Drug Evaluation

Desmopressin for the treatment of adult nocturia

Hashim Hashim[†] & Paul Abrams

[†]Author for correspondence Bristol Urological Institute, Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB, UK Tel.: +44 117 959 5690 Fax: +44 117 950 2229 hashim@doctors.org.uk

Keywords: α-blockers, antimuscarinics, desmopressin, hyponatremia, nocturia, nocturnal polyuria, pharmacodynamics, pharmacokinetics, quality of life, vasopressin

future part of fsg

Nocturia is a bothersome and prevalent condition. It affects men and women equally, with an increasing incidence with age. It has multifactorial etiology and therefore treatment is based on an accurate history and examination with an assessment that should include frequency/volume charts and quality-of-life questionnaires. Treatment is primarily aimed at the etiology and may include referral to an appropriate specialist for administration of specific treatments. Initial treatment is based on lifestyle advice including fluid manipulation. If nocturia is of polyuric origin and is caused by a disturbance in the vasopressin system, the only efficacious medical treatment available with a good level of evidence is desmopressin. This review will look at the pharmacology of desmopressin and will review the evidence in the literature that would support its use in nocturia. Sometimes combination therapy with antimuscarinics and α -blockers may be required to control nocturia secondary to storage and voiding problems associated with nocturnal polyuria; however, no trials have actually looked into this concept to date.

Nocturia is the complaint that an individual has to wake up one or more times to void. Nocturia includes any number of voids and any time during the night, but the person must be asleep and wakes up before voiding and goes back to sleep after voiding [1]. It is the most prevalent storage lower urinary tract symptom (LUTS), almost equally affecting men (48.6%) and women (54.5%) and increasing with age. It is approximately four-times more common than other storage symptoms (frequency, urgency and incontinence) [2]. If the definition of 'significant' or bothersome nocturia is a minimum of two voids per night, the prevalence of nocturia would be reduced substantially in both men (20.9%) and women (24%) but still remains the most common storage LUTS [2].

It has been found that 67% of males [3] and 63% of females [4] find nocturia (≥2 voids/night) bothersome. It negatively affects quality of life (QoL) by causing lack of sleep that can result in excessive daytime sleepiness, mood changes, cognitive dysfunction leading to poor concentration and performance, impaired intellectual functions, endocrine changes (prolactin and cortisone) and car accidents [5,6]. Lack of sleep results in low energy levels that can increase indirect and intangible costs to society through decreased productivity at work and more sick-leave being taken. This impairment seems to increase as the number of voids per night increases [7]. There is also an increased risk of hip fractures in patients suffering with nocturia, which increases health service costs [8].

Nocturia has a multifactorial etiology (Box 1) and patients often have a combination of factors contributing to their nocturia, but they often present to urologists first. It is important to accurately assess the cause of the nocturia (Figure 1) as treatment is aimed at the underlying pathology. This should include a detailed history and thorough physical examination. Initial screening should include urinalysis, a 3-day frequency/volume chart (FVC) and a QoL questionnaire, such as the International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N) [9]. The FVC forms is an indispensable part of the assessment of patients with nocturia and without it, it is not possible to identify those patients with polyuria (nocturnal or 24-h). Free urinary flow rate and postvoid residual will also need to be performed.

Overview of the current available treatments for nocturia *Conservative treatment*

Conservative treatment in the form of fluid manipulation and lifestyle advice is first-line therapy in patients suffering with nocturia. Lifestyle advice includes emptying the bladder before going to bed. Fluid manipulation includes reducing fluid intake approximately 4 h prior to bedtime, for example caffeine and/or alcohol, and limiting excessive fluid-containing foods, such as fruits and vegetables, prior to bedtime. In those with dependent peripheral edema, the patient should be advised of the advantages of exercise, leg elevation above heart level in the afternoon and compression stockings. All these treatments can be effective and they are logical, cheap and easy to perform; however, there is no level 1 evidence to support their use.

If conservative therapy fails to control symptoms, patients are encouraged to return for further evaluation and medical therapy may need to be initiated. Obviously, if patients do not drink fluid before going to bed, do not eat fluid-containing foods in the evening, empty their bladders before going to sleep at night or

Box 1. Etiology of nocturia.

Natural

- Noise inside and outside the house (e.g., crying children)
- Light inside or outside the house
- Partner snoring or moving in bed

Behavioral

- Timing of food eaten and fluid drunk at night
- Type of food eaten and fluid drunk at night

Urological (causing bladder storage/voiding problems)

- Detrusor overactivity
 - Idiopathic
 - Neuroaenic
- Bladder-outlet obstruction with postvoid residual
- Detrusor underactivity with postvoid residual

Gynecological

- Estrogen deficiency
- Pelvic organ prolapse

Medical (causing nocturnal or 24-h polyuria)

- Diabetes insipidus
- Diabetes mellitus
- Congestive cardiac failure
- Chronic obstructive pulmonary disease
- Autonomic dysfunction
- Renal insufficiency
- Neurological problems (e.g., dementia and Parkinson's disease)
- Medications (e.g., β-blockers, diuretics and corticosteroids)
- Pain

Primary sleep disorders

- Obstructive sleep apnea
- Periodic legs syndrome
- Restless leg syndrome
- Parasomnias
- Insomnia

Psychological/psychiatric

- Stress
- Anxiety
- Depression

do not suffer with edema, medical therapy can be initiated on the first visit as there are no conservative treatments that need to be followed. Patients suffering with sleep problems, such as sleep apnea or severe snoring, should be referred to a sleep specialist for further evaluation. Similarly, those suffering with medical, neurological or psychological problems should be referred to the appropriate specialist for further evaluation and treatment of the underlying pathology.

Antimuscarinics

Antimuscarinics are the mainstay of treatment of patients with overactive bladder (OAB) syndrome. The prevalence of nocturia in OAB patients is 84% [10]. Solifenacin [11], tolterodine extended-release [12,13] and trospium chloride [14] may help with nocturia, and even though results from some clinical trials report statistical significance, the clinical significance of these reductions is questionable, probably because other causes for nocturia have not been correctly identified and treated, such as nocturnal polyuria [15]. For example, of 76% women with nocturia $(\geq 2 \text{ voids/night})$ have nocturnal polyuria [16].

Nocturia, due to nocturnal polyuria, was inadequately treated in OAB patients receiving solifenacin monotherapy both at the 5- and 10mg dose compared with placebo. In those patients who did not have nocturnal polyuria, there was a statistically significant difference in reduction of nocturia with solifenacin compared with placebo (although not clinically significant; -0.6 mean reduction on drug vs -0.4 mean reduction on placebo from baseline) [10].

α -blockers

Many patients with benign prostatic obstruction (BPO) have symptoms related to voiding difficulties but can have increased daytime frequency and nocturia, which may be due to incomplete bladder emptying. In total, 71% of patients with BPO have nocturia [17]. The main treatments for patients with BPO are *a*-blockers and 5α -reductase inhibitors (5ARIs) to treat the obstructive component, both of which have limited effects on nocturia and 5ARIs take at least 3-6 months to start working and have any effect on voiding symptoms.

Tamsulosin (α -blocker) had insignificant effect (p = 0.198) on the hours of undisturbed sleep (the time from falling asleep to the first awakening to void), with an increase from baseline of 81 versus 60 min for placebo. Similarly, tamsulosin only (p = 0.099) reduced nocturia by one



nocturnal void versus 0.7 by placebo. So, objectively, tamsulosin had no significant effects. However, subjectively, tamsulosin significantly reduces (p = 0.028) the International Prostate Symptom Score (IPSS) nocturia domain by 57% (mean change of -1.1 from baseline) compared with placebo (mean change -0.7 from baseline) and significantly improves the IPSS QoL question (mean change -2.0 from baseline) by 54% compared with placebo (mean change -1.3 from baseline) [18]. The objective differences are disappointing due to the fact that nocturnal polyuria is a principal cause of nocturia in up to 70% of cases [19]. It is in these patients with nocturnal polyuria that α -blockers would not work. In one study, 85.4% of patients receiving tamsulosin still complained of nocturia due to nocturnal polyuria [20].

