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DRUG EVALUATION



Desmopressin and nocturnal voiding dysfunction: Clinical evidence and safety profile in the treatment of nocturia

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ABSTRACT

Introduction: Nocturia is a common urinary condition experienced by both men and women. While desmopressin has historically been utilized to treat conditions such as central diabetes insipidus and primary nocturnal enuresis, there is an increased interest in the use of desmopressin in the management of adult nocturia.

Areas covered: This article provides a review on the pathophysiology of nocturia and the clinical outcomes and safety profile of desmopressin in the management of adult nocturnal voiding dysfunction.

Expert opinion: To date, desmopressin is the only anti-diuretic hormone that is approved for nocturia. Published literature on desmopressin demonstrate good clinical efficacy in terms of number of nocturnal voids, voided volume and sleep period. Newer formulations have shown that a minimum dosage of 25 µg orally disintegrating sublingual desmopressin appears to be ideal for women, whereas men usually benefit from a minimum of 50 µg. Of the known adverse drug reactions, hyponatremia remains a major concern especially in patients over 65 years of age. At present, long term data on desmopressin remains scarce. Lastly, it is important to stress that no single treatment deals with nocturia in all contexts, and careful assessment remains essential to identify the appropriate and safest treatment in each patient.

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1. Introduction

Nocturia is a common and bothersome lower urinary tract symptom (LUTS) [1], whereby the individual wakes one or more times per night to void [2]. The International Continence Society (ICS) defines nocturia as waking at night to void, with each void preceded and followed by sleep [3,4]. It is agreed that more than two nocturnal voids adversely impact on general health outcomes [5] due to sleep fragmentation experienced by patients on a regular basis. These effects often result in reduced health-related quality of life, mood disturbance, reduced work productivity, poorer overall health, increased falls and fractures, as well as higher mortality risks [6–9].

Epidemiological studies reported that nocturia affects 25–49% of men and 31–55% of women [10–12]. A recent meta-analysis of 43 articles concluded that while nocturia is common across a diverse population, it is more common among older people [10], with benign prostatic hyperplasia being a risk factor for nocturia in older men [13]. Some studies reported higher prevalence of nocturia among patients with chronic medical conditions such as diabetes mellitus, hypertension, obesity, and cardiovascular disease [14].

While desmopressin has been historically utilized to treat conditions such as central diabetes insipidus, recent literature has shown that desmopressin is effective in the treatment of adult nocturia and nocturnal polyuria (NP) [15]. This article provides a review on the pathophysiology of nocturia and

the clinical outcomes and safety profile of desmopressin in the management of adult nocturnal voiding dysfunction.

2. Methods

The following MeSH terms 'desmopressin', 'nocturia', 'nocturnal polyuria' and 'voiding dysfunction' were used to search PubMed database for English-language original and review articles published up to June 2017. Published literature on nocturnal incontinence in pediatric population was excluded. Review articles were included and provided herein to focus on the clinical outcomes and safety of desmopressin in the treatment of adult nocturia and/or NP.

3. Nocturnal voiding dysfunction: nocturia, nocturnal polyuria, and nocturnal incontinence

While nocturia constitutes a voiding symptom as part of overactive bladder [2], it is generally agreed upon that nocturia is more than just a problem relating to bladder storage and can often be multifactorial in nature. Recent literature shows that nocturnal voiding dysfunction can be classified into five major categories based on comprehensive clinical history, examination, and frequency–volume chart [3,4], namely global polyuria, NP, decreased functional bladder capacity, primary sleep disorders, and 'mixed' nocturia [16].

While the ICS definition of nocturia states that an individual complains of waking up to void, it does not take patient's bother into account [17]. Furthermore, the first morning void is excluded from the count because it is not followed by sleep. This is in contrast with night-time frequency, which includes voids that occur after the individual has gone to bed, but before he or she has gone to sleep and voids that occur in the early morning that prevent the individual from getting back to sleep as he or she wishes.

