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Management of Nocturia: The Role of Antidiuretic Pharmacotherapy

Jeffrey P. Weiss,[1]* Kristian V. Juul,[2] and Alan J. Wein[3]
[1]*Department of Urology, SUNY Downstate Medical School, Brooklyn, New York*
[2]*Ferring Pharmaceuticals, Copenhagen, Denmark*
[3]*Division of Urology, Hospital of University of Pennsylvania, Philadelphia, Pennsylvania*

Strategies to manage nocturia include lifestyle modifications and treatment with alpha-blockers, antimuscarinic therapies, and antidiuretics. The concept of achieving success should not be limited to reduction of nighttime voids; it should ideally include proof of improvement of conditions generally associated with nocturia, such as falls, quality of life, and overall health. Few studies have looked specifically at parameters other than nocturnal voids, such as sleep latency, first undisturbed sleep period (FUSP), and total sleep time, including their clinical relevance to patient well-being. Lifestyle modifications, such as voiding before bedtime, limiting caffeine and alcohol, and adjusting medication timing, may be initially effective in mild cases of nocturia. Statistically significant reductions in voiding have been reported with antimuscarinic agents and alpha-blockers as initial therapy, but these reductions generally are not clinically relevant. The antidiuretic therapy desmopressin acetate, a selective vasopressin receptor 2 agonist, is effective in adults with nocturia associated with nocturnal polyuria; however, hyponatremia can occur. The newest formulation—desmopressin orally disintegrating sublingual tablet (ODST)—has greater bioavailability; thus, lower doses can be used, potentially reducing hyponatremia risk. A phase 3 study demonstrated statistically significant reductions in nocturnal voids for desmopressin ODST 50 and 100 μg versus placebo (-1.18 and -1.43 vs. -0.86; $P = 0.02$ and $P < 0.0001$, respectively) in patients with nocturia. Treatment was well-tolerated, and low-dose desmopressin ODST was associated with statistically significant increases in duration of FUSP. Development of a validated composite endpoint may help clinicians identify and compare strategies for treating nocturia. *Neurourol. Urodynam. 33:S19–S24, 2014.* © 2014 Wiley Periodicals, Inc.

Key words: alpha-blocker; antidiuretic; antimuscarinic; lifestyle modifications; nocturia

INTRODUCTION

A highly prevalent condition often associated with a range of other lower urinary tract symptoms, nocturia has long been considered a symptom secondary to underlying bladder (overactive bladder [OAB]) or prostate dysfunction (benign prostatic hyperplasia [BPH]); however, nocturia is a separate clinical entity that requires its own diagnostic evaluation and treatment.[1] It is known that sleep is vital for overall health; discrete sleep stages are important for daytime brain function.[2] The importance of sleep for maintaining metabolic function, specifically glucose homeostasis, is widely accepted.[3] Deep non–rapid eye movement (NREM) sleep, also known as slow-wave sleep (SWS), is considered the most "restorative" or regenerative sleep stage.[4] Data have shown that disturbing SWS may negatively impact the body's natural ability to regulate glucose,[5,6] while disturbing REM sleep does not have the same negative effect on glucose homeostasis.[6] Clinicians are urged to recommend 7 hr of uninterrupted sleep per night as a goal in maintaining a healthy lifestyle.[3] Epidemiologic studies have shown that nocturia is the leading cause of sleep disturbance in older adults.[7] Reducing nocturia episodes would be expected to prolong the first undisturbed sleep period (FUSP) when SWS occurs, resulting in clinically meaningful improvement that may lead to a positive impact on the patient's overall health. Although some studies on nocturia report statistically significant differences in reductions in the number of nocturnal voids between active treatment and placebo, these statistical differences may not necessarily translate into clinically meaningful outcomes, as they do not look into the effect of reduction of voids on improving sleep and other parameters.[8] Understanding the effect on these parameters may further elucidate the underlying pathophysiologic mechanisms associated with nocturia, thereby guiding more specific therapy.