It is therefore important to rule out nocturnal polyuria in all patients with nocturia, as the otherwise standard, and relatively effective, medications for OAB and BPO will not be effective and even if they are statistically effective, they do not seem to produce clinically significant improvements.

Other pharmacotherapeutic agents

Other treatments for nocturia and nocturnal polyuria that have been recommended are loop diuretics (level 2 evidence, grade C recommendation), for example, furosemide 40 mg [21] or bumetanide 1 mg [22] administered 6 h before bedtime. Estrogens in postmenopausal women have also been used in uncontrolled trials with some benefit after 6 months of therapy [23]. Melatonin has also been used but with very little benefit [24].

Therefore, the above medications do not provide adequate treatment of nocturia and nocturnal polyuria. Desmopressin acetate, administered orally, is currently the only medication available for effectively treating nocturia and nocturnal polyuria. The International Consultation on Incontinence have given desmopressin a level 1 evidence and grade A recommendation in the treatment of nocturia and nocturnal polyuria in adults aged under 65 years and grade B recommendation in those aged over 65 years [25,26].

What is desmopressin?

Desmopressin is 1-desamino-8-D-arginine vasopressin monoacetate, trihydrate. It is a synthetic analogue of 8-arginine vasopressin (AVP), the natural antidiuretic hormone found in all mammals except pigs, which increases renal water concentration by acting on V2-aquaporin receptors in the kidney and promoting osmotic reabsorption of solute-free water in the collecting tubules. The structure of vasopressin was determined in the early 1950s [27–29] and it was not until the late 1960s that the first vasopressin analogue was synthesized [30–32]. The aim was to have a metabolically stable but potent antidiuretic. Initial studies conducted in the 1960s and then in Scandinavia [33,34], Europe [35] and the USA [36] in the 1970s led to desmopressin being licensed as the treatment of choice for central diabetes insipidus.

In 1977–1978, desmopressin was first registered for use in nocturnal enuresis [37,38] and in the early 1980s it was found that there was a lack of nocturnal vasopressin in bedwetting children [39,40], and from then on desmopressin became an established treatment for nocturnal enuresis.

In the early 1980s, desmopressin was used offlicense in the treatment of adult nocturia [41]. It was not until 1991 that desmopressin was first licensed in the UK for the treatment of nocturnal polyuria and nocturia in patients with multiple sclerosis [42–49]. It has also been used for nocturia in patients suffering with Parkinson's disease [50]. In 2001, it first became licensed in Panama and Finland for the treatment of nocturia and since then desmopressin has been licensed for this indication in many countries around the world.

Chemistry

The molecular formula of desmopressin is $C_{46}H_{64}N_{14}O_{12}S_2$ and the molecular weight is 1069.22 g/mol. The basic amino acid arginine in position 8 confers antidiuretic activity (Figure 2). There is a disulfide bond forming a bridge between positions 1 and 6 resulting in a ring that is integral to the biological activity of the molecule. Four sites of cleavage, which are affected by a variety of enzymes, have been identified: positions 1–2, 7–8, 8–9 and the



disulfide bond making this molecule more stable $(t_{\frac{1}{2}} \text{ of approximately 3 h})$ than the natural AVP $(t_{\frac{1}{2}} \text{ of approximately 3 min})$.

The physiological effects of desmopressin have resulted because of two structural alterations. The first is by omitting the amino group at position 1 in the N-terminal and the second is by replacing L-arginine with its D-arginine enantiomer at position 8 (Figure 2), hence the name 1-desamino-8-D-arginine vasopressin acetate (DDAVP). This has resulted in an analogue that has an increased antidiuretic potency by approximately ten-times more than endogenous AVP (due to desamination at position 1) and a reduction in vasoconstriction (pressor) effects by approximately 1500-times (due to D-arginine).

Desmopressin is an odorless, tasteless, white, lipophilized powder, which is soluble in water, ethanol and acetic acid. The tablets contain the inactive ingredients lactose, potato starch, magnesium stearate and povidone.

There are generic forms of desmopressin available, mainly in the USA; however, these are not widely available and the main company producing desmopressin is Ferring Pharmaceuticals A/S (Lausanne, Switzerland). It is marketed by Ferring as DDAVP[®], Minirin[®]; Desmotabs[®], Desmospray[®], Octim[®] and others, depending on the formulation and country of license.

Pharmacokinetics

Desmopressin can be administered parenterally (intravenously, subcutaneously and intramuscularly), intranasally or by oral or sublingual lyophilisates (Table 1). We will only discuss the pharmacokinetics of the oral forms.

Desmopressin enters plasma 15–30 min following oral administration [51]. The bioavailability of the oral route ranges between 0.1 [51] and 1.0% [52], with 0.3% being the most widely quoted figure. The bioavailability depends on the dose and formulation used and is different in different parts of the gastrointestinal tract, being highest in the upper tract compared with the lower tract [53]. The bioavailability of oral tablets is approximately 5% compared with intranasal desmopressin, approximately 0.16% compared with intravenous desmopressin, and 0.26% compared with the sublingual formulation.

The median time to reach maximum concentration (T_{max}) after oral administration is 1.5 h (range 1.0–4.1) at night and 1.5 h during the daytime (range 0.5–3.0), and the terminal half-life is 3.1 h at night and 2.8 h in the daytime (p = 0.02) [54]; these are dose independent. In

Table 1. Pharmacokinetics of the different desmopressin formulations.							
	Intravenous	Intranasal	Oral tablet	Oral 'Melt'			
Maximum daily doses	0.001–0.004 mg	0.01 mg, 0.02 mg, 0.04 mg	0.1 mg, 0.2 mg, 0.4 mg	0.06 mg, 0.12 mg, 0.24 mg			
Peak levels	Biphasic	Biphasic	Monophasic	Monophasic			
t _{1/2}	<10 mins (fast) 51–158 mins (slow)	7.8 mins (fast) 75.5 (slow)	1.5–2.5 h	2.8–3 h			
T _{max}	N/A	1.5 h	0.9–1.5 h	0.5–2.0 h			
Terminal half-life	N/A	3 h	2–3.11 h	2.8 h			
Bioavailability	N/A	5–10%	0.08–0.16%	0.28%			

N/A: Not available.

Adapted from [101,102].

another study, the terminal half-life of elimination was 2.97 ± 0.24 h, while the clearance was 1.77 ± 0.10 ml/min/kg and the volume of distribution at steady state was 373 ± 30 ml/kg [55]. The rate and extent of absorption of desmopressin is reduced by 40% if concomitantly administered with food and delayed if administered within 90 min of having a meal, but the antidiuretic action of the drug is not affected, at least for the first 3 h following desmopressin administration [56].

The new sublingual 'Melt' is an improved oral formulation of desmopressin, which, in contrast to the tablets, can be taken without water and has improved compliance since many children and some adults prefer not to swallow tablets.

Desmopressin does not enter the intracellular compartment and therefore its apparent volume of distribution is relatively small (0.2 l/kg) and it does not cross the blood–brain barrier [57,58].

Desmopressin is excreted in the urine [51] with a renal clearance of 0.8 ml/min/kg. The total clearance of desmopressin is 2.6 ml/min/kg body weight [59] and approximately 65% of the amount of desmopressin absorbed after oral administration could be recovered in the urine within 24 h. The remaining 35% is metabolized by enzymatic degradation.

No significant amount of desmopressin is metabolized *in vitro* in human liver microsome preparation studies and therefore *in vivo* human liver metabolism is unlikely to occur.

Pharmacodynamics

The pharmacodynamic effects of oral desmopressin given in the daytime are similar between men and women during the first 6 h after dosing and then recede after 6 h [54]. There is a significant increase in urine osmolality with desmopressin administration and decrease in urine production [51]. There is no lessening of effect in patients treated with tablets for 12–44 months and no detection of serum antibodies to desmopressin.