Global polyuria is defined as 24-h urinary output that exceeds 40 ml/kg body weight or above and can result in increased urinary frequency. Disease states such as diabetes mellitus, diabetes insipidus, hypercalcemia, and primary polydipsia can be associated with global polyuria [18]. Diabetes insipidus can be classified as central (neurogenic) due to insufficient antidiuretic hormone (ADH) synthesis by neurosecretory cells, or nephrogenic, in turn due to renal insensitivity to ADH. In contrast, NP is an abnormally large urine volume produced during the night-time, and the ICS defines NP as nocturnal polyuria index (NPI) >20% of daily urine output at night in young individuals and >33% in elderly [3,4,15]. Excessive urine production remains a commonly reported cause of nocturia with up to 93% of elderly patients having NP [19]. Given the difference used in the definition of 24-h polyuria and NP units (based on a 70 kg person of undefined gender voiding more than 40 ml/kg/24 h vs. patient age and urine production per time unit), it can be difficult to compare these two conditions. Patients with fluid overload states such as congestive heart failure, liver disease with hypoalbuminemia, nephrotic syndrome, or lower extremity venous stasis often exhibit NP [16].

Reduced nocturnal bladder capacity can be related to structural or functional abnormalities of the lower urinary tract, such as overactive bladder, benign prostatic hyperplasia with bladder outlet obstruction, interstitial cystitis, bladder lesions (e.g. calculi, tumor), or reduced nocturnal bladder capacity [5,15,16]. There is a gender mismatch between nocturnal voided volume and bladder capacity with bladder capacity significantly affected in women with nocturia, whereas in men, a higher nocturnal voided volume seems the more common cause for nocturia [20]. This NP correlates not only with impaired urinary osmolality but also with impaired sodium excretion, a phenomenon that becomes more prominent with age [21]. Weiss [22] found a predominance of reduced nocturnal bladder capacity in younger patients and a predominance NP in older patients. More recently, an association between abnormal sleep-wake cycle and nocturnal voiding dysfunction highlights the role of sleep disorders such as periodic limb movements during sleep and habitual voiding as a response to awakening [23].

4. Desmopressin

4.1. Mechanism of action

Vasopressin, also known as ADH, is produced by the posterior pituitary gland. ADH is released from the posterior pituitary in states of hyperosmolality and hypovolemia. ADH analogs have traditionally been used to treat central diabetes insipidus,

bleeding disorders such as von Willebrand disease, and primary nocturnal enuresis [24]. However, recent interest in its role for treating nocturia has stimulated a growing body of literature examining the role and effect of desmopressin. The effects of desmopressin on nocturia due to NP are based on age-related decrease in the secretion of arginine vasopressin (AVP) by the posterior lobe of the pituitary gland at night and ensuing increase in nocturnal urine volume.

4.1.1. Pharmacodynamics

AVP, a nine-amino acid peptide that is secreted from the posterior pituitary in response to high plasma osmolality and hypotension, is central in hypothalamic-neurohypophyseal-vasopressin axis control [25]. Vasopressin has important roles in circulatory and water homeostasis mediated by vasopressin receptor subtypes V1a (vascular), V1b (pituitary), and V2 (vascular and renal). The renal vasopressin type 2 receptor (V2R) plays a critical role in physiological and pathophysiological processes associated with AVP-induced antidiuresis [26].

The V2R facilitates the urine concentrating mechanism through the AVP/V2 type receptor/aquaporin 2 system in the medullary and cortical collecting ducts [27]. The main functions of V2R in principal cells of the collecting duct are water, salt, and urea transport by modifying the trafficking of aquaporin 2, epithelial sodium channels, and urea transporters and vasodilation and stimulation of coagulation factor properties, mainly seen with pharmacological doses of 1-desamino-8-D-AVP. The AVPR2 gene is located on the X chromosome, in a region with high probability of escape from inactivation; this may lead to phenotypic sex differences, with females expressing higher levels of transcript than males [28]. The sex differences in vasopressin secretion and action could explain why vasopressin plasma concentration is significantly higher in males than in females, and that vasopressin-mediated effects on renal and vascular targets are more pronounced in males than in females, making men more susceptible than females to diseases such as hypertension, cardiovascular and chronic kidney diseases, and urolithiasis.

