin group and 15/142 (10.5%) participants in placebo group not included in analysis.
Incomplete outcome data (attrition bias) Duration of first sleep episode	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Time to first void	Low risk	Comment: 2/243 (0.9%) participants in desmopressin group and 0/142 (0.0%) participants in placebo group not included in analysis.
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Low risk	Quote: "All primary, secondary and exploratory end points were analyzed based on the full analysis set which included all randomized and exposed patients with at least 1 efficacy assessment after dosing initiation." Comment: all participants included in analysis.
Selective reporting (reporting bias)	Low risk	Comment: protocol (NCT01262456) published, and all predefined review outcomes were well described.
Other bias	Low risk	Comment: not detected

Yamaguchi 2013

Methods	Design: randomised, double-blind, placebo-controlled, parallel trial. Randomisation ratio: 1:1:1:1:1 (placebo, desmopressin 10 µg, 25 µg, 50 µg, or 100 µg). Setting: multicentre (36)/Japan.
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Desmopressin for treating nocturia in men (Review)

Yamaguchi 2013 (Continued)

Dates when study was conducted: July 2010 to April 2011.

Participants	<p>Inclusion criteria: adults aged 55 to 75 years, with mean ≥ 2 voids/night in a 3-day frequency volume chart.</p> <p>Exclusion criteria: bladder obstruction or a urine flow < 5 mL/s, surgical treatment of bladder obstruction or prostatic hyperplasia ≤ 6 months before study, symptoms of BPH, overactive bladder or interstitial cystitis, mean number of nocturnal voids > 4/night in a consecutive 3-day period during screening, or hyponatraemia (serum sodium < 135 mEq/L) after desmopressin administration.</p> <p>Total number of participants randomly assigned: 139.</p> <p>Experimental group:</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 28/25/29/30 (10 μg/25 μg/50 μg/100 μg) • age (years): not reported • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported <p>Control group:</p> <ul style="list-style-type: none"> • number of all participants randomly assigned: 27 • age (years): not reported • prostate volume (mL): not reported • PSA (ng/mL): not reported • IPSS: not reported • $Q_{\max}$ (mL/s): not reported • PVR (mL): not reported
Interventions	<p>Run-in period: no.</p> <p>Experimental: desmopressin 10 μg, 25 μg, 50 μg, and 100 μg ODT once daily, 1 h before bedtime.</p> <p>Control: placebo once daily, 1 h before bedtime.</p> <p>Duration: 4 weeks.</p>
Outcomes	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • change in mean number of nocturnal voids <p>Secondary endpoints:</p> <ul style="list-style-type: none"> • change in initial period of undisturbed sleep • change in diuresis (nocturnal urine volume) • change in nocturnal polyuria index • change in QoL from baseline <p>Safety and tolerability:</p> <ul style="list-style-type: none"> • adverse events • serum sodium values • clinical laboratory results (haematology, serum chemistry, and urine analysis), vital signs (diastolic blood pressure, systolic blood pressure, heart rate, and body temperature) and physical exams
Funding sources	Ferring Pharmaceuticals A/S.

Yamaguchi 2013 (Continued)

Declarations of interest Osamu Yamaguchi and Osamu Nishizawa are consultants to Ferring Pharmaceuticals. Osamu Nishizawa, Kristian Vinter Juul, and Jens Peter Nørgaard are employees of Ferring Pharmaceuticals.

Notes **Protocol:** NCT01184859.

Language: English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "according to a computer-generated randomization list and stratified by age and gender to ensure balanced groups."
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Desmopressin ODT and placebo were supplied by Ferring Pharmaceuticals A/S and were indistinguishable with respect to appearance, smell, taste and packaging." "Treatments were packaged according to the computer-generated randomization code to ensure that patients, investigators and the sponsor remained fully blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Desmopressin ODT and placebo were supplied by Ferring Pharmaceuticals A/S and were indistinguishable with respect to appearance, smell, taste and packaging." "Treatments were packaged according to the computer-generated randomization code to ensure that patients, investigators and the sponsor remained fully blinded."
Incomplete outcome data (attrition bias) Number of nocturnal voids	High risk	Comment: 30/112 (26.7%) participants in desmopressin group and 5/27 (18.5%) participants in placebo group were not included in analysis.
Incomplete outcome data (attrition bias) QoL	High risk	Comment: 24/112 (21.4%) participants in desmopressin group and 5/27 (18.5%) participants in placebo group were not included in analysis.
Incomplete outcome data (attrition bias) Duration of first sleep episode	High risk	Comment: 30/112 (26.7%) participants in desmopressin group and 5/27 (18.5%) participants in placebo group were not included in analysis.
Incomplete outcome data (attrition bias) Time to first void	Unclear risk	Comment: not described
Incomplete outcome data (attrition bias) Major adverse events/minor adverse events/treatment withdrawal due to adverse event	Unclear risk	Comment: 19/112 (16.9%) participants in desmopressin group and 4/27 (14.8%) participants in placebo group were not included in analysis.
Selective reporting (reporting bias)	Low risk	Protocol (NCT01184859) published, and predefined study outcomes were well described.
Other bias	Unclear risk	Comment: no stratification based on gender

Desmopressin for treating nocturia in men (Review)

BPH: benign prostatic hyperplasia; FDA: US Food and Drug Administration; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; ODT: orally disintegrating tablet; PSA: prostate-specific antigen; PVR: postvoid residual; $Q_{\max}$: maximum flow rate; QoL: quality of life; RCT: randomised controlled trial; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmed 2015b	Duplicate
Asplund 1999	Wrong participant population (men and women)
Cho 2015	Wrong comparator
Cho 2016	Duplicate
Fu 2011	Wrong intervention
Gilbert 2011	Wrong study design
Holm-Larsen 2013a	Wrong study design
Kaminetsky 2016	Duplicate
Lam 2017	Wrong participant population (not defined)
Malli 2014	Wrong outcomes
Moon 2002	Wrong study design
Moon 2003	Wrong study design
Shin 2014b	Duplicate
van Kerrebroeck 2007	Wrong participant population (men and women)
Wang 2011b	Duplicate
Weiss 2012b	Duplicate
Yassin 2010	Wrong participant population

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Holm-Larsen 2013b](#)

Methods	Randomised, controlled, double-blind study.
Participants	People with ≥ 2 voids/night.
Interventions	Not reported.
Outcomes	Improvement in initial period of undisturbed sleep and sleep quality.
Notes	Abstract only.