There is a lack of information on pharmacodynamic and pharmacokinetic relations in adult nocturia patients, at different ages, as opposed to pediatric bedwetting. However, the dynamic differences in these patients could possibly be explained by the differences in safety profile between the young and elderly.

In the oral formulation, women obtain significantly higher plasma desmopressin concentration than men (p = 0.0012) and more adverse events. There is no correlation between plasma desmopressin at 2 h after dosing and the withinpatient response in any of the effect variables, but the number of nocturnal voids and nocturnal diuresis were half that with placebo. The time to the first nocturnal void is almost doubled compared with placebo [60].

Like vasopressin, desmopressin can increase concentrations of factor VIII:C, factor VIII:Ag and plasminogen activator; however, the dosages required to stimulate the coagulation factors are ten-times higher than the antidiuretic ones. Desmopressin in higher dosages has been licensed worldwide for the hematological indications of hemophilia and von Willebrand disease.

Clinical efficacy in nocturia

Oral desmopressin has been shown to be effective in the treatment of vasopressin-sensitive cranial diabetes insipidus and in nocturnal enuresis in children and adults. Following an extensive clinical trials program, in 2002, oral desmopressin became licensed for the treatment of nocturia in adults in many countries around the world (see Regulatory affairs section).

DRUG EVALUATION - Hashim & Abrams

Table 2. Sun	nmary of Phase	e II and Phase III trials co	onducted using desmop	oressin among adults wit	h nocturia.	
Study	Study population	Design	Treatments	Primary end point	Key findings (including secondary end points)	Ref.
Phase II						
Asplund et al.	17 men, 6 women (mean age: 68.1 years)	Open-label dose-titration study	Oral desmopressin 0.1, 0.2 and/or 0.4 mg at bedtime for 3 weeks	Effect on nocturnal diuresis	Significant decrease in nocturnal diuresis from 1.6 ml/min before treatment to 1.1 ml/min using 0.1 mg. Further decrease to 0.9 ml/min using 0.2 mg dose and 1.0 ml/min using 0.4 mg	[62]
Asplund et al.	12 men, 5 women (mean age: 67.7 years)	Randomized, double- blind, crossover exploratory study	Oral desmopressin 0.1, 0.2 or 0.4 mg for 2 weeks and placebo for 2 weeks	Effect on nocturnal diuresis compared with placebo	Desmopressin resulted in lower nocturnal diuresis; no change in 24-h diuresis; increase in time to first void after sleeping; increase in longest duration of sleep between voids, compared with placebo	[63]
Phase III						
Mattiasson <i>et al.</i> NOCT 2A	86 men on desmopressin, 65 on placebo	Open-label dose titration for 3 weeks followed by double-blind, placebo- controlled, randomized trial	Oral desmopressin 0.1, 0.2 or 0.4 mg for 3 weeks or placebo for 3 weeks	Proportion of patients who had ≥50% reduction in mean number of nocturnal voids after treatment compared with baseline	34% of patients on desmopressin had \geq 50% reduction in number of nocturnal voids. Desmopressin caused 43% reduction in mean number of nocturnal voids; 59% increase in mean duration of the first sleep period; 36% decrease in mean nocturnal diuresis	[69]
Lose <i>et al.</i> NOCT 3A	72 women on desmopressin, 72 on placebo	Open-label dose titration for 3 weeks followed by double-blind, placebo- controlled, randomized trial	Oral desmopressin 0.1, 0.2 or 0.4 mg for 3 weeks or placebo for 3 weeks	Proportion of patients who had ≥50% reduction in mean number of nocturnal voids after treatment compared with baseline	46% of patients on desmopressin had ≥50% reduction in number of nocturnal voids. Desmopressin caused 46% reduction in mean number of nocturnal voids; 78% increase in mean duration of the first sleep period; 46% decrease in mean nocturnal diuresis	[70]
Kerrebroeck <i>et al.</i> NOCT 4	61 ondesmopressin,66 on placebo,men andwomen	Open-label dose titration for 3 weeks followed by double-blind, placebo- controlled, randomized trial	Oral desmopressin 0.1, 0.2 or 0.4 mg for 3 weeks or placebo for 3 weeks	Proportion of patients who had ≥50% reduction in mean number of nocturnal voids after treatment compared with baseline	33% of patients on desmopressin had ≥50% reduction in number of nocturnal voids. Desmopressin caused 39% reduction in mean number of nocturnal voids; 100% increase in mean duration of the first sleep period	[71]
Lose <i>et al.</i> NOCT 2B/3B	95 men, 85 women from NOCT 2A and NOCT 3A	Open-label long-term study	Oral desmopressin 0.1, 0.2 or 0.4 mg for 10 or 12 months	Mean number of nocturnal voids	Males: Mean number of nocturnal voids was 1.3–1.6; increase from 37 to 52% at 10 months and 67% at 12 months in number showing ≥50% decrease in the number of voids; mean duration of first sleep period was 281 mins at 10 months and 288 mins at 12 months Females: Mean number of nocturnal voids was 1.2–1.3; increase from 46 to 66% at 10 months and 67% at increase from 46 to 66% at 10 months and 67% at 12 months in number showing ≥50% decrease in the number of voids; mean duration of first sleep period was 307 mins at 10 months and 310 mins at 12 months	[72]

Phase I studies

Results from these studies were discussed previously in the Pharmacokinetic and Pharmacodynamic sections.

Phase II studies

In Phase II, there were two randomized, controlled studies in 103 patients with nocturia. The first was a double-blind, randomized, 4-week study in 80 healthy women with nocturia who were randomized into one of four parallel groups receiving oral desmopressin 0.2, 0.4 or 0.8 mg or placebo [61]. This trial showed no significant differences between the four groups regarding the change in mean number of nocturnal voids and mean number of 24-h voids. However, 78% of the subjects felt they had an improvement in nocturia. No serious adverse events occurred but 15 subjects withdrew due to an adverse event. There was no increase in body weight or blood pressure. Three patients had a reduction in sodium levels that returned to normal spontaneously and the patients continued on the trial.

The second Phase II trial (Table 2) was a dosetitration study [62] in 23 healthy subjects (17 men, 6 women) aged 60-74 years (mean age: 68.1 years) with two or more nocturnal voids and nocturnal urinary output of greater than or equal to 0.9 ml/min (arbitrarily chosen). There was a run-in week to establish baseline, which was followed by an open dose-titration week for each dose (0.1, 0.2 and 0.4 mg) of oral desmopressin at bedtime. Subjects were allowed to progress to the next dose if nocturnal diuresis was 0.5 ml/min or greater. If they did not progress to the next dose, they remained on the same dose for the trial period (total 3 weeks). Nocturnal diuresis decreased significantly from 1.6 ml/min before treatment to 1.1 ml/min after treatment with desmopressin 0.1 mg. The 0.2 mg dose resulted in a further decrease to 0.9 ml/min but the 0.4 mg dose did not result in a further decrease (1.0 ml/min). Those with a higher pre-treatment nocturnal diuresis experienced a more marked reduction in urine volume. There were no serious adverse events. One patient discontinued the study due to experiencing sleeping discomfort and voiding difficulties in the morning. Two occasional findings of slightly lower than normal serum sodium levels were documented but were of no clinical significance.

The 23 patients that entered the previous trial were offered to enter a double-blind, crossover study comparing oral desmopressin with placebo [63]. A total of 17 subjects (12 men, 5 women) entered the trial following a washout period of 1–2 weeks. Subjects received the dose selected during titration for 2 weeks followed by placebo for 2 weeks or vice versa. Desmopressin resulted in statistically significant lower nocturnal diuresis (1.0 vs 1.6 ml/min on placebo) and fewer nocturnal voids (1.1 vs 1.7 on placebo) but with no change in 24-h diuresis (1.3 vs 1.4 on placebo). Time to first void after sleeping (4.7 h on desmopressin vs 3.3 h on placebo) and the longest duration of sleep between voids (5.4 h on desmopressin vs 4 h on placebo) were longer on desmopressin compared with placebo.