This article provides an overview of current management strategies and evolving treatment options for nocturia, with a focus on efficacy and safety of the arginine vasopressin (AVP) analog desmopressin in a novel, low-dose orally disintegrating sublingual tablet (ODST) formulation in one of the few studies that looks at reduction of voids in combinations of secondary outcomes such as sleep latency, FUSP, and total length of sleep.

ASSESSMENT OF CURRENT AND EMERGING MANAGEMENT STRATEGIES

Lifestyle Modifications

Clinicians often prescribe lifestyle modifications as the initial intervention to reduce nocturia. These include preemptive voiding before bedtime, nocturnal and late-afternoon dehydration, dietary restrictions (e.g., caffeine, alcohol), adjustment of medication timing (e.g., use of late-afternoon diuretic), use of compression stockings with afternoon and evening leg

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*Correspondence to: Jeffrey P. Weiss, Department of Urology, SUNY Downstate Medical School, Brooklyn, NY.
E-mail: urojock@aol.com
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elevation to mobilize fluids, use of sleep medications/aids, and use of protective undergarments.[1,9] A few clinical trials have examined the efficacy of behavior modifications, alone[10,11] or in combination with pharmacologic approaches (usually an antimuscarinic).[12–15] Behavior modifications that were studied included biofeedback-assisted pelvic floor muscle exercises, urge suppression techniques, delayed voiding, fluid management and caffeine/alcohol restriction, and use of a frequency-volume chart.[10–15] Although all studies reported a statistically significant decrease in nocturia episodes of 0.1–0.7 episodes per night from baseline, whether this translated to changes that were clinically meaningful for the patient remains unclear.

Drug Therapies

The ideal drug for nocturia should (i) improve bladder emptying, thereby improving nocturnal bladder storage capacity; (ii) increase the volume at which bladder activity is elicited; or (iii) decrease nocturnal production of urine.[8] BPH therapies treat bladder emptying, and OAB treatments address threshold volumes for bladder activity; thus, these drugs were considered for nocturia.[16] Available therapies, such as alpha-blockers for BPH to address bladder emptying and antimuscarinic agents for OAB to address threshold volumes for bladder activity, have been only modestly successful in treating nocturia.[17–24] Several randomized, controlled clinical trials have compared these agents as monotherapy or as combination therapy against placebo by assessing the change in frequency of nocturia episodes,[17–22] with fewer analyzing key parameters such as interruption of sleep and its impact on health-related quality of life (QOL).[8] However, agents that decrease the nocturnal production of urine have side effects and metabolic sequelae that require careful clinical monitoring.[8] For these reasons, most urologists continue to pursue the agents that improve bladder emptying or increase the volume at which bladder activity is elicited, despite marginal therapeutic impact.[8]

Antimuscarinic therapies and alpha-blockers in nocturia. Given the effectiveness of antimuscarinic agents and alpha-blockers in treating OAB and BPH, respectively, these therapies have often been used as initial pharmacotherapy for nocturia. Although statistically significant reductions in the number of voids have been reported (range: 0.16–0.2 fewer nocturnal voids for antimuscarinics than for placebo, and 0.1–0.3 fewer nocturnal voids for alpha-blockers than for placebo), further evaluation shows that these reductions may not be clinically relevant (Tables I[17–19] and II[20–22]). Results of studies on antimuscarinic therapies suggest that these agents would provide the greatest benefit to patients with severe nocturnal urgency, not to those with nocturnal polyuria[1]—the main underlying cause of nocturia.[18,25] With respect to pharmacotherapy for BPH, success in treating nocturia with alpha-blockers has been limited. Statistical success has been reported in some placebo-controlled trials,[20,22] but results have been considered to have doubtful clinical significance.[1]