Desmopressin for treating nocturia in men (Review)

NCT01694498

Methods	Parallel, randomised, double-blind (participants and investigator) trial.
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • given written consent prior to any trial-related activity performed • men aged ≥ 20 years • ≥ 2 nocturnal voids every night in a consecutive 3-day period as documented in the diary during the screening period • given agreement about contraception during trial. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • suspicion of bladder outlet obstruction or a urine flow < 5 mL/s as confirmed by uroflowmetry after suspicion of bladder outlet obstruction • surgical treatment for bladder outlet obstruction or prostatic hyperplasia within the past 6 months • symptoms of benign prostatic obstruction; interstitial cystitis; overactive bladder, defined as > 6 daytime voids, ≥ 1 urgency episode, and ≥ 1 urge urinary incontinence episode/24 h as documented in 3-day diary period; severe stress urinary incontinence • chronic prostatitis/chronic pelvic pain syndrome • psychogenic or habitual polydipsia • urinary retention or a postvoid residual volume > 150 mL as confirmed by bladder ultrasound performed after suspicion of urinary retention • cancer • history of urologic malignancies or history of cancer that has not been in remission for the last 5 years • genitourinary tract pathology • neurogenic detrusor activity • suspicion or evidence of heart failure • uncontrolled hypertension • uncontrolled diabetes mellitus • hepatobiliary diseases: aspartate aminotransferase > 80 U/L or alanine aminotransferase > 90 U/L; total bilirubin > 1.5 mg/dL • renal insufficiency: serum creatinine level > 1.09 mg/dL; estimated glomerular filtration rate < 50 mL/minute • hyponatraemia: serum sodium level < 135 mEq/L • central or nephrogenic diabetes insipidus • syndrome of inappropriate antidiuretic hormone • obstructive sleep apnoea • previous desmopressin treatment • treatment with another investigational product within the past 3 months • concomitant treatment with any prohibited medication • alcohol or substance abuse • job or lifestyle that may interfere with regular nighttime sleep • mental condition, lack of decision-making ability, dementia, speech handicap, or any other reason which, in the judgement of the investigator (subinvestigator), would impair participation in trial
Interventions	<p>Experimental: desmopressin 25 µg/50 µg.</p> <p>Control: placebo.</p> <p>Duration: 12 weeks.</p>

NCT01694498 (Continued)

Outcomes

Primary outcome:

- change from baseline in mean number of nocturnal voids

Secondary outcomes:

- change from baseline in mean number of nocturnal voids
- change from baseline in mean time to first void
- responder status (33% reduction in nocturnal voids)
- change from baseline in mean nocturnal urine volume
- change from baseline in nocturnal polyuria index
- change from baseline in effect on sleep disturbance
- change from baseline in impact on quality of life
- adverse events, changes from baseline in serum sodium level, laboratory values
- change from baseline in effect on sleep disturbance
- change from baseline in impact on quality of life
- adverse events, changes from baseline in serum sodium level, laboratory value

Notes

June 2013 (final data collection date for primary outcome measure).

Salvatore 1996

Methods

NA.

Participants

NA.

Interventions

NA.

Outcomes

NA.

Notes

Title only (only indexed in Cochrane Central Register of Controlled Trials (CENTRAL)).

Weiss 2001

Methods

NA.

Participants

NA.

Interventions

NA.

Outcomes

NA.

Notes

Title only (no Supplement 5 issue in *Journal of Urology*).

NA: not available.

Characteristics of ongoing studies [ordered by study ID]

NCT02904759

Trial name or title	Trial of desmopressin orally disintegrating tablets for nocturia due to nocturnal polyuria in Japanese male subjects.
Methods	Parallel, randomised, double-blind (participant, investigator) trial.
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> written informed consent prior to performance of any trial-related activity man ≥ 20 years of age nocturia symptoms present for ≥ 6 months prior to trial entry at visit 1 ≥ 2 nocturnal voids at the end of screening period prior to visit 2 nocturnal polyuria at the end of screening period prior to visit 2 bothered by nocturia on the Hsu 5-point Likert bother scale at visit 1 and visit 2 has given agreement about contraception during the trial. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> evidence of any significant voiding dysfunction resulting in abnormally low bladder capacity at end of screening period prior to visit 2 history or evidence of significant obstructive sleep apnoea history or diagnosis of any of following urological diseases at visit 1: interstitial cystitis or bladder pain disorder; suspicion of moderate or severe benign prostate hyperplasia, defined as International Prostate Symptom Score ≥ 8 points and urinary flow < 5 mL/s or postvoid residual volume > 150 mL, stress urinary incontinence or mixed incontinence, where stress incontinence was predominant component based on prior history of chronic pelvic pain syndrome surgical treatment, including transurethral resection, for bladder outlet obstruction or benign prostatic hyperplasia within the past 6 months prior to visit 1 symptoms of severe overactive bladder: defined as overactive bladder symptom score ≥ 12 at visit 1, or defined as mean of > 8 voids and mean of ≥ 1 urgency episode/24 hours at end of screening period prior to visit 2 genitourinary tract pathology that in investigator's opinion can be responsible for urgency or urinary incontinence at visit 1 complication of cancer or a history of cancer that has not been in remission for last 5 years at visit 1 current or history of urologic malignancies, any lower urinary tract surgery, previous pelvic irradiation, or neoplasia at visit 1 history of any neurological disease affecting bladder function or muscle strength at visit 1 habitual or psychogenic polydipsia based on medical history at visit 1 or 24-hour urine output of > 2.8 L based on the voiding diary at visit 2 central or nephrogenic diabetes insipidus at visit 1 syndrome of inappropriate antidiuretic hormone secretion at visit 1 suspicion or evidence of cardiac failure at visit 1 uncontrolled hypertension at visit 1 uncontrolled diabetes mellitus at visit 1 hyponatraemia (serum sodium level < 135 mmol/L) at visit 1 renal insufficiency at visit 1 hepatic or biliary (or both) diseases at visit 1 known or suspected hypersensitivity to desmopressin orally disintegrating tablets or previous desmopressin treatment for nocturia at visit 1 known alcohol or substance abuse at visit 1 work or lifestyle that may interfere with regular nighttime sleep at visit 1, e.g. shift worker any other medical condition, laboratory abnormality, psychiatric condition, mental incapacity, or language barrier that, in the judgement of the investigator, would impair participation in the trial at visit 1 use of any prohibited therapy during the trial period

NCT02904759 (Continued)

Interventions	Experimental: desmopressin 25 µg/50 µg. Control: placebo. Duration: 12 weeks.
Outcomes	Primary outcome: <ul style="list-style-type: none"> change from baseline in mean number of nocturnal voids Secondary outcomes: <ul style="list-style-type: none"> change from baseline in mean time to first awakening to void change from baseline in mean nocturnal urine volume change from baseline in mean nocturnal polyuria index change from baseline in Nocturia-Quality of Life questionnaire change from baseline in insomnia severity index change from baseline in bother score frequency and severity of adverse events
Starting date	14 September 2016.
Contact information	DK0-Disclosure@ferring.com.
Notes	Study is currently recruiting participants.