A few other trials have been conducted to see if desmopressin affected nocturia but these were nonrandomized, open-label studies [64–67] or used intranasal desmopressin [68]. The Phase I/II studies demonstrated that in healthy subjects with nocturia, oral desmopressin:

- Reduces overnight urine production
- Increases urine osmolality
- Reduces the number of nocturnal voids

Essentially, the Phase I/II studies established the pharmacokinetic and pharmacodynamic parameters for oral desmopressin tablets and supported the Phase III program to investigate desmopressin tablets once-daily, at bedtime, for the treatment of nocturia in adults.

Phase III studies

Phase III studies (Table 2) comprised three shortterm, large-scale, multicenter, randomized, double-blind, placebo-controlled studies (one in men, one in women and one in both men and women) and one long-term (<12 months), open, extension study in men and women. These studies are referred to as the NOCTUPUS trials and their aim was to assess the efficacy and safety of desmopressin tablets in nocturia.

The three short-term placebo-controlled studies were of identical design (Figure 3) and were designed to identify the most effective dose regimen as well as establishing criteria for selecting those patients most likely to respond safely to desmopressin. Following that, patients participating in the male and female studies were offered the option to continue into the long-term studies designed to demonstrate the safety of desmopressin tablets during open-label treatment for 10 or 12 months.

The study medication in the male (NOCT 2A) [69], female (NOCT 3A) [70] and the combined male and female (NOCT 4) [71] studies



was administered in a similar design to the Phase II study mentioned previously [63]. This design helped to individualize treatment according to patients response. In the initial dose-titration period, patients received oral desmopressin 0.1 mg daily for the first week. This was increased to 0.2 mg daily in week 2 for 7 days, in patients who did not respond during the first dose-titration week. Patients then having no nocturnal voids or a 20% or greater reduction in nocturnal diuresis were maintained on 0.2 mg. The dose was increased to 0.4 mg in the third week in those who did not respond to 0.2 mg (i.e., had less than 20% decrease in nocturnal diuresis). Patients who experienced a less than 20% decrease in nocturnal diuresis at all doses during dose titration were classified as not responding and did not continue in the study. If patients had zero nocturnal voids during a dosetitration week, this was chosen as the optimal dose for the double-blind period. If subjects did not achieve zero nocturnal voids from any of the doses or experienced treatment-related adverse events, the tolerated dose giving the lowest nocturnal diuresis was selected for the double-blind phase. During the dose-titration phase, the optimal dose (the best tolerated dose with the greatest clinical response) for each patient was

established. Patients who did not obtain greater than or equal to 20% reduction in nocturnal diuresis and patients who did not return to 78% or higher of baseline nocturnal diuresis values after the 1-week washout period did not enter the double-blind treatment period and were excluded from the study.

The primary end point was the proportion of patients with 50% or greater reduction in mean number of nocturnal voids. The secondary end points were:

- Change in mean number of nocturnal voids
- Change in mean number of hours of sleep from bedtime until the first nocturnal void
- Change in mean nocturnal diuresis (not in NOCT 4)
- Change in mean ratio of night-time:24-h urine volume and night-time:daytime urine volume (not in NOCT 4)

Adults were included in the trials during the screening week if they had at least two voids per night, with a nocturnal urine production greater than the maximum voided volume (checked using FVCs). Patients were excluded if they had nocturia due to other well-defined causes of increased urinary frequency such as diagnosed or suspected diabetes insipidus, primary polydipsia, neurogenic

bladder dysfunction, urgency incontinence, evidence of estrogen deficiency or significant bladder-outlet obstruction. They were also excluded if serum sodium levels were below the normal range or if they had uncontrolled hypertension, conditions characterized by fluid and/or electrolyte imbalance, such as congestive cardiac failure, or were receiving diuretic treatment. Females who had actual or planned pregnancy were excluded.

In the male study (NOCT 2A), 151 patients entered the double-blind period. A total of 28 patients (34%) in the desmopressin group had fewer than half the number of nocturnal voids relative to baseline compared with two patients (3%) in the placebo group (p < 0.001). The mean number of nocturnal voids decreased by 43% on desmopressin compared with 12% on placebo. The mean duration of the first sleep period increased by 59% (from 2.7 to 4.5 h) on desmopressin compared with 21% (from 2.5 to 2.9 h) on placebo. Mean nocturnal diuresis decreased by 36% on desmopressin but only by 6% on placebo. All other parameters changed significantly (Table 3) in favor of desmopressin versus placebo (p < 0.001).

Quality of life in the NOCT 2A study was assessed by an abbreviated form of the ICS male questionnaire. The degree of bother caused by nocturia and the proportion of patients considering nocturia to be 'quite a problem' or a 'serious problem' decreased in the desmopressin group but remained almost unchanged in the placebo group. A detailed analysis of the results was not presented in the published paper. The female study (NOCT 3A) revealed similar results to the male study (Table 3). QoL in this study was assessed by an abbreviated version of the Bristol female LUTS (BFLUTS) questionnaire during screening and at the end of the study. Bothersomeness caused by nocturia was reduced in both the desmopressin (from 97 to 75%) and placebo groups (from 98 to 84%). The proportion of patients who considered nocturia to be 'quite a problem' or 'a serious problem' was also reduced in the desmopressin (from 73 to 21%) and placebo (from 80 to 52%) groups. There were improvements in bother following treatment of nocturia with desmopressin compared with placebo (p = 0.01).

In the double-blind phase, 144 patients were recruited. In total, 33 patients (46%) on desmopressin had a 50% or greater reduction in nocturnal voids from baseline compared with five patients (7%) on placebo (p < 0.0001). The mean number of nocturnal voids reduced by 46% on desmopressin compared with 17% on placebo. All other secondary variables changed significantly in favor of desmopressin versus placebo (p < 0.0001).

In the combined male and female study (NOCT 4) [72], 127 adult men and women aged 18 years or over were recruited. A total of 20 out of 61 (33%) desmopressin-treated patients compared with seven out of 66 (11%) placebotreated patients showed greater than or equal to 50% reduction in the number of nocturnal voids compared with baseline (p = 0.0014). There was a 39% reduction in nocturnal voids

Table 3. Results of secondary end points in the three short-term Phase III desmopressin studies.							
Variable	NOCT 2A		NOCT 3A		NOCT 4		
	Desmopressin treatment (baseline)	Placebo treatment (baseline)	Desmopressin treatment (baseline)	Placebo treatment (baseline)	Desmopressin treatment (baseline)	Placebo treatment (baseline)	
No. of nocturnal voids	1.7 (3.0)	2.7 (3.2)	1.61 (2.92)	2.36 (2.91)	2.01 (3.26)	2.42 (2.82)	
Duration of first sleep period	270 (160)	174 (150)	272 (142)	181 (144)	247 (139)	196 (156)	
Nocturnal diuresis (ml/min)	0.9 (1.5)	1.5 (1.7)	0.82 (1.51)	1.35 (1.44)	N/M	N/M	
Ratio of nocturnal/24-h urine volume (%)	30.7 (41.6)	43.7 (44.5)	28.3 (41.5)	39.6 (40.7)	N/M	N/M	
Ratio of nocturnal/day urine volume	0.52 (0.84)	0.94 (0.95)	0.49 (0.84)	0.77 (0.79)	N/M	N/M	

N/M: Not measured.

with desmopressin versus 15% with placebo (p < 0.0001). An average of at least 5 h of unbroken first sleep period per night was experienced during the double-blind phase by 27% of patients in desmopressin versus 9% on placebo, with an improvement in the quality of sleep [71].

Quality of life in the NOCT 4 study was assessed by means of two questions. In the first question, the patients were asked, 'During the last week, did you often feel fresh in the mornings when you got up?' and 26.6% of patients on desmopressin improved, compared with only 13.6% on placebo (p = 0.02). In the second question, they were asked, 'During the last week, did you often feel tired during the day?' and 21.6% of patients in the desmopressin group improved compared with 12.1% on placebo (p = 0.14).