Antidiuretics in nocturia. Ideally, drugs for nocturia should target the underlying pathophysiological abnormality. An estimated 76–88% of patients with nocturia have nocturnal polyuria by definition. Nocturnal polyuria is the production of an abnormally large volume of urine during sleep.[16,25,26] The International Continence Society defines nocturnal polyuria as age-dependent nocturnal urine volume greater than 20–33% of the 24-hr urine volume.[16,25] Decreased nocturnal secretion of AVP (i.e., antidiuretic hormone) has been associated with increased nocturnal urine output.[27,28] Desmopressin acetate, a synthetic analog of AVP, is a selective vasopressin receptor 2 (V_2) agonist that induces antidiuresis and, in clinical studies, has been an effective and well-tolerated treatment for adults with nocturia associated with nocturnal polyuria.[26,28–31] Desmopressin mimics the action of AVP, decreasing urine production and increasing urine osmolality.[28]

Desmopressin has been used for approximately 40 years to treat central diabetes insipidus and primary nocturnal enuresis.[32] However, hyponatremia, a potentially serious but uncommon event, has been reported in pediatric and adult patients treated with different desmopressin formulations for enuresis or nocturia.[30,33,34] In children, most cases occurred with the intranasal spray (as of 2007, it was no longer indicated for treatment of primary nocturnal enuresis in this age group[35]) rather than with oral formulations.[36] The spray has been available longer than the oral tablets, and this may account for the higher incidence; more likely, however, the higher incidence was caused by variability in absorption and bioavailability and inadvertent (caused by uncertainty of drug delivery by the spray) or purposeful (''just to be sure'') overdosing.[36]

To increase the absorption and bioavailability of desmopressin while retaining the benefits of the oral administration route, an ODST formulation was developed.[26] This new desmopressin ODST dissolves rapidly when placed in the

TABLE I. Collected Results of Randomized Controlled Trials of Antimuscarinics

			Mean number of nocturnal voids			
Drug class	Drug	First author of manuscript	Baseline	Study end	Change from baseline	Difference from placebo
Antimuscarinic[3]	Solifenacin 10 mg	Yamaguchi O	1.78	NR	−0.46	0.16 ($P = 0.021$)
	Propiverine		195	NR	−0.43	0.13 (ns)
	Placebo		1.84	NR	−0.30	NA
Antimuscarinic[4]	Solifenacin[a]	Brubaker L				
	5 mg		1.66/2.32	NR	−0.61/−0.72	0.18 ($P = 0.006$)/0.08 (ns)
	10 mg		1.66/2.27	NR	−0.61/−0.68	0.18 ($P = 0.026$)/0.04 (ns)
	Placebo[a]		1.70/2.33	NR	−0.43/−0.64	NA
Antimuscarinic + alpha-blocker[5]	Tolterodine ER + tamsulosin	Kaplan SA	2.07	NR	−0.59	∼0.2 ($P = 0.02$)
	Placebo		2.02	NR	−0.39	NA

ER, extended-release; NA, not applicable; NP, nocturnal polyuria; NR, not reported; ns, nonsignificant.
[a]Without NP/with NP.

TABLE II. Collected Results of Randomized Controlled Trials in Alpha-Blockers

Drug class	Drug	First author of manuscript	Mean number of nocturnal voids			
			Baseline	Study end	Change from baseline	Difference from placebo
Alpha-blocker + 5-alpha-reductase inhibitor[6]	Terazosin	Johnson TM	2.5	1.8	−0.7	0.3 ($P = 0.0001$)
	Finasteride		2.5	2.1	−0.4	0.1 (NR)
	Combination		2.4	2.0	−0.4	0.1 ($P = 0.03$)
	Placebo		2.4	2.1	−0.3	NA
Alpha-blocker[7]	Tamsulosin	Djavan B	2.9	NR	−1.0	0.3 (ns)
	Placebo		2.9[a]	NR	−0.7	NA
Alpha-blocker + 5-alpha-reductase inhibitor[8]	Doxazosin	Johnson TM	2.3	NR	−0.54	0.19 ($P < 0.05$)
	Finasteride		2.4	NR	−0.40	0.05 (ns)
	Combination		2.3	NR	−0.58	0.23 ($P < 0.05$)
	Placebo		2.3	NR	−0.35	NA

NA, not applicable; NR, not reported; ns, nonsignificant.