DATA AND ANALYSES

Comparison 1. Desmopressin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of nocturnal voids (short term) (subgroup route)	6	1982	Mean Difference (IV, Random, 95% CI)	-0.61 [-0.96, -0.27]
1.1 Intranasal	1	870	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.34, -0.06]
1.2 Sublingual	3	851	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.71, -0.03]
1.3 Oral	2	261	Mean Difference (IV, Random, 95% CI)	-1.14 [-1.41, -0.86]
2 Number of nocturnal voids (intermediate term)	1	115	Mean Difference (IV, Random, 95% CI)	-0.85 [-1.17, -0.53]
3 Major adverse events (short term) (subgroup route and dose)	2	536	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.10, 9.03]
3.1 Sublingual/low dose	1	385	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.73, 8.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Oral/high dose	1	151	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.37]
4 Major adverse events (intermediate term)	1	115	Risk Ratio (M-H, Random, 95% CI)	3.05 [0.13, 73.39]
5 Duration of first sleep episode (short term)	4	652	Mean Difference (IV, Random, 95% CI)	54.61 [13.97, 95.25]
6 Duration of first sleep episode (intermediate term)	1	115	Mean Difference (IV, Random, 95% CI)	18.40 [11.60, 25.20]
7 Time to first void (short term) [minutes]	1	383	Mean Difference (IV, Random, 95% CI)	40.8 [17.07, 64.53]
8 Minor adverse events (short term)	3	594	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.13]
9 Minor adverse events (intermediate term)	1	115	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.49, 1.49]
10 Treatment withdrawal due to adverse event (short term)	4	614	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.56, 2.15]
11 Treatment withdrawal due to adverse event (intermediate term)	1	115	Risk Ratio (M-H, Random, 95% CI)	3.05 [0.13, 73.39]
12 Number of nocturnal voids (short term) (subgroup dose)	6	1982	Mean Difference (IV, Random, 95% CI)	-0.65 [-0.98, -0.33]
12.1 Very low dose ($\leq 1.5 \mu\text{g}$)	1	870	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.34, -0.06]
12.2 Low dose ($< 100 \mu\text{g}$)	3	711	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.72, 0.06]
12.3 High dose ($\geq 100 \mu\text{g}$)	4	401	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.41, -0.66]
13 Number of nocturnal voids (short term) (subgroup nocturnal polyuria)	6	1982	Mean Difference (IV, Random, 95% CI)	-0.61 [-0.96, -0.27]
13.1 Men with nocturia	5	1867	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.73, -0.17]
13.2 Men with nocturia and nocturnal polyuria	1	115	Mean Difference (IV, Random, 95% CI)	-1.28 [-1.64, -0.92]
14 Number of nocturnal voids (short term) (sensitivity run-in period)	4	966	Mean Difference (IV, Random, 95% CI)	-0.66 [-1.17, -0.14]
15 Major adverse events (short term) (sensitivity run-in period)	1	385	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.73, 8.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Number of nocturnal voids (short term) (sensitivity clinical dosage)	6	1586	Mean Difference (IV, Random, 95% CI)	-0.76 [-1.15, -0.38]
17 Major adverse events (short term) (sensitivity clinical dosage)	2	417	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.10, 9.71]
17.1 Sublingual/low dose	1	266	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.71, 10.11]
17.2 Oral/high dose	1	151	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.37]

Analysis 1.1. Comparison 1 Desmopressin versus placebo, Outcome 1 Number of nocturnal voids (short term) (subgroup route).

Analysis 1.2. Comparison 1 Desmopressin versus placebo, Outcome 2 Number of nocturnal voids (intermediate term).

Analysis 1.3. Comparison 1 Desmopressin versus placebo, Outcome 3 Major adverse events (short term) (subgroup route and dose).

Analysis 1.4. Comparison 1 Desmopressin versus placebo, Outcome 4 Major adverse events (intermediate term).

Analysis 1.5. Comparison 1 Desmopressin versus placebo, Outcome 5 Duration of first sleep episode (short term).

Analysis 1.6. Comparison 1 Desmopressin versus placebo, Outcome 6 Duration of first sleep episode (intermediate term).

Analysis 1.7. Comparison 1 Desmopressin versus placebo, Outcome 7 Time to first void (short term) [minutes].

Analysis 1.8. Comparison 1 Desmopressin versus placebo, Outcome 8 Minor adverse events (short term).

Analysis 1.9. Comparison 1 Desmopressin versus placebo, Outcome 9 Minor adverse events (intermediate term).

Analysis 1.10. Comparison 1 Desmopressin versus placebo, Outcome 10 Treatment withdrawal due to adverse event (short term).

Analysis 1.11. Comparison 1 Desmopressin versus placebo, Outcome 11 Treatment withdrawal due to adverse event (intermediate term).

Study or subgroup	Desmopressin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable Test for overall effect: Z=0.69(P=0.49)					
Favors desmopressin 0.01 0.1 1 10 100 Favors placebo					

Analysis 1.12. Comparison 1 Desmopressin versus placebo, Outcome 12 Number of nocturnal voids (short term) (subgroup dose).

Study or subgroup	Desmopressin		Placebo		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.12.1 Very low dose ($\leq 1.5 \mu\text{g}$)							
Serenity Pharmaceuticals 2016	612	-1.4 (0.9)	258	-1.2 (1)		15.32%	-0.2[-0.34,-0.06]
Subtotal ***	612		258			15.32%	-0.2[-0.34,-0.06]
Heterogeneity: Not applicable Test for overall effect: Z=2.82(P=0)							
1.12.2 Low dose ($< 100 \mu\text{g}$)							
Weiss 2012a	246	-0.8 (1.2)	45	-0.8 (1.1)		13.3%	0.02[-0.33,0.37]
Weiss 2013	241	-1.3 (0.9)	142	-1 (1)		14.9%	-0.31[-0.51,-0.11]
Yamaguchi 2013	31	-1.1 (0.5)	6	-0.2 (0.8)		9.78%	-0.94[-1.58,-0.3]
Subtotal ***	518		193			37.97%	-0.33[-0.72,0.06]
Heterogeneity: Tau ² =0.08; Chi ² =7.04, df=2(P=0.03); I ² =71.59% Test for overall effect: Z=1.65(P=0.1)							
1.12.3 High dose ($\geq 100 \mu\text{g}$)							
Mattiasson 2002	83	1.7 (0.9)	63	2.7 (1.2)		13.25%	-1[-1.35,-0.65]
Wang 2011a	57	3.3 (0.8)	58	4.6 (1.1)		13.21%	-1.28[-1.64,-0.92]
Weiss 2012a	80	-1.4 (1.3)	45	-0.8 (1.1)		12.39%	-0.54[-0.96,-0.12]
Yamaguchi 2013	10	-1.7 (0.8)	5	-0.2 (0.8)		7.85%	-1.53[-2.35,-0.71]
Subtotal ***	230		171			46.7%	-1.03[-1.41,-0.66]
Heterogeneity: Tau ² =0.09; Chi ² =8.46, df=3(P=0.04); I ² =64.52% Test for overall effect: Z=5.42(P<0.0001)							
Total ***	1360		622			100%	-0.65[-0.98,-0.33]
Heterogeneity: Tau ² =0.17; Chi ² =59.11, df=7(P<0.0001); I ² =88.16% Test for overall effect: Z=3.98(P<0.0001) Test for subgroup differences: Chi ² =16.83, df=1 (P=0), I ² =88.12%							
Favors desmopressin -2 -1 0 1 2 Favors placebo							