The long-term optional extension open-label study (NOCT 2B/3B) included patients who previously responded to desmopressin in NOCT 2A and 3A [72]. They received active treatment with desmopressin tablets orally at bedtime, for 10 or 12 months, using their optimal dose (0.1, 0.2 or 0.4 mg) found during dose titration in the short-term studies. A total of 92% of males (132) from NOCT 2A and 83% of females (117) from NOCT 3A continued in the long-term study. After treatment, patients were followed for a further month (11 or 13 months) to provide data on symptom reversibility. The primary end point was to assess the safety of long-term desmopressin treatment in patients with nocturia who responded during a short-term study. The secondary end point was to evaluate long-term efficacy by assessing the number of nocturnal voids, time from bedtime to the first nocturnal void, night-time duration (time from bedtime until rising in the morning) and the proportion responding (≥50% decrease in the number of nocturnal voids compared with baseline). QoL was assessed using the ICS male or BFLUTS questionnaires.

A total of 95 males (72%) and 87 females (75%) completed the study, including 62 males (47%) and eight females (7%) who completed 11 months and 33 males (25%) and 79 females (68%) who completed 13 months of treatment. Desmopressin was well tolerated during long-term treatment. The frequency and type of adverse events were similar to those in short-term studies (see section on Adverse events). In males, the clinical response increased from 37% at the start of long-term treatment to 52% at 10 months and 67% at 12 months. In

females it was from 46% at the start of the study to 66% at 10 months and 67% at 12 months. The results were affected by the number of patients withdrawing from the study. The number of nocturnal voids was decreased throughout the study in males to 1.3–1.6 from a baseline of 3.1 and in females from 2.9 to 1.2–1.3. After the 1-month follow-up, the number of nocturnal voids increased following cessation of treatment.

The mean duration of the first sleep period gradually increased in males from 157 mins at baseline to 288 min at 12 months and in females from 142 at baseline to 310 min at 12 months. After follow-up, the mean duration of the first sleep period decreased, confirming that increased sleep is a real treatment-related benefit of desmopressin. There was an improvement in QoL with more than a 50% decrease in patients reporting nocturia as the most bothersome symptom as assessed by the ICS male and BFLUTS questionnaires.

Safety & tolerability

Desmopressin was well tolerated in all the studies and resulted in significant improvements compared with placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL.

In NOCT 2A, 67% of the adverse events related to the study drug were mild, 27% were moderate and 6% were severe. In NOCT 3A, 53% of the adverse events were mild, 37% were moderate and 10% were severe (Table 3). In NOCT 4, 67% of adverse events were mild and 3% were serious. Most of the treatment-related adverse events were reported during the dose-titration phase, with 50 out of 210 patients being withdrawn due to adverse events that included headache, nausea, diarrhea, hypertension and hyponatremia (Figure 4). In the double-blind phase, treatment-related adverse events declined.

In NOCT 2B/3B, the frequency and type of adverse events were similar to those in the shortterm studies (Table 4). In total, 46% of adverse events were mild, 45% were moderate and 12% were severe. The frequency of patients experiencing treatment-related adverse events was similar at all three doses in females but increased slightly in males with increasing doses. Patients aged over 65 years experienced a higher incidence of adverse events. Serious adverse events included dizziness, cardiac failure, headache, vomiting, chest pain, hypertension, hyponatremia, nausea and vertigo.



There were three deaths reported in the three short-term Phase III trials and one in the longterm study. Two females died after withdrawal from the dose-titration period. The first female developed respiratory insufficiency and was withdrawn from the trial and then recovered but died subsequently of unrelated causes. The second female developed pneumonia and died due to underlying diabetic complications. One man developed bronchitis and died 4 months after drug withdrawal and therefore it was considered unlikely to be related to study medication. The death in the NOCT 2B/3B was due to renal cell carcinoma in a man and therefore was unrelated to the drug.

Hyponatremia is a side effect of desmopressin usage that can lead to a variety of adverse events ranging from mild headache, anorexia, nausea and vomiting to loss of consciousness, seizures and death. The risk of hyponatremia seems to increase with age, cardiac disease and increasing 24-h urine volume [73]. It has been reported in a meta-analysis of previous studies to be approximately 7.6% [74].

During the dose-titration phase of the above Phase III studies, 95 out of 632 patients (15%) experienced at least one episode of serum sodium concentration below the normal range (<135 mmol/l), with 64 (10%) having borderline (130–134 mmol/l) and 31 (3%) having significant (<130 mmol/l) hyponatremia, and 13 out of 31 having a serum sodium level of less than 125 mmol/l; 29 out of the 95 were reported as an adverse event, with two being serious adverse events [75]. There was one hyponatremia recorded in the double-blind phase, but this was in the placebo group.

Table 4. Adverse events from oral desmopressin short-term Phase III clinical trials.						
Period	Dose titration	Double-blind		Open-label		
	Desmopressin (n)	Desmopressin (n)	Placebo (n)	Desmopressin (n)		
Total patients enrolled	632	219	203	249		
Total patients with AE	358	56	56	182		
Serious adverse events	9	2	5	26		
Deaths	3	0	0	1		
Adverse events	221	19	13	61		
Headache	93	11	7	14		
Hyponatremia	28	0	1	35		
Nausea	27	0	0	5		
Diarrhea	9	0	0	0		
Dizziness	16	0	0	8		
Abdominal pain	17	0	0	0		
Dry mouth	14	0	0	0		
Micturition frequency	8	0	0	5		
Fatigue	7	0	0	0		
Peripheral edema	7	0	0	7		
Hypertension	3	0	0	0		
Insomnia	3	0	0	0		
Urinary tract infection	0	0	0	4		

AE: Adverse events related to study medications and occurring most frequently (\geq 3% in NOCT 2A and NOCT 3A; \geq 2% in NOCT 4).

Those who experienced hyponatremia tended to be, on average, older and smaller, with lower creatinine clearances, higher total and nocturnal urine volumes, and had a tendency to have lower basal serum sodium concentrations. However, it is not possible to assess the relationship between hyponatremia and doses because of the design of the dose titration. All hyponatremia (31 patients) occurred in those aged over 55 years, with 28 of them being over the age of 65 years. In the longterm study, 35 patients developed hyponatremia but only two of these had symptomatic hyponatremia with serum sodium between 125 and 130 mmol/l.

We currently have no predictive factors about who may be at increased risk of hyponatremia. However, to reduce the risk of hyponatremia, it is recommended that patients aged over 79 years or with a 24-h urine volume greater than 28 ml/kg should not be administered desmopressin [75]. In those aged over 65 years, serum sodium levels should be checked at baseline and at 3 and 7 days after commencing treatment or changing dose. We would recommend that these serum sodium measurements are also applied to those aged under 65 years, and would also recommend to check sodium levels at 3 weeks post-treatment or change the dose, as there is the potential for levels of sodium to change within a 3-week period [76]. One study showed that hyponatremia can develop after 6 months of administration, although not clinically significant [77], and therefore serum sodium levels may be checked at 6 months following administration and then 6-monthly thereafter. Long-term use of desmopressin does not seem to affect baseline antidiuretic hormone secretion [77]. The fluid intake will need to be limited to a minimum from 1 h before the dose until 8 h afterwards, and there needs to be periodic blood pressure and weight measurements to monitor for fluid overload.

Postmarketing surveillance

Desmopressin has been in clinical use since 1972. It is estimated that since 1995 at least 13 million people have been treated with desmopressin for more than 3 months, and approximately 1.2 million are being treated with it per year [78]. A total of 60% of sales are for nocturnal enuresis in children, approximately 20% for nocturia, approximately 14% for diabetes insipidus and 6% for hemostasis usage. Until June 2005, there have been 2158 cases (409 using the oral route) of adverse events reported, with 61% being nonserious. The most common events are hyponatremia, convulsions and headache, especially when using the intranasal route. This has led to the recent withdrawal of the intranasal formulation as an indication for nocturnal enuresis in children in many countries around the world, including the USA, Canada and the UK.