[a]Reported overall, not by treatment arm.

mouth and can be administered without water. The greater bioavailability of desmopressin ODST permits lower but clinically effective desmopressin dosing.[26]

A phase 3, 4-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study assessed the efficacy and safety of desmopressin ODST in nocturia.[26] Adults (N = 799) with an average of ≥2 voids/night and baseline serum sodium levels >135 mmol/L were randomly assigned to one of five treatment groups (placebo or desmopressin 10, 25, 50, or 100 μg daily to be taken 1 hr before bedtime). The two primary endpoints were change in mean number of nocturnal voids from baseline and proportion of subjects with >33% reduction in mean number of nocturnal voids from baseline. Greater doses of desmopressin ODST were associated with decreasing numbers of nocturnal voids (Fig. 1, Table III) and with reduced total nocturnal voided volume (Fig. 2, Table III). Reductions in the number of nocturnal voids were statistically significant, compared with placebo, for the 50- and 100-μg doses (−1.18 and −1.43 vs. −0.86, $P = 0.02$ and $P < 0.0001$, respectively; Table III) and were associated with improved QOL; one fewer nocturnal void was associated with an increased score of 4.68 on the Nocturia QOL Questionnaire ($P < 0.05$). Dose-dependent increases in the proportions of patients achieving a >33% reduction in mean number of nocturnal voids and decreases in diuresis were also observed. However, in retrospect, the selection of >33% as an endpoint may not represent the most clinically meaningful measure of improvement. Compared with placebo, desmopressin ODST (25–100 μg) was associated with statistically significant increases in the duration of the initial sleep period, which translated to an additional 44–68 min of uninterrupted sleep per night (Fig. 3, Table III). Therefore, the recommended/utilized doses, 25 and 50 μg, provide an additional 44 and 46 min, respectively, of uninterrupted initial sleep nightly compared with placebo.[26,37]

Overall, desmopressin ODST was well-tolerated in the study (Table IV),[38,39] as is seen by the low number of serious adverse events across placebo and desmopressin groups. The main reason for study withdrawal was serum sodium levels decreasing to below 125 mmol/L, as dictated by the protocol; this occurred in nine patients (1.1%), including 6 of 137 women who were receiving 50 or 100 μg desmopressin, and two men, aged 67 and 82 years, of 80 who were receiving 100 μg. The incidence of serum sodium fluctuations was age related (28 of 34 patients with serum sodium fluctuations were ≥65 years old) and tended to increase with desmopressin ODST dose. Serum sodium <125 mmol/L was not observed at the 25-μg dose. Based on these data, the authors recommended early sodium monitoring in men aged ≥65 years because of the increased risk associated with advanced age and the higher dose used for men.[26]

One unanticipated result in this study was an unprecedented high placebo effect. Although a high placebo response is typical of clinical studies in patients with lower urinary tract symptoms, it must be noted that in this and other studies on desmopressin ODST, the placebo effect was exceptionally high (i.e., improvements were seen in patients given placebo). This could be the result of increased awareness of nocturia on the part of patients and thus unconscious self-assignment of behavior modification.[26]

In an exploratory post hoc analysis of data from this study and from two unpublished phase I trials in healthy volunteers, Juul et al. reported that no hyponatremia events were observed for women ≤50 years and men ≤65 years at any dose of desmopressin ODST up to 100 μg or for women ≤65 years receiving desmopressin ODST 25 μg.[40] Although no dose-response relationship was noted between desmopressin and hyponatremia for men and women ≤50 years, decreases in serum sodium concentration were approximately twofold

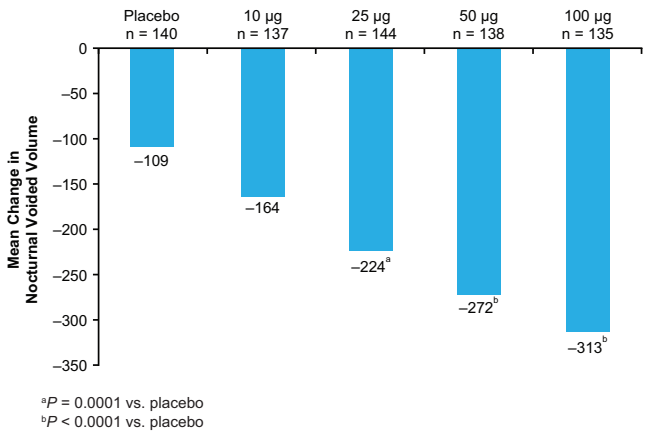


Fig. 1. Treatment with desmopressin ODST decreases nocturnal total urine output in a dose-dependent manner from baseline to day 28 (overall population).[26] ODST, orally disintegrating sublingual tablet.