4.1.2. Pharmacokinetics and metabolism

Desmopressin is a synthetic analog of the AVP. The difference lies in the desamination of cysteine and substitution of L-arginine by the D-arginine. These structural differences with vasopressin result in a significant increase of the antidiuretic activity, while the vasopressor activity is reduced considerably.

Desmopressin's antidiuretic action (DOA) increases water reabsorption in the renal collecting ducts and the ascending limb of Henle's loop, reducing urine volume and increasing urine osmolality. At the cellular level, this effect is manifested through V2 receptor-mediated elevation of intracellular adenylate cyclase [29]. The translocation of aquaporin channels associated with cytosolic vesicles to the apical/luminal membrane of collecting duct cells allows for free water to passively be reabsorbed from the nephron back into systemic circulation. The antidiuretic effects of desmopressin, which are 4000-fold greater than the drug's vasodilating action, are long sustained [30]. After oral administration, the duration of effect of 6–14 h is to be expected. The antidiuretic effects are 3–10-fold greater than vasopressin [31]. When given orally, the

drug's bioavailability is reduced by the presence of a variety of enzymes to approximately 0.1% of that of subcutaneous injection [22]. Published literature showed that desmopressin administered as crushed or chewed tablets, or as an oral solution, has the same net effect on decreasing urine volume and increasing urine osmolality as swallowing tablets whole [32].

4.2. Clinical outcomes

In one of the earliest double-blind placebo-controlled study in men with nocturia, Mattiasson [33] found that up to a third of patients in the desmopressin group had fewer than half the number of nocturnal voids relative to baseline (compared to 3% in placebo group; $P < 0.001$) with the mean number of nocturnal voids decreased from 3.0 to 1.7 and from 3.2 to 2.7, respectively, reflecting a mean decrease of 43% and 12% ($P < 0.001$) (Table 1). The mean duration of the first sleep period was more than double (59%) and the mean nocturnal diuresis decreased by 36% in the desmopressin group ($P < 0.001$). Similarly, Lose [34] reported that more than a third of patients (46%) reported a 50% or greater reduction in nocturnal voids against baseline levels compared with 5 (7%) patients in placebo group ($P < 0.0001$) during a 3-week dose-titration period. The mean number of nocturnal voids, duration of sleep until the first nocturnal void, nocturnal diuresis, and ratios of nocturnal per 24 h and nocturnal per daytime urine volumes changed significantly in favor of desmopressin versus placebo ($P < 0.0001$). In another study, Van Kerrebroeck [35] demonstrated that desmopressin compared with placebo resulted in a significant reduction in the mean number of nocturnal voids (39% reduction with desmopressin vs. 15% with placebo; absolute difference -0.84 , $P < 0.0001$) and duration of the first sleep period (prolonged by 108 min with desmopressin vs. 41 min with placebo; $P < 0.0001$). In addition, the quality of sleep was also significantly improved in the desmopressin group.

In terms of drug compliance, Lose [36] reported 95 (72%) men and 87 (75%) women completed long-term treatment, and that desmopressin was well tolerated (less than 15% patients withdrew due to adverse effects). Clinical outcomes showed a decrease in mean number of nocturnal voids and an increase in months the mean duration of the first sleep period. In men with benign prostatic hyperplasia (BPH) and nocturia, Wang [37] found that desmopressin significantly decreased nocturnal urine output and the number of nocturia episodes and prolonged the first sleep period ($P < 0.01$). Compared to before treatment, desmopressin did not result in any serious systemic complications and there was a gradually decreased serum sodium and induced statistically but not clinically significant hyponatremia after 12 months of treatment.