Hyponatremia is the single most important adverse event during clinical practice. The extent of this is difficult to quantify due to limitations of the postmarketing environment. In total, 468 cases of hyponatremia have been reported, usually when using the intranasal route (299 out of 468) with 71 out of 468 (15%) due to oral tablets. Hyponatremia has been reported at a rate of approximately five cases per 10 million doses for nasal formulations and approximately one case per 10 million doses for oral formulations.

Rare cases of emotional disturbance have been reported in children treated for enuresis, and isolated cases of allergic skin reactions and more general allergic reactions have also been reported.

Overall, desmopressin seems to have an acceptable safety profile if taken appropriately with specific precautions and thus reducing the risk of hyponatremia.

Regulatory affairs

Desmopressin is currently licensed for the treatment of nocturia in the oral Melt form in 25 countries around the world and in the oral tablet form in 68 countries, including Canada, New Zealand, France, Scandinavian countries and other European, Middle-Eastern, Asian and South American countries. In the USA, it is still undergoing trials, and in the UK further trials are awaited to show cost-benefit before licensure.

Conclusion

Desmopressin is currently the only medication licensed and available for the treatment of nocturia. Its efficacy and safety have been demonstrated in Phase III trials. However, first it is important to make an accurate diagnosis of the cause and type of nocturia. If nocturia is of polyuric origin, desmopressin should be the first-line medical treatment. In clinical trials, 38% (81 out of 214) of patients experienced a reduction of at least 50% in nocturnal voids but only 7% (14 out of 206) of patients on placebo. The mean number of nocturnal voids was reduced by 41% in the desmopressin group (3 to 1.8) compared with 16% in the placebo group (3 to 2.5). The mean duration of the first period of undisturbed sleep was increased by 79% in the desmopressin group (147 to 263 min) compared with 22% in the placebo group (150 to 184 min). All differences between desmopressin and placebo were statistically significant.

The main side effect is hyponatremia, especially in those aged over 65 years. In these patients, precautionary measures need to be taken to minimize the risk of water intoxication.

Expert commentary

Desmopressin has been in use for several decades in different formulations for various indications. Its use in the treatment of nocturia stems from its use in children with nocturnal enuresis. By affecting the absorption of urine in the kidney, it reduces the amount of urine in the bladder and therefore reduces nocturia, if taken at night. It is particularly useful in the treatment of nocturnal polyuria.

It was used off-license in the 1980s as an antidiuretic for nocturia patients as there were no adequate clinical trials. It then became licensed in multiple sclerosis patients with nocturia. It was not until 2001 that it became licensed in the treatment of nocturia after a good clinical trials program, although not in all countries. There has been reluctance from some doctors to use it because of the risk of hyponatremia. This risk is present in approximately 4–8% of patients; however, it could be easily reduced if adequate precautions are taken.

Nonetheless, desmopressin is the only medication that is available with level 1 evidence for the treatment of nocturia. Furosemide, a diuretic, has been tried for the treatment of nocturia but not enough trials have been conducted to make conclusions on its efficacy, although it can certainly be tried in some patients. Antimuscarinics and a-blockers have also been tried in patients with nocturia with limited success, possibly because many patients have nocturnal polyuria in addition to nocturia secondary to OAB syndrome and bladder-outlet obstruction and they have not been properly evaluated. In these situations, combination therapy of desmopressin with antimuscarinics and/or α -blockers may be more appropriate. Further trials will need to be conducted to look at the concept of combination therapy. These trials can use the new Melt formulation in the treatment of nocturia. The Melt formulation dissolves very rapidly under the tongue. Studies have shown it is bioequivalent to the tablet formulation and therefore it would seem reasonable to conduct any new trials using this formulation rather than the tablets.

Although desmopressin is the only drug available for the treatment of nocturia, it has some limitations in terms of efficacy (approximately 40% of patients have clinical response) and cannot be used without caution due to the risk of hyponatremia, particularly in the elderly (approximately 8% in those aged over 65 years). This means there is a potential for the development of a new drug with improved pharmacokinetics and pharmacodynamics that has a more consistent oral bioavailability, resulting in better efficacy and fewer side effects. The improved pharmacology should also aim to reduce the variability in the duration of action, giving more control over symptoms over a defined period of time.

In the elderly, the cause of hyponatremia may be due to delayed clearance of desmopressin by the kidneys because of a decrease in glomerular filtration rate and urinary excretion resulting in a prolonged duration of action. It may also be due to increased absorption in some cases. A new drug would therefore need to produce antidiuresis for approximately 8 h and stop acting within 12 h to minimize the potential risk of hyponatremia.

Some patients with nocturnal polyuria seem to be resistant to desmopressin treatment. Some factors causing this include disordered renal sodium handling, hypercalciuria, increased prostaglandins and/or osmotic excretion, abnormalities in the circadian rhythm of glomerular filtration rate [79] or an increase in atrial natriuretic peptide [80]. These factors will need to be investigated further if patients fail to respond to desmopressin treatment.

Future perspective

Nocturia is a very important clinical condition that has multifactorial etiology and affects the QoL of adults of all ages. It is therefore important that an accurate diagnosis of the etiology is made as this affects the success of treatment.

The past few years have seen an increasing interest in the treatment of nocturia not only from urologists but from other specialists, such as endocrinologists, cardiologists, sleep specialists and gynecologists. This trend is expected to remain and probably increase over the next 5 years, with further trials on the effective treatment of nocturia using desmopressin, probably of different formulations, either alone or in combination with other treatments. We may even see the emergence of multidisciplinary meetings for the treatment of nocturia, just like there are such meetings for incontinence and cancer.

Education and awareness, both of doctors and patients, is an important part of the treatment of nocturia and it is important that this is continued in the future. One of the most important steps forward is the increasing use of FVCs by both doctors and patients and with the advent of electronic versions, the use of these indispensable tools is likely to increase.

Executive summary

- Nocturia is the most prevalent lower urinary tract symptom; it affects adult men and women equally and increases with age.
- Nocturia has multifactorial etiology and the cause is not always urological.
- Nocturnal polyuria has been shown to be present in up to 70% of patients complaining of nocturia.
- Frequency/volume charts are probably the most important tool in the assessment of patients with nocturia.
- The effect that nocturia has on the quality of life of patients will dictate whether it needs treatment or not.
- Referral to the appropriate specialist to treat the nocturia is based on a thorough history and examination and the results of the frequency/volume chart.
- Lifestyle interventions should be given to patients with nocturia and identifiable possible causes, such as excessive fluid intake at night.
- Antimuscarinic use in nocturia alone, as opposed to for overactive bladder, has been shown to be clinically ineffective.
- α-blockers use in nocturia alone, as opposed to for benign prostatic obstruction, have been shown to be clinically ineffective.
- Desmopressin is the only medication available with level 1 evidence for the treatment of nocturia of polyuric origin.
- Desmopressin is safe to use in patients aged under 65 years, but has to be used with caution in those aged over 65 years.
- Hyponatremia is the most serious adverse event, and sodium levels need to be checked at baseline before starting desmopressin and 3 and 7 days after starting the medication or at any time that there is a dose change. Further serum sodium checks at 3 weeks and 6 months are also recommended.
- Combination therapy may be required to treat nocturia of mixed etiology, but studies are needed to address this concept.

Acknowledgements

We would like to thank Prof. Jens Peter Norgaard for his valuable input and advice regarding the paper.