Analysis 1.13. Comparison 1 Desmopressin versus placebo, Outcome 13 Number of nocturnal voids (short term) (subgroup nocturnal polyuria).

Study or subgroup	Desmopressin		Placebo		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.13.1 Men with nocturia							
Mattiasson 2002	83	1.7 (0.9)	63	2.7 (1.2)		16.45%	-1[-1.35,-0.65]
Serenity Pharmaceuticals 2016	612	-1.4 (0.9)	258	-1.2 (1)		19.28%	-0.2[-0.34,-0.06]
Weiss 2012a	326	-1 (1.2)	90	-0.8 (1.1)		17.87%	-0.12[-0.38,0.14]
Favors desmopressin -4 -2 0 2 4 Favors placebo

Analysis 1.14. Comparison 1 Desmopressin versus placebo, Outcome 14 Number of nocturnal voids (short term) (sensitivity run-in period).

Analysis 1.15. Comparison 1 Desmopressin versus placebo, Outcome 15 Major adverse events (short term) (sensitivity run-in period).

Analysis 1.16. Comparison 1 Desmopressin versus placebo, Outcome 16 Number of nocturnal voids (short term) (sensitivity clinical dosage).

Analysis 1.17. Comparison 1 Desmopressin versus placebo, Outcome 17 Major adverse events (short term) (sensitivity clinical dosage).

Comparison 2. Desmopressin versus behaviour modification

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of first sleep episode (short term)	1	60	Mean Difference (IV, Random, 95% CI)	90.0 [1.95, 178.05]

Analysis 2.1. Comparison 2 Desmopressin versus behaviour modification, Outcome 1 Duration of first sleep episode (short term).

Comparison 3. Desmopressin versus alpha-blocker

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of nocturnal voids (short term)	1	31	Mean Difference (IV, Random, 95% CI)	0.30 [-0.20, 0.80]
2 Quality of life (short term)	1	31	Mean Difference (IV, Random, 95% CI)	0.0 [-0.35, 0.35]
3 Major adverse events (short term)	1	31	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Minor adverse events (short term)	1	31	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.07, 15.57]
5 Treatment withdrawal due to adverse event (short term)	1	31	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Desmopressin versus alpha-blocker, Outcome 1 Number of nocturnal voids (short term).

Analysis 3.2. Comparison 3 Desmopressin versus alpha-blocker, Outcome 2 Quality of life (short term).

Analysis 3.3. Comparison 3 Desmopressin versus alpha-blocker, Outcome 3 Major adverse events (short term).

Analysis 3.4. Comparison 3 Desmopressin versus alpha-blocker, Outcome 4 Minor adverse events (short term).

Analysis 3.5. Comparison 3 Desmopressin versus alpha-blocker, Outcome 5 Treatment withdrawal due to adverse event (short term).

Comparison 4. Desmopressin plus alpha-blocker versus alpha-blocker

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of nocturnal voids (short term) (subgroup route and dose)	3	341	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.73, -0.21]
1.1 Sublingual/low dose	1	210	Mean Difference (IV, Random, 95% CI)	-0.66 [-0.90, -0.42]
1.2 Oral/high dose	2	131	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.60, -0.02]
2 Number of nocturnal voids (short term) (subgroup nocturnal polyuria)	3	341	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.73, -0.21]
2.1 Men with nocturia	1	45	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.74, 0.14]
2.2 Men with nocturia and nocturnal polyuria	2	296	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.86, -0.18]
3 Quality of life (short term) (subgroup route and dose)	3	341	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.51, -0.07]
3.1 Sublingual/low dose	1	210	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.49, 0.03]
3.2 Oral/high dose	2	131	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.85, -0.03]
4 Quality of life (short term) (subgroup nocturnal polyuria)	3	341	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.51, -0.07]
4.1 Men with nocturia	1	45	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.84, 0.44]
4.2 Men with nocturia and nocturnal polyuria	2	296	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.67, -0.01]
5 Major adverse events (short term) (subgroup route and dose)	3	402	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.32]
5.1 Sublingual/low dose	1	248	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Oral/high dose	2	154	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.32]
6 Major adverse events (short term) (subgroup nocturnal polyuria)	3	402	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.32]
6.1 Men with nocturia	1	45	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Men with nocturia and nocturnal polyuria	2	357	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.32]
7 Minor adverse events (short term)	3	402	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.15, 16.82]
8 Treatment withdrawal due to adverse event (short term)	3	402	Risk Ratio (M-H, Random, 95% CI)	2.84 [0.46, 17.66]

Analysis 4.1. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 1 Number of nocturnal voids (short term) (subgroup route and dose).

Analysis 4.2. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 2 Number of nocturnal voids (short term) (subgroup nocturnal polyuria).

Analysis 4.3. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 3 Quality of life (short term) (subgroup route and dose).

Analysis 4.4. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 4 Quality of life (short term) (subgroup nocturnal polyuria).

Analysis 4.5. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 5 Major adverse events (short term) (subgroup route and dose).

Analysis 4.6. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 6 Major adverse events (short term) (subgroup nocturnal polyuria).

Analysis 4.7. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 7 Minor adverse events (short term).

Analysis 4.8. Comparison 4 Desmopressin plus alpha-blocker versus alpha-blocker, Outcome 8 Treatment withdrawal due to adverse event (short term).

Comparison 5. Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of nocturnal voids (short term)	1	405	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.97, 0.11]
2 Major adverse events (short term)	1	427	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Minor adverse events (short term)	1	427	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.98]
4 Treatment withdrawal due to adverse event (short term)	1	427	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.98]

Analysis 5.1. Comparison 5 Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic, Outcome 1 Number of nocturnal voids (short term).