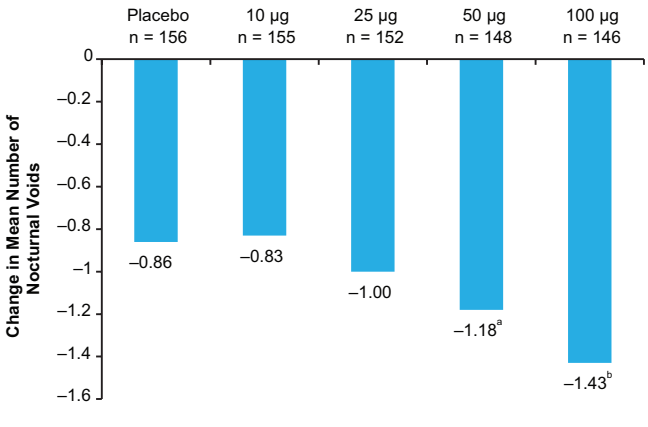
TABLE III. Efficacy End Points in Study to Assess Minimum Effective Desmopressin ODST Dose (Change From Baseline)[23]

		Desmopressin			
Mean values	Placebo	10 μg	25 μg	50 μg	100 μg
No. of patients	140	137	144	138	135
Mean urinary volume, nocturnal, ml	−109	−164	−224[a]	−272[a]	−313[a]
No. of patients	156	155	152	148	146
Mean number of nocturnal voids	−0.86	−0.83	−1.00	−1.18[b]	−1.43[a]
No. of patients	126	126	121	123	121
Mean FUSP, minutes	39	51	83[c]	85[d]	107[a]

FUSP, first undisturbed sleep period; ODST, orally disintegrating sublingual tablet.
[a]$P \leq 0.0001$ vs. placebo.
[b]$P = 0.02$ vs. placebo.
[c]$P = 0.001$ vs. placebo.
[d]$P = 0.0008$ vs. placebo.

greater in women >50 years receiving desmopressin ODST 25–100 μg compared with men, suggesting higher desmopressin sensitivity in women than in men.[40] These findings suggest that the minimum effective dose was lower for women than for men and support lower, sex-specific dosing to reduce the small but clinically significant risk of hyponatremia, that is, use of 50–100 μg desmopressin ODST for men and 25 μg desmopressin ODST for women.

Two randomized, controlled, phase 3 studies confirmed the safety and efficacy of 50 μg desmopressin ODST as the minimally effective dose for men and 25 μg for women. In these trials, desmopressin ODST at 50 and 75 μg was evaluated in 385 men (age range: 20–87 years)[38]; the 25-μg dose was evaluated in 261 women (age range: 19–87 years).[39] After 3 months of treatment, men treated with the 50-μg dose were 1.42 times more likely to have a reduction in the number of nocturnal voids and were nearly twice as likely to achieve >33% reduction in the number of voids than were patients given placebo (Table V). In women, the 25-μg dose was almost twice as likely (1.85 times more likely) to cause a >33% reduction in the number of voids (Table V). Increases in undisturbed sleep and QOL and decreases in nocturnal urine volume were also observed with 50- and 25-μg doses in men and women, respectively, compared with placebo (Table V). In both studies, desmopressin was well-tolerated (Table IV); only two men receiving the 50-μg dose and three women receiving 25 μg had serum sodium levels of <130 mmol/L.