In the treatment of men with persistent nocturia on α -blocker monotherapy, Kim [38] showed that desmopressin add-on group was significantly superior to placebo in terms of the change from baseline in the mean number of nocturia episodes (-1.13 ± 0.92 vs. -0.68 ± 0.79 , $P = 0.034$), the changes in nocturnal urine volume ($P < 0.001$), the NPI ($P = 0.001$) and the International Consultation on Incontinence Questionnaire-Nocturia ($P = 0.001$). The combination of systematized

Table 1. Summary of randomized clinical trial outcomes of desmopressin in nocturia.

Study (reference)	Target population	Effective dose	Decrease in nocturnal voids	Sleep period prolongation	Incidence of hyponatremia (%)
Mattiasson [33]	Men	0.1, 0.2, and 0.4 mg (dose titration)	43% vs. 12%	59% (2.7–4.5 h) vs. 21% (2.5–2.9 h)	8
Lose [34]	Women	0.1, 0.2, and 0.4 mg (dose titration)	46% vs. 7%	33% vs. 6% (more than 5 h sleep)	12
Kim [38]	Men	0.2 mg and alpha blocker	Mean number of nocturia episodes (-1.13 ± 0.92 vs. -0.68 ± 0.79 , $P = 0.034$)	Not reported	Not reported
Rovner [40]	Women	25 μ g and 4 mg tolterodine	Mean nocturnal void volume (-64.16 mL; $P = 0.103$)	Not reported	1
Van Kerrebroeck [35]	Men and women	0.1, 0.2, and 0.4 mg (dose titration)	39% vs. 15%	108 vs. 41 min	3
Wang [37]	Men	0.1 mg	61% vs. 14%	120 vs. 101 min	6
Weiss [41]	Men	50 or 75 μ g	Reduction by -0.37 to -0.41 compared to placebo	Increase time to first void by 40 min compared to placebo	3
Yamaguichi [43]	Men and women	10, 25, 50, or 100 μ g	50% more reduction than placebo	Increase time to first void by ≥ 50 min compared to placebo	7
Sand [45]	Women	25 μ g	Reduction by -0.22 compared to placebo	Not available	1

behavioral modification education program with desmopressin in patients with nocturia has resulted in a significant difference in NPI (0.37 vs. 0.29, $P = 0.028$) and the change in the maximal bladder capacity (-41.3 vs. 13.3 mL, $P < 0.001$) [39]. Combination treatment did not have any additional benefits in relation to reducing nocturnal voids in patients with NP; however, combination therapy is helpful because it increases the maximal bladder capacity and decreases the NPI. Furthermore, combination therapy improved NP patient compliance with desmopressin.

The effects of combining desmopressin with an anti-cholinergic drug in women with overactive bladder have been explored with desmopressin orally disintegrating tablet (ODT) 25 μg and tolterodine 4 mg, and Rovner [40] reported low-dose desmopressin could be safely combined with tolterodine for treating nocturia in women with overactive bladder. A significant benefit was observed although the reduction in mean number of nocturnal voids with combination was not clinically significant (full analysis set: adjusted treatment contrast [TC] -0.34 ; $P = 0.112$). The change in mean nocturnal void volume (TC -64.16 mL; $P = 0.103$), mean time to first nocturnal void (TC 18.00 min; $P = 0.385$), and Nocturia Impact Diary scores were comparable between combination therapy and monotherapy.