Analysis 5.2. Comparison 5 Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic, Outcome 2 Major adverse events (short term).

Analysis 5.3. Comparison 5 Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic, Outcome 3 Minor adverse events (short term).

Analysis 5.4. Comparison 5 Desmopressin plus alpha-blocker versus alpha-blocker plus anticholinergic, Outcome 4 Treatment withdrawal due to adverse event (short term).

ADDITIONAL TABLES

Table 1. Baseline characteristics

Study	Setting	Trial period	Description of participants	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up)
Ahmed 2015a	Outpatient/Egypt	2011 to 2014	People with LUTS/BPH aged ≥ 50 years with nocturia (≥ 2 voids/night), nocturnal polyuria (nocturnal urine volume $> 30\%$ of 24-hour urine volume)	I: desmopressin 60 μg ODT + tamsulosin C: tamsulosin	3 months
Cannon 1999	UK	NR	Men aged > 50 years with nocturnal polyuria (using 48-hour inpatient monitoring or 1-week frequency volume chart)	I: desmopressin nasal spray 20 μg C: placebo	4 weeks
Ceylan 2013	Outpatient/Turkey	2011	Men with advanced age, complaints of LUTS and nocturia (≥ 3 times/night)	I: desmopressin nasal spray 20 μg C: doxazosin	2 months
Kim 2017	Multicentre/South Korea	NR	Men aged 40 to 65 years with LUTS (IPSS > 13), nocturia (≥ 2 episodes/night), and nocturnal polyuria (NPI $> 33\%$)	I: desmopressin 0.2 mg oral + alpha-blocker C: placebo + alpha-blocker	8 weeks
Koca 2012	Outpatient/Turkey	NR	Men aged 50 to 70 years with LUTS and nocturia (≥ 2 /night)	I: desmopressin 0.2 mg oral with alfuzosin C: alfuzosin	3 months
Mattiasson 2002	Multicentre/Denmark, Sweden, Netherlands, the UK, and the USA	NR	Men aged ≥ 18 years with nocturia (2 voids/night, nocturia index scores > 1)	I: desmopressin 0.1 mg/0.2 mg/0.4 mg oral; dose titration C: placebo	3 weeks
Rezakhaniha 2011	Outpatient/single centre/Iran	2008 to 2009	Older men (mean age about 63 to 64 years) with voiding ≥ 2 /night	I: desmopressin 0.1 mg oral C: placebo	8 weeks
Serenity Pharmaceuticals 2016	Multicentre/USA and Canada	NR	Men or women aged ≥ 50 years with nocturia (≥ 2 nocturic episodes/night)	I: desmopressin nasal spray 0.75 μg , 1.0 μg , or 1.5 μg C: placebo	12 weeks
Shin 2014a	South Korea	2010 to 2013	Men aged ≥ 50 years with LUTS due to bladder outlet obstruction ($Q_{\max} \leq 15$ mL/second, IPSS ≥ 14) and nocturia (≥ 1 void/night)	I: desmopressin 0.2 mg oral + tamsulosin C: solifenacin + tamsulosin	4 weeks

Table 1. Baseline characteristics (Continued)

Wang 2011a	Single centre/Taiwan	2007 to 2009	Men aged ≥ 65 years with BPH (IPSS > 13), nocturia (≥ 2 voids/night), and nocturnal polyuria (nocturnal urine volume $> 30\%$)	I: desmopressin 0.1 mg oral C: placebo	12 months
Wang 2012	Outpatient/single centre/China	2009 to 2010	Older men (age not reported)	I: desmopressin 0.1 mg oral C: placebo	8 weeks
Weiss 2012a	Multicentre/Canada and the USA	2007 to 2008	Men and women aged ≥ 18 years with nocturia (≥ 2 voids/night)	I: desmopressin 10 μg , 25 μg , 50 μg , or 100 μg ODT C: placebo	4 weeks
Weiss 2013	Multicentre/Canada and the USA	2010 to 2013	Men aged ≥ 18 years with nocturia (≥ 2 voids/night)	I: desmopressin 50 μg , 75 μg ODT C: placebo	3 months
Yamaguchi 2013	Multicentre/Japan	2010 to 2011	Men and women aged 55 to 75 years with nocturia (≥ 2 voids/night)	I: desmopressin 10 μg , 25 μg , 50 μg , or 100 μg ODT C: placebo	4 weeks

BPH: benign prostatic hyperplasia; C: comparator; I: intervention; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; NPI: nocturnal polyuria index; NR: not reported; ODT: orally disintegrating tablet; $Q_{\max}$: maximum flow rate.

Table 2. Participant disposition

	Intervention(s) and comparator(s)	Sample size	Screened/eligible (n)	Ran-domised (n)	ITT (n)	Analysed (n: to-tal/male)	Finishing trial (n)	Ran-domised finishing trial (%)	Follow-up (extended fol-low-up) ¹
Ahmed 2015a	I: desmopressin + tamsulosin	100	397/273	139	123	123	107	77.0	3 months
	C: tamsulosin	100		134	125	125	103	76.9	
	Total:			273	248	248	210	76.9	
Cannon 1999	I: desmopressin	-	-/-	-	-	-	-	-	8 weeks (cross-over study design)
	C: placebo	-		-	-	-	-	-	
	Total:			20	-	18	18	90.0	
Ceylan 2013	I: desmopressin	-	84/31	15	15	15	15	100.0	2 months
	C: doxazosin	-		16	16	16	16	100.0	
	Total:			31	31	31	31	100.0	
Kim 2017	I: desmopressin + alpha-blocker	-	121/109	57	57	47	47	82.4	8 weeks
	C: placebo + alpha-blocker	-		52	52	39	39	75.0	
	Total:			109	109	86	86	78.9	
Koca 2012	I: desmopressin + alfuzosin	-	-/49	-	-	22	22	-	3 months
	C: alfuzosin	-		-	-	23	23	-	
	Total:			49	-	45	45	91.8	
Mattias-son 2002	I: desmopressin	55	341/224	86	86	86	81	94.2	3 weeks
	C: placebo	55		65	65	65	62	95.4	
	Total:			151	151	151	143	94.7	

Table 2. Participant disposition (Continued)