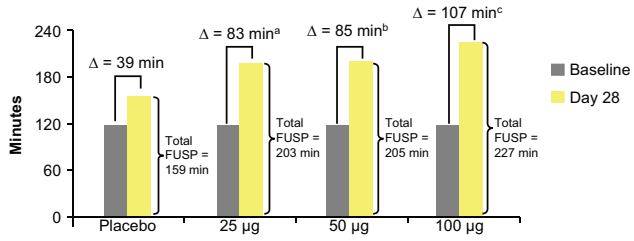


[a]$P = 0.02$ vs. placebo
[b]$P \leq 0.0001$ vs. placebo

Fig. 2. Treatment with desmopressin ODST decreases mean number of nocturnal voids in a dose-dependent manner from baseline to day 28 (overall population).[26] ODST, orally disintegrating sublingual tablet.

MANAGEMENT STRATEGIES: DESMOPRESSIN AND FLUCTUATIONS IN SERUM SODIUM LEVELS

The antidiuretic effect of desmopressin simultaneous with excessive patient intake of fluids is well known to cause water retention and to increase the risk for hyponatremia. Therefore, early evaluation of serum sodium fluctuations and reduction of fluid intake are essential for avoiding the sequelae of serum sodium reduction, especially in elderly patients. Early and regular evaluation of serum sodium levels should always be performed in men >65 years of age.[26] Although most cases are asymptomatic, it is recommended that serum sodium be assessed in men >65 years on days 4 and 28 after initiation of desmopressin therapy.[26] In addition, all women receiving desmopressin at doses in excess of 25 μg and men receiving doses >50 μg should be monitored for sodium levels, regardless of age. Risk for hyponatremia can be further reduced by restricting fluid intake only to levels necessary to satisfy thirst. Although European nations and countries in other regions currently follow the recommendations of their countries for the respective desmopressin ODST labels (i.e., 60–240 μg), we hope,



[a]$P = 0.001$ vs. placebo
[b]$P < 0.0008$ vs. placebo
[c]$P < 0.0001$ vs. placebo

Fig. 3. Desmopressin ODST increases initial period of undisturbed sleep in a dose-dependent manner from baseline to day 28.[26] Note: Data for 10-μg dose not shown. Data shown assume baseline FUSP of 120 min. △, change from baseline; FUSP, first undisturbed sleep period; ODST, orally disintegrating sublingual tablet.

TABLE IV. Incidence of Adverse Events in Phase 3 Desmopressin ODST Trials

	Dose-ranging study in men and women[23]					Low-dose study in men[34]			Low-dose study in women[35]	
		Desmopressin					Desmopressin			
	Placebo	10 μg	25 μg	50 μg	100 μg	Placebo	50 μg	75 μg	Placebo	Desmopressin 25 μg
n	160	163	158	158	160	143	119	122	126	135
All AEs, n (%)	76 (48)	92 (56)	78 (49)	92 (59)	99 (62)	58 (41)	46 (39)	49 (40)	57 (45)	60 (44)
Serious AEs, n (%)	1 (<1)[a]	1 (<1)[b]	1 (<1)[c]	1 (<1)[d]	0	1 (<1)[e]	4 (3)[f]	5 (4)[g]	2 (2)[h]	0
AEs leading to discontinuation, n (%)	7 (4)	6 (4)	2 (1)	13 (8)	14 (9)	7 (5)	4 (3)	7 (6)	1 (<1)	4 (3)
ADRs leading to discontinuation, n (%)	NR	NR	NR	NR	NR	4 (3)	4 (3)	5 (4)	0	3 (2)
Severe AEs, n (%)	2 (1)	6 (4)	3 (2)	11 (7)	7 (4)	2 (1)	2 (2)	2 (2)	3 (2)	1 (<1)
ADRs, n (%)	47 (29)	55 (34)	57 (36)	69 (44)	73 (46)	22 (15)	23 (19)	20 (16)	15 (12)	26 (19)
Serum sodium, n (%)										
≤125 mmol/L[i]	1 (<1)	0	0	4 (3)	4 (3)	0	2 (2)	4 (3)	0	0
126–129 mmol/L[j]	1 (<1)	1 (<1)	2 (1)	7 (4)	14 (9)	0	0	5 (4)	0	3 (2)[k]

AE, adverse event; ADR, AE assessed by the investigator as possibly/probably related to study drug; NR, not reported; ODST, orally disintegrating sublingual tablet.