In a dose formulation study, Weiss [41] performed a 3-month, randomized, double-blind, parallel study 50 and 75 μg desmopressin compared with placebo. The co-primary efficacy end points were changes from baseline in mean number of nocturnal voids and proportions of patients achieving at least a 33% reduction from baseline in nocturnal voids (33% responders) during a 3-month treatment period. Full analysis showed 50 and 75 μg doses significantly reduced the number of nocturnal voids (-0.37 , $P < 0.0001$ and -0.41 , $P = 0.0003$, respectively) and increased the odds of a 33% or greater response (OR 1.98, $P = 0.0009$ and OR 2.04, $P = 0.0004$, respectively) compared with placebo at 3 months. Desmopressin 50 and 75 μg increased the time to first void from baseline by approximately 40 min compared to placebo ($P = 0.006$ and 0.003 , respectively). The response to desmopressin was seen by 1 week of treatment and was clinically sustained as well as well tolerated. Treatment with 50 μg desmopressin provided a sustained improvement of nocturia throughout the study and meaningful benefits to patients with an improved safety profile. In another study, Weiss [42] showed that increasing doses of desmopressin were associated with decreasing numbers of nocturnal voids and voided volume, greater proportions of subjects with $>33\%$ reduction in nocturnal voids, and increased duration of first sleep period. The lowest dose reaching statistical significance ($P < 0.05$ vs. placebo) varied by end point. Improvements were clinically meaningful, meaning that patients had fewer nightly voids. Post hoc analyses by gender suggested a lower minimum effective dose for women and that lower and gender-specific dosing to reduce the small but clinically significant risk of hyponatremia.

When comparing the response of desmopressin between genders, Yamaguichi [43] undertook a phase II multicenter, randomized, placebo-controlled, double-blind, parallel-group, comparative clinical trial with randomization to placebo or

one of four doses of desmopressin ODT: 10, 25, 50, or 100 μg . Overall, the duration of DOA (time with urine osmolality >200 mOsm/kg) for the 25, 50, and 100 μg doses was 2 h ($P = 0.010$), 3.45 h ($P < 0.001$), and 5.74 h ($P < 0.001$), respectively; all statistically significant compared with placebo. Female patients were found to be more sensitive to desmopressin, and that the DOA in female patients was longer than in male patients who received desmopressin 25 and 50 μg . Data extrapolation in this study suggests that male patients require approximately 58 μg to achieve similar DOA to females receiving 25 μg . A dose-response relationship was also seen in treatment period with a greater reduction in mean number of nocturnal voids from baseline to day 28 at higher doses, and with significant reductions in the 25- ($P = 0.015$), 50- ($P < 0.001$), and 100- μg ($P = 0.001$) dose groups compared with placebo. A pooled analysis of three randomized controlled trials reported that these effects can be maintained or even enhanced over the course of a year [44]. Similar dose-response relationships were also seen when the data were analyzed by gender. Desmopressin ODT was well tolerated with no serious or severe adverse events. In women, Sand [45] showed in a 3-month, randomized, double-blind, parallel group study that 25 μg desmopressin once daily significantly reduced the mean number of nocturnal voids and increased the odds of a 33% or greater response compared to placebo at 3 months, assessed by longitudinal analysis (-0.22 , $P = 0.028$, and OR 1.85, $P = 0.006$, respectively). Desmopressin increased the mean time to first nocturnal void by 49 min compared to placebo at 3 months ($P = 0.003$). Similarly, the response to desmopressin was seen by week 1 of treatment and was sustained throughout the trial with significant increases in health-related quality of life and sleep quality were observed compared to placebo. The risk of desmopressin-associated hyponatremia was rare and usually transient in nature.

In an intermediate term follow-up study on desmopressin using pooled analysis of three short-term efficacy studies [44], desmopressin administered as ODT or solid tablet in nocturia treatment reported that the mean decrease in number of nocturnal voids during short-term treatment was maintained and was further reduced in the longer term. At 52 weeks, the mean reduction in number of nocturnal voids from baseline reached 1.4–2.1 voids for desmopressin ODT 25–100 μg . Following 40-week tablet treatment, the decrease in number of nocturnal voids was 0.8–1.5 for desmopressin 100–400 μg . The mean reduction in nocturnal voids (25–50 μg ODT) was greater for females than males. For females, the improvement in initial period of undisturbed sleep was 2.5–3 h for desmopressin ODT 25–100 μg compared with 1.3–2.6 h for males. No gender difference in efficacy was seen in the tablet studies. The decrease in nocturnal voids and improvement in sleep with short-term desmopressin treatment were maintained throughout long-term treatment. A durable gender difference in efficacy in favor of females was observed with desmopressin ODT 25 μg . Further, large-scale long-term trials are needed to confirm the durability of efficacy with gender-specific doses of desmopressin.