Reza-khaniha 2011	I: desmopressin	-	93/60	30	30	30	30	100.0	8 weeks
	C: placebo	-		30	30	30	30	100.0	
	Total:			60	60	60	60	100.0	
Serenity Pharmaceuticals 2016²	I1: desmopressin 0.75 µg	-	3565/1707	458	448	448/252	401	87.5	12 weeks
	I2: desmopressin 1.0 µg	-		188	183	183/109	163	86.7	
	I3: desmopressin 1.5 µg	-		452	439	439/251	387	85.6	
	C: placebo	-		458	446	446/258	408	89.0	
	Total:			1556	1516	1516/870	1359	87.3	
Shin 2014a	I: desmopressin + tamsulosin	-	435/427	205	205	205	196	95.6	8 weeks (cross-over study design)
	C: tamsulosin + solifenacin	-		222	222	222	209	94.1	
	Total:			427	427	427	405	94.8	
Wang 2011a	I: desmopressin	45	-/136	NR	-	57	57	-	12 months
	C: placebo	45		NR	-	58	58	-	
	Total:			126	-	115	115	91.3	
Wang 2012	I: desmopressin	-	-/60	30	30	30	30	100.0	8 weeks
	C: placebo	-		30	30	30	30	100.0	
	Total:			60	60	60	60	100.0	
Weiss 2012a²	I1: desmopressin 10 µg	-	1412/799	163	155	155/82	144	88.3	4 weeks
	I2: desmopressin 25 µg	-		158	152	152/87	148	93.7	
	I3: desmopressin 50 µg	-		158	148	148/77	138	87.3	
	I4: desmopressin 100 µg	-		160	146	146/80	135	84.4	

Table 2. Participant disposition (Continued)

	C: placebo	-	160	156	156/90	145	90.6		
	Total:		799	757	757/416	710	88.9		
Weiss 2013	I1: desmopressin 50 µg	130	1013/395	-	119	119	100	-	3 months
	I2: desmopressin 75 µg	130		-	124	124	103	-	
	C: placebo	130		-	142	142	120	-	
	Total:		395	385	385	323	81.8		
Yam- aguchi 2013 ²	I1: desmopressin 10 µg	-	177/139	28	28	23/11	23	82.1	3 months
	I2: desmopressin 25 µg	-		25	25	22/11	22	88.0	
	I3: desmopressin 50 µg	-		29	29	21/10	21	72.4	
	I4: desmopressin 100 µg	-		30	30	23/11	23	76.6	
	C: placebo	-		27	27	23/11	23	85.1	
	Total:		139	139	112/54	112	80.5		
Overall total	Men	-		-	-	2966	-		
	Women			-		1045			
	Total:		4195			4011			

- denotes not reported; C: comparator; I: intervention; ITT: intention-to-treat; n: number of participants.

¹Follow-up under randomised conditions until end of trial or if not available, duration of intervention; extended follow-up refers to follow-up of participants once the original study was terminated as specified in the power calculation.

²Study included men and women.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)
Cochrane Register of Studies Online
MEDLINE (state platform/delete as appropriate: OvidSP/PubMed/other)
Ovid
EMBASE (state platform/delete as appropriate: OvidSP/other)
Ovid
ClinicalTrials.gov (state platform/delete as appropriate: Basic/Advanced search)
available from: clinicaltrials.gov/
ICTRP Search Portal (state platform/delete as appropriate: Standard/Advanced search)
available from: pps.who.int/trialsearch/default.aspx

Appendix 2. The Cochrane Library (via Wiley) search strategy

1. desmopressin:ti,ab,kw
2. desmopressine:ti,ab,kw
3. (minirin OR minurin):ti,ab,kw
4. (DDAVP OR stimulate):ti,ab,kw
5. ("1-Desamino-8-arginine Vasopressin" OR "1-Deamino-8-D-arginine Vasopressin"):ti,ab,kw
6. (nocutil OR desmospray OR desmogladen OR wetirin):ti,ab,kw
7. ("deamino arginine vasopressin" OR "desamino arginine vasopressin"):ti,ab,kw
8. MeSH descriptor: [Deamino Arginine Vasopressin]
9. MeSH descriptor: [Antidiuretic Agents]
10. MeSH descriptor: [Diuretics]
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. MeSH descriptor: [Nocturia]
13. (nocturia OR nycturia):ti,ab,kw
14. ("nocturnal polyuria" OR "nocturnal diuresis"):ti,ab,kw
15. #12 OR #13 OR #14
16. MeSH descriptor: [Urination Disorders]
17. MeSH descriptor: [Urination]

18. MeSH descriptor: [Lower Urinary Tract Symptoms]
19. ("lower urinary tract symptoms" OR LUTS OR prostatism OR micturition):ti,ab,kw
20. #16 OR #17 OR #18 OR #19
21. (nocturnal OR nocturia OR nycturia OR night*):ti,ab,kw
22. #20 AND #21
23. #15 OR #22
24. #11 AND #23
25. ((women NOT men) OR (female* NOT male*)):ti,ab,kw
26. #24 NOT #25
27. MeSH descriptor: [Male]
28. #24 AND #27
29. #26 OR #28
30. ((child* OR adolescen* OR infant* OR teen*) NOT adult):ti,ab,kw
31. #29 NOT #30
32. MeSH descriptor: [Adult]
33. #29 AND #32
34. #31 OR #33

Appendix 3. MEDLINE (via Ovid) search strategy

1. desmopressin.tw
2. desmopressine.tw
3. (minirin OR minurin).tw
4. (DDAVP OR stimulate).tw
5. ("1-Desamino-8-arginine Vasopressin" OR "1-Deamino-8-D-arginine Vasopressin").tw
6. (nocutil OR desmospray OR desmogladen OR wetirin).tw
7. ("deamino arginine vasopressin" OR "desamino arginine vasopressin").tw
8. exp Deamino Arginine Vasopressin/
9. exp antidiuretic agents/ OR exp diuretics/
10. OR/1-9
11. exp Nocturia/
12. (nocturia OR nycturia).tw
13. ("nocturnal polyuria" OR "nocturnal diuresis").tw
14. OR/11-13
15. exp Urination Disorders/
16. exp Urination/
17. exp Lower Urinary Tract Symptoms/

18. ("lower urinary tract symptoms" OR LUTS OR prostatism OR micturition).tw

19. OR/15-18

20. (nocturnal OR nocturia OR nycturia OR night\$).tw

21. 19 AND 20

22. 14 OR 21

23. 10 AND 22

24. 23 NOT ((women NOT men) OR (female\$ NOT male\$)).tw

25. 23 AND male/

26. 24 OR 25

27. 26 NOT ((child\$ OR adolescen\$ OR infant\$ OR teen\$) NOT adult).tw

28. 26 AND adult/

29. 27 OR 28

Appendix 4. Embase (via Ovid) search strategy

1. exp desmopressin/

2. (desmopressin OR desmopressine).tw

3. (minurin OR minirin).tw

4. (DDAVP OR stimulate).tw

5. (nocutil OR desmospray OR desmogladen OR wetirin).tw

6. ("1-Desamino-8-arginine Vasopressin" or "1-Deamino-8-D-arginine Vasopressin").tw