[a]Prostate cancer.

[b]Diverticulitis.

[c]Myalgia.

[d]Metastasis.

[e]Pyrexia.

[f]Two patients with hyponatremia, one patient with acute myocardial infarction, and one patient with osteoarthritis.

[g]Four patients with hyponatremia and one patient with transient global amnesia.

[h]Cellulitis and pulmonary embolism.

[i]<125 mmol/L in Weiss et al.[23]

[j]125–130 mmol/L in Weiss et al.[23]

[k]Two patients with baseline serum sodium levels less than 135 mmol/L were included.

TABLE V. Treatment Effect of Desmopressin ODST Relative to Placebo Effect by Sex

	Baseline, mean (SD)		Mean change from baseline at 3 months		
Endpoint	Placebo	Desmopressin	Placebo	Desmopressin	Treatment effect relative to placebo effect
Men (desmopressin, 50 μg)[34]					
Voids, n	2.90 (0.81)	2.88 (0.86)	−0.88	−1.25	1.42
FUSP, minutes	147 (58)	146 (53)	73	112	1.53
33% responder odds	NA	NA	1.02	2.01	1.97
NQoL total	NA	NA	13.9	18.4	1.32
Nocturnal U-Vol, ml	620 (313)	607 (325)	131	209	1.60
Women (desmopressin, 25 μg)[35]					
Voids, n	2.88 (0.798)	2.84 (0.887)	−1.24	−1.46	1.18
FUSP, minutes	143 (57.6)	147 (56.9)	106	155	1.46
33% responder odds	NA	NA	1.75	3.23	1.85
NQoL total	NA	NA	21.9	27.2	1.24
Nocturnal U-Vol, ml	607 (338)	627 (328)	151	235	1.56

FUSP, first undisturbed sleep period; NA, not applicable, NQoL, nocturia quality of life; ODST, orally disintegrating sublingual tablet; U-Vol, volume of urine.
Reanalyzed from Weiss et al.[35] and Sand et al.[34]

based on these emerging data, that in the future, recommended doses for desmopressin ODST will be 25 μg for women and 50–100 μg for men. Headache, nausea, vomiting, fatigue, dizziness, ataxia, and weight gain are potential symptoms of clinically relevant hyponatremia.[41]

CONCLUSION

Current treatment options for nocturia do not consistently address underlying causes of nocturia, and, although they may provide some benefit, improvement is modest at best. Cumulative patient exposure across tablet and ODST formulations of desmopressin is estimated to exceed 25 million patients in 101 countries. The newest formulation, desmopressin ODST, administered sublingually without water at 60–240 μg, is approved in approximately 60 countries. Desmopressin ODST shows clinical efficacy and a tolerable safety profile in men and women with nocturia. Differential dosing between men and women may help achieve effectiveness while minimizing sodium fluctuations.

We as clinicians must consider what an actual "relevant clinical treatment difference measure" should be for nocturia,[8] and we must remember that for patients, nocturia is bothersome and inconvenient, but its impact on quality of sleep[13] is

associated with decreased QOL[42,43]; this may have an adverse impact on overall health,[44] including cardiometabolic aspects affected by poor glucose homeostasis.[5] Furthermore, treatment for nocturia can be considered efficacious only if it results in a decrease in nocturnal voiding episodes that is not merely statistically significant but is clinically meaningful to the patient.[8] Such reduction must also improve conditions secondary to nocturia, including falls, fractures, mood and QOL, sleep latency, and total daily sleep time. Thus a clinically relevant treatment effect could be based on a composite endpoint that includes reduction in the number of voids, lengthening of FUSP, and enhancement of QOL.[8] Although some of the endpoints that could make up a composite measure were included in the desmopressin studies, further research is warranted to develop an endpoint that identifies agents that make a truly clinically important difference to best serve our patients.

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