Financial & competing interests disclosure

Hashim Hashim and Paul Abrams have acted as investigators, speakers and/or consultants for pharmaceutical companies producing or developing drugs for lower urinary tract

Bibliography

- van Kerrebroeck P, Abrams P, Chaikin D et al.: The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol. Urodyn.* 21(2), 179–183 (2002).
- Irwin DE, Milsom I, Hunskaar S et al.: Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur. Urol. 50(6), 1306–1314 (2006).
- Jolleys JV, Donovan JL, Nanchahal K, Peters TJ, Abrams P: Urinary symptoms in the community: how bothersome are they? *Br. J. Urol.* 74(5), 551–555 (1994).
- Swithinbank LV, Donovan J, Shepherd AM, Abrams P: Female urinary symptoms: just how much "bother" are they? (Abstract 59A). *Neurourol. Urodyn.* 16(5), 431–432 (1997).
- Asplund R, Aberg H: Nocturnal micturition, sleep and well-being in women of ages 40–64 years. *Maturitas* 24(1–2), 73–81 (1996).
- Roth T: Prevalence, associated risks, and treatment patterns of insomnia. *J. Clin. Psychiatry* 66(Suppl. 9), 10–13 (2005).
- Kobelt G, Borgstrom F, Mattiasson A: Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. *BJU Int.* 91(3), 190–195 (2003).
- Asplund R: Hip fractures, nocturia, and nocturnal polyuria in the elderly. *Arch. Gerontol. Geriatr.* 43(3), 319–326 (2006).
- Avery K, Hashim H, Gardener N, Abrams P, Donovan J, Abraham L: Development and psychometric evaluation of the ICIQ nocturia module: the ICIQ-N. Presented at: *International Continence Society Annual Conference.* Paris, France, August 25–27 2004 (Abstract 595).
- Brubaker L, Fitzgerald MP: Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. *Int. Urogynecol. J. Pelvic. Floor Dysfunct.* 18(7), 737–741 (2007).

- Chapple CR, Cardozo L, Steers WD, Govier FE: Solifenacin significantly improves all symptoms of overactive bladder syndrome. *Int. J. Clin. Pract.* 60(8), 959–966 (2006).
- Nitti VW, Dmochowski R, Appell RA, Wang JT, Bavendam T, Guan Z: Efficacy and tolerability of tolterodine extendedrelease in continent patients with overactive bladder and nocturia. *BJU Int.* 97(6), 1262–1266 (2006).
- Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z: Nighttime dosing with tolterodine reduces overactive bladderrelated nocturnal micturitions in patients with overactive bladder and nocturia. *Urology* 67(4), 731–736 (2006).
- Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R: Multicenter Phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 67(2), 275–280 (2006).
- Norgaard JP, Hashim H, Malmberg L, Robinson D: Antidiuresis therapy: mechanism of action and clinical implications. *Neurourol. Urodyn.* 26(7), 1008–1013 (2007).
- Swithinbank LV, Vestey S, Abrams P: Nocturnal polyuria in communitydwelling women. *BJU Int.* 93(4), 523–527 (2004).
- Yoshimura K, Ohara H, Ichioka K *et al.*: Nocturia and benign prostatic hyperplasia. Urology 61(4), 786–790 (2003).
- Djavan B, Milani S, Davies J, Bolodeoku J: The impact of tamsulosin oral controlled absorption system (OCAS) on nocturia and the quality of sleep: preliminary results of a pilot study. *Eur. Urol.* 4(Suppl. 2), 61–68 (2005).
- Rembratt A, Norgaard JP, Andersson KE: What is nocturnal polyuria? *BJU Int.* 90(Suppl. 3), 18–20 (2002).
- Yoong HF, Sundaram MB, Aida Z: Prevalence of nocturnal polyuria in patients with benign prostatic hyperplasia. *Med. J. Malaysia* 60(3), 294–296 (2005).

symptoms, including Ferring Pharmaceuticals A/S, in the last 5 years. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

- Reynard JM, Cannon A, Yang Q, Abrams P: A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. *Br. J. Urol.* 81(2), 215–218 (1998).
- Pedersen PA, Johansen PB: Prophylactic treatment of adult nocturia with bumetanide. *Br. J. Urol.* 62(2), 145–147 (1988).
- 23. Kok AL, Burger CW, van de Weijer PH, Voetberg GA, Peters-Muller ER, Kenemans P: Micturition complaints in postmenopausal women treated with continuously combined hormone replacement therapy: a prospective study. *Maturitas* 31(2), 143–149 (1999).
- Drake MJ, Mills IW, Noble JG: Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. *J. Urol.* 171(3), 1199–1202 (2004).
- Andersson KE, Appell R, Cardozo L et al.: Pharmacological treatment of urinary incontinence. In: Incontinence (3rd International Consultation on Incontinence Edition). Abrams P, Cardozo L, Khoury S, Wein A (Eds). Health Publication Ltd, Paris, France, 809–854 (2005).
- Fonda D, DuBeau C, Harari D, Ouslander JG, Palmer M, Roe B: Incontinence in the frail elderly. In: *Incontinence (3rd International Consultation on Incontinence Edition)*. Abrams P, Cardozo L, Khoury S, Wein A (Eds). Health Publication Ltd, Paris, France, 1163–1240 (2005).
- du Vigneaud V: Hormones of the posterior pituitary gland: oxytocin and vasopressin. *Harvey Lect.* 50, 1–26 (1954).
- Acher R, Light A, du Vigneaud V: Purification of oxytocin and vasopressin by way of a protein complex. *J. Biol. Chem.* 233(1), 116–120 (1958).
- Turner RA, Pierce JG, du Vigneaud V: The purification and the amino acid content of vasopressin preparations. *J. Biol. Chem.* 191(1), 21–28 (1951).
- Kimbrough RDJ, Cash WD, Branda LA, Chan WY, Du Vigneaud V: Synthesis and biological properties of 1-desamino-8lysine-vasopressin. *J. Biol. Chem.* 238, 1411–1414 (1963).

- Studer RO, Cash WD: Synthesis of 1-acetyl-8-argininevasopressin and a study of its effects in the rat pressor assay. *J. Biol. Chem.* 238, 657–659 (1963).
- Vavra I, Machova A, Krejci I: Antidiuretic action of 1-deamino-(8-D-arginine)vasopressin in unanesthetized rats. *J. Pharmacol. Exp. Ther.* 188(1), 241–247 (1974).
- Andersson KE, Arner B: Effects of DDAVP, a synthetic analogue of vasopressin, in patients with cranial diabetes insipidus. *Acta Med. Scand.* 192(1–2), 21–27 (1972).
- Andersson KE, Arner B, Hedner P, Mulder JL: Effects of 8-lysine-vasopressin and synthetic analogues of release of ACTH. *Acta Endocrinol. (Copenh.)* 69(4), 640–648 (1972).
- Edwards CR, Kitau MJ, Chard T, Besser GM: Vasopressin analogue DDAVP in diabetes insipidus: clinical and laboratory studies. *Br. Med. J.* 3(5876), 375–378 (1973).
- Robinson AG: DDAVP in the treatment of central diabetes insipidus. *N. Engl. J. Med.* 294(10), 507–511 (1976).
- 37. Dimson SB: Desmopressin as a treatment for enuresis. *Lancet* 1(8024), 1260 (1977).
- Tuvemo T: DDAVP in childhood nocturnal enuresis. *Acta Paediatr. Scand.* 67(6), 753–755 (1978).
- Puri VN: Urinary levels of antidiuretic hormone in nocturnal enuresis. *Indian Pediatr.* 17(8), 675–676 (1980).
- Norgaard JP, Pedersen EB, Djurhuus JC: Diurnal anti-diuretic-hormone levels in enuretics. *J. Urol.* 134(5), 1029–1031 (1985).
- Mansson W, Sundin T, Gullberg B: Evaluation of a synthetic vasopressin analogue for treatment of nocturia in benign prostatic hypertrophy. A double-blind study. *Scand. J. Urol. Nephrol.* 14(2), 139–141 (1980).
- Hilton P, Hertogs K, Stanton SL: The use of desmopressin (DDAVP) for nocturia in women with multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* 46(9), 854–855 (1983).
- Valiquette G, Abrams GM, Herbert J: DDAVP in the management of nocturia in multiple sclerosis. *Ann. Neurol.* 31(5), 577 (1992).
- Eckford SD, Swami KS, Jackson SR, Abrams PH: Desmopressin in the treatment of nocturia and enuresis in patients with multiple sclerosis. *Br. J. Urol.* 74(6), 733–735 (1994).
- Eckford SD, Carter PG, Jackson SR, Penney MD, Abrams P: An open, in-patient incremental safety and efficacy study of

desmopressin in women with multiple sclerosis and nocturia. *Br. J. Urol.* 76(4), 459–463 (1995).