7. ("desamino arginine vasopressin" OR "deamino arginine vasopressin").tw

8. "argipressin[1 deamino]"/

9. exp antidiuretic agent/

10. OR/1-9

11. exp nocturia/

12. (nocturia OR nycturia).tw

13. ("nocturnal polyuria" OR "nocturnal diuresis").tw

14. OR/11-13

15. exp micturition disorder/

16. exp micturition/

17. exp lower urinary tract symptom/

18. ("urination disorders" OR urination OR "lower urinary tract symptoms" OR LUTS OR prostatism).tw

19. OR/15-18

20. (nocturnal OR nocturia OR nycturia OR night\$).tw

21. 19 AND 20

22. 14 OR 21

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23. 10 AND 22
24. 23 NOT ((women NOT men) OR (female\$ NOT male\$)).tw
25. 23 AND male/
26. 24 OR 25
27. 26 NOT ((child\$ OR adolescen\$ OR infant\$ OR teen\$) NOT adult).tw
28. 26 AND adult/
29. 27 OR 28

Appendix 5. Scopus search strategy

TITLE-ABS-KEY(desmopressin* OR minirin OR minurin OR DDAVP OR stimate OR "deamino arginine vasopressin" OR "1-Desamino-8-arginine Vasopressin" OR "1-Deamino-8-D-arginine Vasopressin" OR nocutil OR desmospray OR desmogladden OR wetirin OR "deamino arginine vasopressin" OR "desamino arginine vasopressin" OR antidiuretic*) AND TITLE-ABS-KEY(nocturia OR nycturia OR "nocturnal polyuria" OR "nocturnal diuresis" OR ((urination OR "lower urinary tract symptoms" OR LUTS OR prostatism OR micturition) AND (nocturnal OR nocturia OR nycturia OR night*))) AND TITLE-ABS-KEY(male OR men OR males) AND TITLE-ABS-KEY(adult*)

Appendix 6. Google Scholar search strategy

allintitle: (desmopressin OR minirin OR DDAVP OR +stimate OR "deamino arginine vasopressin")(nocturia OR nycturia OR "nocturnal polyuria" OR "nocturnal diuresis")(men OR male OR males)

Appendix 7. Web of Science search strategy

1. TS=(desmopressin* OR minirin OR minurin OR DDAVP OR stimate OR "deamino arginine vasopressin" OR "1-Desamino-8-arginine Vasopressin" OR "1-Deamino-8-D-arginine Vasopressin" OR nocutil OR desmospray OR desmogladden OR wetirin OR "deamino arginine vasopressin" OR "desamino arginine vasopressin" OR antidiuretic*)
2. TS=(nocturia OR nycturia OR "nocturnal polyuria" OR "nocturnal diuresis")
3. TS=((urination OR "lower urinary tract symptoms" OR LUTS OR prostatism OR micturition) AND (nocturnal OR nocturia OR nycturia OR night*))
4. #2 OR #3
5. #1 AND #4
6. TS=((women NOT men) OR (female* NOT male*))
7. #5 NOT #6
8. TS=((child* OR adolescen* OR infant* OR teen*) NOT adult*)
9. #7 NOT #8

Appendix 8. Western Pacific Region Index Medicus search strategy

1. All:desmopressin
2. All:desmopressine
3. All:minirin
4. All:minurin
5. All:DDAVP
6. All:stimate
7. All:"1-Desamino-8-arginine Vasopressin"
8. All:"1-Deamino-8-D-arginine Vasopressin"
9. All:nocutil

10. All:desmospray
11. All:desmogladen
12. All:wetirin
13. All:"deamino arginine vasopressin"
14. All:"desamino arginine vasopressin"
15. MeSH:Deamino Arginine Vasopressin
16. MeSH:antidiuretic agents
17. MeSH:diuretics
18. #17 or #16 or #15 or #14 or #13 or #12 or #11 or #10 or #9 or #8 or #7 or #6 or #5 or #4 or #3 or #2 or #1
19. MeSH:Nocturia
20. All:nocturia
21. All:nycturia
22. All:"nocturnal polyuria"
23. All:"nocturnal diuresis"
24. #23 or #22 or #21 or #20 or #19
25. MeSH:Urination Disorders
26. MeSH:Urination
27. MeSH:Lower Urinary Tract Symptoms
28. All:"lower urinary tract symptoms"
29. All:LUTS
30. All:prostatism
31. All:micturition
32. #31 or #30 or #29 or #28 or #27 or #26 or #25
33. All:nocturnal
34. All:nocturia
35. All:nycturia
36. All:night*
37. #36 or #35 or #34 or #33
38. #37 and #32
39. #38 or #24
40. #39 and #18
41. All:((women NOT men) OR (female* NOT male*))
42. #40 NOT #41
43. MeSH:male
44. #40 and #43

45. #42 or #44

46. All:((child* or adolescen* or infant* or teen*) not adult)

47. #45 NOT #46

48. MeSH:adult

49. #45 and #48

50. #47 or #49

Appendix 9. ClinicalTrials.gov search strategy

Condition: nocturia OR nycturia OR "nocturnal polyuria" OR "nocturnal diuresis" OR ((urination OR "lower urinary tract symptoms" OR LUTS OR prostatism OR micturition) AND (nocturnal OR nocturia OR nycturia OR night*))

Intervention/Treatment: desmopressin* OR minirin OR minurin OR DDAVP OR stimulate OR "deamino arginine vasopressin" OR nocutil OR desmospray OR desmogladen OR wetirin OR "deamino arginine vasopressin" OR "desamino arginine vasopressin" OR antidiuretic*

Applied filters: Male, Adult (18-65) or Senior (66+)

Appendix 10. WHO ICTRP search strategy

Condition: nocturia OR nycturia OR nocturnal polyuria OR nocturnal diuresis

Intervention: desmopressin OR minirin OR minurin OR DDAVP OR stimulate OR deamino arginine vasopressin OR nocutil OR desmospray OR desmogladen OR wetirin OR deamino arginine vasopressin OR desamino arginine vasopressin OR antidiuretic

Recruitment status: All

FEEDBACK

Ferring Pharmaceuticals (Dr. Kristian Vinter Juul), 5 January 2018

Summary

We were interested to read the recent Cochrane systematic review entitled “Desmopressin for treating nocturia in men” by Han et al. (2017). However, we are compelled to draw attention to three areas where the available data on desmopressin orally disintegrating tablet (ODT) from the NOCDURNA® trial programme are either misrepresented or inexplicably omitted. In light of these issues, we consider the authors’ conclusions highly questionable.