Published literature examining the efficacy of oral desmopressin has focused on elderly, given this group's predilection

toward hyponatremia. Among the elderly patients taking desmopressin, Rembratt [46] reported no serious adverse events and that patients' sensitivity to change in serum sodium were pharmacological responders with desmopressin having a greater effect on their 24 h diuresis, indicating that the drug effect was not limited to the night only. The risk (OR, 95% confidence interval (CI)) increased with increasing age (1.3, 1.1–1.6), concomitant cardiac disease (10.0, 0.9–105.8), and increasing baseline 24 h urine output (1.2, 1.0–1.5). Similarly, Kuo [47] showed that less than a quarter of older patients prescribed with oral desmopressin 0.1 mg at bedtime reported side effects. Interestingly, symptomatic improvement was observed in six (24%) patients after discontinuing the medication for 4 weeks. More recent retrospective study in elderly men with and without NP in real life by Chen [48] found a significant reduction of nocturnal voids from 4.22 ± 1.38 to 2.31 ± 0.98 ($P < 0.001$) in the non-NP group and from 4.52 ± 1.23 to 2.07 ± 0.89 ($P < 0.001$) in the NP group, with the reduction in nocturnal voids more significant in the NP group (2.44 ± 1.15 vs. 1.91 ± 1.48 , $P = 0.003$).

A systematic review and meta-analysis of desmopressin for the treatment of nocturia [49] revealed five studies involving 619 participants were included for the meta-analysis and eight RCTs of cross-over design were also identified for the systematic review. The analysis showed that desmopressin can significantly decrease the frequency of nocturnal voids, nocturnal urine volume, and nocturnal diuresis, potentially resulting in an extended duration of the first sleep period and improved sleep quality. The adverse effects of desmopressin were no different to those observed in the placebo group. Recent Cochrane review showed that desmopressin may have a positive effect on the number of nocturnal voids (mean difference (MD) -0.46 , 95% CI -0.94 to 0.01 ; low-quality evidence) in the shorter term [50]. For intermediate-term follow-up (3–12 months), desmopressin may reduce the number of nocturnal voids in an appreciable number of participants (MD -0.85 , 95% CI -1.17 to -0.53 ; low-quality evidence) with little or no difference in major adverse events (RR 3.05, 95% CI 0.13–73.39; low-quality evidence). Subgroup analyses suggest a larger effect with oral, higher-dose formulations of desmopressin especially in men with NP.

4.3. Adverse effect profile

Adverse drug reaction (ADR) characteristically appeared early in treatment and was observed predominantly in patients aged 65 years and older [36]. Some researchers found a correlation between ADR and desmopressin dose [51], but other researchers reported no dose dependence [36]. In most cases, ADRs were mild or moderate in severity and were resolved with discontinuation of drug treatment or by limiting water intake. The most common ADRs were headache, lower-extremity edema, nausea, dizziness, and hyponatremia. Of these, hyponatremia has been reported and requires further medical attention [24,47,49,52]. An increased sodium excretion overnight secondary to water and sodium retention during the daytime could increase the risk of side effects and that the restriction of desmopressin to patients with normal sodium handling could potentially decrease the side effect risk [53].

Hyponatremia after desmopressin intake, defined as a serum concentration <130 mmol/L but not necessarily associated with symptoms and signs, has been reported in 5–7.6% of individuals and has most frequently been observed in patients >65 years of age, especially in women, and individuals with low serum sodium concentration at baseline and higher 24 h urine volume per body weight [46,54]. Education of patients and their partners in recognizing hyponatremia should be undertaken to ensure rapid identification if it occurs. Relevant factors that could affect the sodium level in patients include gender, low baseline serum sodium, reduced kidney function, cardiac or renal comorbidity, polypharmacy with diuretics, and injudicious liquid intake [15,54].