- Valiquette G, Herbert J, Maede-D'Alisera P: Desmopressin in the management of nocturia in patients with multiple sclerosis. A double-blind, crossover trial. *Arch. Neurol.* 53(12), 1270–1275 (1996).
- Fredrikson S: Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. *Acta Neurol. Scand.* 94(1), 31–34 (1996).
- Valiquette G, Herbert J, Maede-D'Alisera P: Desmopressin in the management of nocturia in patients with multiple sclerosis. A double-blind, crossover trial. *Arch. Neurol.* 53(12), 1270–1275 (1996).
- Ferreira E, Letwin SR: Desmopressin for nocturia and enuresis associated with multiple sclerosis. *Ann. Pharmacother.* 32(1), 114–116 (1998).
- Suchowersky O, Furtado S, Rohs G: Beneficial effect of intranasal desmopressin for nocturnal polyuria in Parkinson's disease. *Mov. Disord.* 10(3), 337–340 (1995).
- Fjellestad-Paulsen A, Hoglund P, Lundin S, Paulsen O: Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. *Clin. Endocrinol. (Oxf.)* 38(2), 177–182 (1993).
- Vilhardt H, Lundin S: Biological effect and plasma concentrations of DDAVP after intranasal and peroral administration to humans. *Gen. Pharmacol.* 17(4), 481–483 (1986).
- 53. d'Agay-Abensour L, Fjellestad-Paulsen A, Hoglund P, Ngo Y, Paulsen O, Rambaud JC: Absolute bioavailability of an aqueous solution of 1-deamino-8-D-arginine vasopressin from different regions of the gastrointestinal tract in man. *Eur. J. Clin. Pharmacol.* 44(5), 473–476 (1993).
- Rembratt A, Graugaard-Jensen C, Senderovitz T, Norgaard JP, Djurhuus JC: Pharmacokinetics and pharmacodynamics of desmopressin administered orally versus intravenously at daytime versus night-time in healthy men aged 55–70 years. *Eur. J. Clin. Pharmacol.* 60(6), 397–402 (2004).
- Callreus T, Hoglund P: Pharmacokinetics and antidiuretic effect of intravenous administration of desmopressin in orally overhydrated male volunteers. *Pharmacol. Toxicol.* 83(6), 259–262 (1998).
- Rittig S, Jensen AR, Jensen KT, Pedersen EB: Effect of food intake on the pharmacokinetics and antidiuretic activity of oral desmopressin (DDAVP) in hydrated normal subjects. *Clin. Endocrinol. (Oxf.)* 48(2), 235–241 (1998).

- Stegner H, Artman HG, Leake RD, Fisher DA: Does DDAVP (1-desamino-8-Darginine-vasopressin) cross the blood-CSF barrier? *Neuroendocrinology* 37(4), 262–265 (1983).
- Sorensen PS, Vilhardt H, Gjerris F, Warberg J: Impermeability of the bloodcerebrospinal fluid barrier to 1-deamino-8-D-arginine-vasopressin (DDAVP) in patients with acquired, communicating hydrocephalus. *Eur. J. Clin. Invest.* 14(6), 435–439 (1984).
- Vilhardt H, Lundin S, Falch J: Plasma kinetics of DDAVP in man. *Acta Pharmacol. Toxicol. (Copenh.)* 58(5), 379–381 (1986).
- Hvistendahl GM, Riis A, Norgaard JP, Djurhuus JC: The pharmacokinetics of 400 μg of oral desmopressin in elderly patients with nocturia, and the correlation between the absorption of desmopressin and clinical effect. *BJU Int.* 95(6), 804–809 (2005).
- Salvatore S, Hill S, Cardozo L, Khullar V, Boos K, Athanasiou S: Safety assessment of high dose of oral desmopressin (Abstract 162). *Int Urogynecol J.* 8(1), S132 (1997).
- 62. Asplund R, Sundberg B, Bengtsson P: Desmopressin for the treatment of nocturnal polyuria in the elderly: a dose titration study. *Br. J. Urol.* 82(5), 642–646 (1998).
- Asplund R, Sundberg B, Bengtsson P: Oral desmopressin for nocturnal polyuria in elderly subjects: a double-blind, placebocontrolled randomized exploratory study. *BJU Int.* 83(6), 591–595 (1999).
- Asplund R, Aberg H: Desmopressin in elderly women with increased nocturnal diuresis. A short-term study. *Br. J. Urol.* 72(1), 42–45 (1993).
- Asplund R, Aberg H: Desmopressin in elderly subjects with increased nocturnal diuresis. A two-month treatment study. *Scand. J. Urol. Nephrol.* 27(1), 77–82 (1993).
- Chancellor MB, Atan A, Rivas DA, Watanabe T, Tai HL, Kumon H: Beneficial effect of intranasal desmopressin for men with benign prostatic hyperplasia and nocturia: preliminary results. *Tech. Urol.* 5(4), 191–194 (1999).
- Kuo HC: Efficacy of desmopressin in treatment of refractory nocturia in patients older than 65 years. *Urology* 59(4), 485–489 (2002).
- Hilton P, Stanton SL: The use of desmopressin (DDAVP) in nocturnal urinary frequency in the female. *Br. J. Urol.* 54(3), 252–255 (1982).

- Mattiasson A, Abrams P, Van Kerrebroeck P, Walter S, Weiss J: Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int.* 89(9), 855–862 (2002).
- Lose G, Lalos O, Freeman RM, Van Kerrebroeck P: Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am. J. Obstet. Gynecol.* 189(4), 1106–1113 (2003).
- Van KP, Rezapour M, Cortesse A, Thuroff J, Riis A, Norgaard JP: Desmopressin in the treatment of nocturia: a double-blind, placebocontrolled study. *Eur. Urol.* 52(1), 221–229 (2007).
- Lose G, Mattiasson A, Walter S *et al.*: Clinical experiences with desmopressin for long-term treatment of nocturia. *J. Urol.* 172(3), 1021–1025 (2004).
- Rembratt A, Norgaard JP, Andersson KE: Desmopressin in elderly patients with nocturia: short-term safety and effects on urine output, sleep and voiding patterns. *BJU Int.* 91(7), 642–646 (2003).

- Weatherall M: The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and metaanalysis. *Neurourol. Urodyn.* 23(4), 302–305 (2004).
- Rembratt A, Riis A, Norgaard JP: Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia. *Neurourol. Urodyn.* 25(2), 105–109 (2006).
- Callreus T, Ekman E, Andersen M: Hyponatremia in elderly patients treated with desmopressin for nocturia: a review of a case series. *Eur. J. Clin. Pharmacol.* 61(4), 281–284 (2005).
- Bae JH, Oh MM, Shim KS *et al.*: The effects of long-term administration of oral desmopressin on the baseline secretion of antidiuretic hormone and serum sodium concentration for the treatment of nocturia: a circadian study. *J. Urol.* 178(1), 200–203 (2007).
- Vande Walle J, Stockner M, Raes A, Norgaard JP: Desmopressin 30 years in clinical use: a safety review. *Curr. Drug Safety* 2(3), 232–238 (2007).

- De Guchtenaere A, Vande Walle C, Van Sintjan P *et al.*: Nocturnal polyuria is related to absent circadian rhythm of glomerular filtration rate. *J. Urol.* 178(6), 2626–2629 (2007).
- Carter PG, Cannon A, McConnell AA, Abrams P: Role of atrial natriuretic peptide in nocturnal polyuria in elderly males. *Eur. Urol.* 36(3), 213–220 (1999).
- Vilhardt H: Basic pharmacology of desmopressin: a review. *Drug Invest.* 2(Suppl. 5), 2–8 (1990).

Websites

pdf

- 101. Ferring Pharmaceuticals: Summary of product characteristics www.ferringuk.com/index.php?option=com _docman&task=doc_download&gid=95&Clt emid=52
- 102. Medicines and Healthcare products Regulatory Agency: Summary of product characteristics www.mhra.gov.uk/home/groups/l-unit1/ documents/websiteresources/con2033808.