1. Weiss et al. (Weiss 2013) efficacy data not included in the efficacy analysis:

Ferring’s pivotal Phase III study of low-dose (50/75 µg) desmopressin ODT in men (Weiss 2013) is referred to in the text as being one of the fourteen studies included in the analyses, and yet appears to be totally excluded from the analysis of data on short-term (<3 months) efficacy of desmopressin versus placebo (evaluated in terms of reduction in number of nocturnal voids). No explanation of this omission is given. This is also true for the subgroup analyses according to dose and formulation. This omission weakens the review because it does not use relevant, pivotal data from the NOCDURNA® trial programme, which appears to fulfil all the inclusion criteria of the review. The study (Weiss 2013) is included in safety analyses, however.

2. Improper dose subgroups:

The review includes subgroup analyses to investigate the effect of dose on efficacy. Results of all doses >1.5µg to <100µg are combined to form a “low dose” category. This therefore incorporates results that were obtained in males randomised to treatment with doses below the 50 µg minimum level recommended for men in the NOCDURNA® label in the dose-finding studies Weiss et al. (Weiss 2012b)- referred to as (Weiss 2012b) in the Cochrane review - and Yamaguchi et al. (Yamaguchi 2013). Consequently, the Cochrane analysis pools data from below recommended dose levels with data from the effective dose for desmopressin ODT. The authors’ conclusion that low dose desmopressin (>1.5 µg to <100 µg) demonstrates a mean difference in number of voids versus placebo of -0.42 (95% CI -1.36 to 0.52) therefore includes a large proportion of patients known to be on a dose below that recommended in the label.

3. Erroneous data used

The use of the (Yamaguchi 2013) study in the review contains several errors, including:

a. In analysis 1.1 (p83) showing desmopressin efficacy according to formulation, the Yamaguchi study (which is one of only two included for desmopressin ODT) is presented as demonstrating a reduction of 1.7 voids/night for placebo – this is incorrect, as the reduction

reported in the publication is in fact 10 times lower (0.17 voids). Presumably, this will have contributed greatly to the authors' findings that desmopressin ODT shows no difference in nocturnal void reduction compared with placebo (mean difference 0.08 [-0.45, 0.61]).

This error is repeated in analysis 1.3 (p85), where studies are grouped according to nocturnal polyuria status of patients.

b. In Table 2, showing "participant disposition" (p111), the Yamaguchi study ([Yamaguchi 2013](#)) is presented as having an alpha blocker (alfuzosin) comparator arm and lasting for 3 months. On the contrary, this study had no alpha blocker arm and was a one month trial.

It is concerning that this Cochrane review of evidence for the treatment of nocturia in men with desmopressin lacks the scientific rigour one would expect. In particular, the limitations as described above lead the authors to a number of unjustified conclusions which underestimate the benefit conferred by desmopressin in general, and by low-dose desmopressin ODT used at recommended levels (50 µg in men) in particular.

(Summary of comments from Ferring Pharmaceuticals (Dr. Kristian Vinter Juul), 05 January 2018)

Reply

Thank you very much for your comments that we welcome. We have addressed these line by line below and also made changes to the review, which will be republished.

1. Initially, we did not include these results in the analysis since the study ([Weiss 2013](#)) did not report the SDs for each group. However, we have since been able to calculate these based on Table 3.

2. Thank you for your comments on this issue. Our analyses followed an a priori protocol which underwent peer review. Therefore, we would keep it as is. However, in response to your comment we have added a sensitivity analysis that includes the very low doses from the pooled effect sizes estimates.

3a. This was an indeed an error on our part. -0.17 is the correct value. We have revised the review accordingly.

3b. As mentioned, Yamaguchi 2013 ([Yamaguchi 2013](#)) did indeed not have alfuzosin group as a comparator. We have corrected this issue, which however, has no implications for the analyses.

While we are happy to acknowledge some minor shortcomings of the published review (as detailed above) we respectfully disagree with this global assessment of our review. We sought clarification from Ferring during the review process but our efforts to obtain more information about these studies were unsuccessful. We look forward to enhanced collaboration on such matters when the time comes to update this review.

(Summary of response from Philipp Dahm and co-authors)

Contributors

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WHAT'S NEW

Date	Event	Description
23 May 2018	Feedback has been incorporated	Added feedback from Ferring Pharmaceuticals and point-by-point responses by authors.

HISTORY

Protocol first published: Issue 1, 2016

Review first published: Issue 10, 2017

Date	Event	Description
10 May 2018	Amended	In response to feedback received, minor errors and omissions were addressed and an additional sensitivity analysis was added.

CONTRIBUTIONS OF AUTHORS

PD, JH, and MHE: responsible for the conception of the protocol.

CJB: responsible for developing the search strategy and for undertaking the searches.

JH and JHJ: responsible for obtaining copies of trials.

PD, JH, and JHJ: responsible for screening records against the eligibility criteria and appraising risk of bias and the quality of evidence.

JH and JHJ: responsible for extracting data.

JH, JHJ, and MHE: responsible for carrying out the analysis.

PD, JH, and JHJ: responsible for interpreting the analysis.

PD, JH, JHJ, and MHE: responsible for drafting and updating the final review.

DECLARATIONS OF INTEREST

JH: none known.

JHJ: none known.

CJB: none known.

MHE: none known.

PD: none known.

SOURCES OF SUPPORT

Internal sources

- Departmental, USA.

External sources

- No sources of support provided, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol ([Han 2016](#)); differences from this protocol are described here.

- We changed the title to focus on men with nocturia (August 2017), and revised the [Background](#) section accordingly to reflect this modified focus.
- We revised the definition of nocturia to be one or more voids per night.
- We added detailed methods and defined clinically important differences for outcome measurement in the 'Method and timing of outcome measurement' section.
- We added additional subgroup analyses based on the routes of administration of desmopressin and the presence or absence of nocturnal polyuria. We also subdivided the dose into three groups.
- We added additional sensitivity analyses by considering the clinically recommended dose level for desmopressin, excluding the studies with a dose of desmopressin that was less than clinically recommended.
- In accordance with Cochrane Urology guidance, we limited sensitivity and subgroup analyses to the primary outcomes only.

NOTES

We have based parts of the [Methods](#) section of this review on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by Cochrane Urology.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-Antagonists [therapeutic use]; Antidiuretic Agents [adverse effects] [*therapeutic use]; Cholinergic Antagonists [therapeutic use]; Deamino Arginine Vasopressin [adverse effects] [*therapeutic use]; Drug Therapy, Combination; Nocturia [*drug therapy]; Quality of Life; Randomized Controlled Trials as Topic; Withholding Treatment

MeSH check words

Aged; Humans; Male; Middle Aged