Recent meta-analysis showed from three clinical trials of desmopressin in nocturia [55] found that potential predictors of clinically significant hyponatremia were actual desmopressin dose, age, baseline serum sodium level, and kidney function. In men, arthritis and use of drugs for bone disease were also predictive of hyponatremia, while in women, raised monocytes and absence of lipid-modifying drugs increased the risk of hyponatremia. The use of the vigilant patient monitoring and minimal effective dose would have omitted all the patients with clinically significant hyponatremia from further treatment [15,55]. The incidence of hyponatremia can be reduced by using minimum effective gender-specific dosing with the ODT formulation of desmopressin (25 μ g in women and 50 μ g in men).

Systematic review by the European Association of Urology Guidelines Panel for Male Lower Urinary Tract Symptoms [56] advocated that screening for hyponatremia (<130 mmol/L) must be undertaken at baseline, after initiation or dose titration, and during treatment. Another systematic review of desmopressin-induced hyponatremia showed one report of hyponatremia developing in 7.6% of cases, including asymptomatic cases [54], indicating that the occurrence of hyponatremia might be higher than anticipated in an actual clinical setting. Hyponatremia-induced symptoms are frequently complicated by general symptoms, such as lower extremity spasm and generalized spasm, so if hyponatremia is observed the drug should be immediately discontinued and appropriate measures should be taken, such as restriction of water intake and the use of diuretics as needed. To reduce the occurrence of ADR, desmopressin should be discontinued, and the patient's water intake should be strictly controlled (e.g. limiting water intake to 1 L a day) [52]. It is important to re-examine the patient within 3 days after discontinuation of treatment, with an overall clinical evaluation (checking for headache, peripheral edema, bodyweight increase, etc.) and an electrolyte assessment. The same procedures should also be followed when increasing the therapeutic dose especially in the older patients [15,24,36,51].

5. Regulatory affairs

While there is a long history of the use of desmopressin in the treatment of pediatric nocturnal enuresis, clinical studies over the last decade have shown desmopressin to be an effective and well-tolerated treatment for patients with NP, with females requiring lower effective doses compared to males [44]. Nasal spray, oral tablet, and sublingual melt

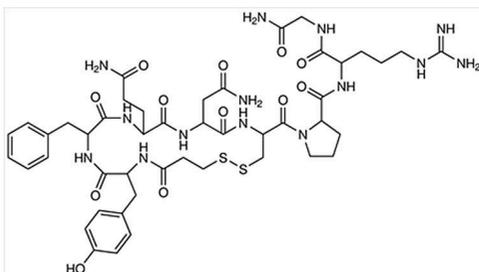
formulations of desmopressin have been developed, although not all formulations and doses are available in every country. Each of these has specific pharmacological properties and doses. A once-daily, low-dose, gender-specific formulation of desmopressin has been approved in several countries: 25 µg for women and 50 µg for men [57]. This formulation has the benefits of reducing the antidiuretics activity to a maximum of 3–5 h during the nightly sleep [57], whilst also limiting the risk of hyponatremia, a significant adverse event associated with higher doses of desmopressin. Current regulatory affair advocates that desmopressin should be taken at least 1 h before going to bed (with the intention of sleeping) without water and with fluid restricted to a minimum until 8 h after dosing, otherwise, fluid retention and/or hyponatremia may result [57]. Postmarketing drug safety monitoring on ADR or quality-of-life problems experienced with the use of desmopressin should be mandatory for reporting to regulatory bodies to ensure long term safety and efficacy of the drug.

6. Conclusion

Nocturia is a common urinary condition experienced by both men and women. While desmopressin has historically been utilized to treat conditions such as central diabetes insipidus and primary nocturnal enuresis, there is an increased interest in the use of desmopressin in the management of adult nocturia, for whom NP is prevalent. The newer ODT formulation of desmopressin has shown good clinical efficacy, safety, and tolerability profile (Box 1). Regardless of formulation or dosing, judicious care should be taken for elderly patients (over 65 years of age) due to increased hyponatremia in such vulnerable individuals.

Box 1. Drug summary.

Drug name	Desmopressin
Phase	3
Indication	Nocturnal polyuria
Pharmacology description	Vasopressin 2 agonist
Route of administration	Sublingual wafer
Chemical structure	



Pivotal trial(s) Van Kerrebroeck [35], Weiss [41], Yamaguchi [43], Juul [44]

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7. Expert opinion

To date, desmopressin is the only ADH that is approved for nocturia. Oral preparation of desmopressin has certain advantages and disadvantages. These advantages include excellent outcome, with clinical response observed within a week, and a prolonged initial sleep period [58]. Furthermore, oral desmopressin is generally well tolerated. While many studies have demonstrated the efficacy of desmopressin in decreasing nocturia severity while improving quality of life when compared to placebo, the safety profile of desmopressin, however, is paramount to its clinical utility. At present, there is no randomized double-blind placebo-controlled trial reported on long-term use of desmopressin, and only one report describes longer-term administration was found in the literature [18,35,36]. The therapeutic effects of desmopressin appear sustained throughout the treatment period, and the level and severity of ADR are similar to those seen in short-term studies. Clinical effects usually wear off with return of nocturnal symptoms within 1 month after the discontinuation of desmopressin treatment. Recent studies suggest that female patients are more sensitive to desmopressin ODT, achieving the same efficacy at lower doses than male patients. A minimum dosage of 25 µg ODT desmopressin appears to be ideal for women, whereas men usually benefit from a minimum of 50 µg. It provides further evidence that the optimal desmopressin dose for the treatment of nocturia is lower in females than in males. The risk of hyponatremia is often associated with higher doses of desmopressin or in elderly population. There is a need to screen for hyponatremia (<130 mmol/L) at baseline and 3 days after initiation of therapy or an increase in dosage, as well as at other times during treatment as deemed necessary by the treating physician; patients who are over 65 years old or who are at risk of hyponatremia also require serum sodium monitoring monthly or every 2–3 months, depending on their risk of hyponatremia.

Desmopressin, the synthetic vasopressin analog, acts on the V2R of the distal collecting tubules with the aim of concentrating urine at night. Treatment with desmopressin is useful only in patients with idiopathic NP with excessive water diuresis or in patients with central diabetes insipidus as indicative of suppressed vasopressin levels [59]. However, where there is nocturnal sodium diuresis, treatment to restore a normal sodium clearance pattern could be indicated as this would act to lower nocturnal urine production [59]. The higher sensitivity to desmopressin found in women and older patients with NP has partially been unraveled, leading to adaptation of the dosage based on gender [60]. However, besides age and gender, other factors might play a role in differences in sensitivity and side effects. Gender, body weight, and results of nocturnal-free water and sodium clearance will be required for more accurate individualized treatment to maximize response rates and minimize side effects. Regardless of formulation or dosing, judicious care should be taken especially in elderly patients (≥ 65 years of age) due to the increased risk of hyponatremia in such vulnerable individuals. Tailoring the dose according to gender and possible age will likely improve

the therapeutic window with the benefits of a decreased risk of hyponatremia without compromising clinical efficacy. It is important to stress that no single treatment deals with nocturia in all context, and careful patient assessment remains essential to identify an appropriate and safe treatment selection. In cases with multifactorial etiology in nocturia, treatment strategies should always involve lifestyle changes and behavioral modifications, with the use of two or more drugs to target different underlying causes for nocturia.

At present, many clinical trials lack specific instruments for evaluation of other aspects of nocturia such as sleep disturbance, quality of sleep, and health-related quality-of-life measures. Existing clinical trials were specifically designed to evaluate the impact of nocturia as part of LUTS and/or overactive bladder, rather than nocturia itself. Future research should focus on the development of unambiguous terminology regarding various nocturnal voiding dysfunction, the utility of renal function profiles such as water and/or sodium excretion in tailoring treatment, and the role of behavioral sleep–awake disorders (e.g. periodic limb movements during sleep and habitual voiding as a response to awakening) in nocturnal voiding dysfunction.

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