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Efficacy and Safety of Low Dose Desmopressin Orally Disintegrating Tablet in Women with Nocturia: Results of a Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study

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Abbreviations and Acronyms

ADR = adverse drug reaction
AEs = adverse events
MED = minimum effective dose
NP = nocturnal polyuria
N-QoL = nocturia quality of life
OAB = overactive bladder
ODT = orally disintegrating tablet
QoL = quality of life
WPAI = work productivity and activity impairment

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Purpose: Previous studies suggest a lower dose of desmopressin orally disintegrating tablet may be effective in females compared to males with nocturia. We confirm the efficacy and safety of 25 μg desmopressin orally disintegrating tablet compared to placebo in female patients.
Materials and Methods: In this 3-month, randomized, double-blind, parallel group study 25 μg desmopressin once daily was compared to placebo in women with nocturia (2 or more nocturnal voids). The co-primary efficacy end points were change from baseline in mean number of nocturnal voids and proportion of patients achieving at least a 33% reduction from baseline in the mean number of nocturnal voids (33% responders).
Results: The full analysis set comprised 261 patients (age range 19 to 87 years). Desmopressin significantly reduced the mean number of nocturnal voids and increased the odds of a 33% or greater response compared to placebo during 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 minutes compared to placebo at 3 months ($p = 0.003$). The response to desmopressin was seen by week 1 of treatment and was sustained throughout the trial. Significant increases in health related quality of life and sleep quality were observed compared to placebo. Desmopressin was well tolerated. Serum sodium levels remained greater than 125 mmol/L throughout the trial and 3 transient decreases to less than 130 mmol/L were recorded.
Conclusions: At a dose of 25 μg, desmopressin orally disintegrating tablet is an effective and well tolerated treatment for women with nocturia. Treatment provides rapid and sustained improvement in nocturia and quality of life.

Key Words: nocturia, deamino arginine vasopressin, placebos, quality of life

Nocturia is defined by the International Continence Society and the International Urogynecological Association as the need to wake to void once or more per night.[1,2] It is a highly prevalent condition[3] that has a clinically significant impact on morbidity, mortality, quality of life and productivity.[4–7] The detrimental impact on health is considered mainly to be due to sleep fragmentation[8,9] when 2 or more nocturnal voids are experienced.[5,7,10]

The etiology of nocturia is multifactorial. Treatment based on advice re-

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garding fluid restriction or overactive bladder syndrome therapies such as antimuscarinics has provided little therapeutic benefit.[11,12] However, nocturnal polyuria, defined as nocturnal urine output greater than 20% to 33% of 24-hour output, depending on age,[1,9] is seen in 72% to 85% of females in nocturia trials.[13] NP is associated with decreased secretion of the antidiuretic hormone arginine vasopressin.[14,15]

Desmopressin acetate, a synthetic analogue of arginine vasopressin, mimics the antidiuretic action of the natural hormone,[15] and has been proven to be a well tolerated and effective treatment for nocturia.[16–18] Desmopressin is the only agent specifically approved for the treatment of nocturia (in more than 80 countries outside the United States) and has a grade A level 1 recommendation from the International Consultation on Incontinence and European Association of Urology for the treatment of nocturia associated with polyuria.[19,20] The safety profile of desmopressin in clinical trials is similar to that of placebo except for the possibility of hyponatremia, which is rare, and associated with elderly patients and at higher dose levels (100 to 400 μg solid tablet).[21]

Desmopressin has recently been formulated as an orally disintegrating tablet that overcomes issues related to swallowing difficulty, avoids ingestion of extra fluids and has improved bioavailability compared with the standard tablet.[10] The ODT was used in clinical trials to determine the MED of this new formulation, and to optimize the balance between therapeutic effect and tolerability. Interestingly a gender difference in sensitivity to desmopressin was found with a relative male-to-female dose ratio of 2.7, and 25 μg was effective with no associated reports of serum sodium 125 mmol/L or less in female patients.[10,22] Therefore, this study in women (NCT01223937) was designed to confirm the safety and efficacy of 25 μg desmopressin ODT and establish dose recommendations for nocturia.

MATERIALS AND METHODS

Patients

Eligible patients were females older than 18 years with nocturia (2 or more voids per night determined via a 3-day bladder diary completed immediately before randomization). Inclusion and exclusion criteria are listed in supplementary table 1 (http://jurology.com/). Key exclusion criteria included evidence of urinary disorders, polydipsia and hyponatremia (serum sodium less than 135 mmol/L). Patients on stable doses of OAB medication for 3 months were allowed to participate. The trial was performed in accordance with the Declaration of Helsinki and approved by the institutional review board/ethics committee for each site. All patients provided written informed consent.

Study Design and Procedures

This was a randomized, double-blind, placebo controlled, parallel group, multicenter study. Patients were randomized 1:1 to placebo or 25 μg desmopressin once daily using a computer generated list prepared before enrollment. Randomization was stratified by age (younger than 65 vs 65 years old or older). Desmopressin and placebo ODT were supplied by Ferring Pharmaceuticals, and were indistinguishable with respect to appearance, smell, taste and packaging.

Participants were instructed to empty their bladder before bed, drink only to satisfy thirst, and limit evening intake of fluids with a diuretic effect such as coffee, tea, caffeinated soft drinks and alcoholic beverages. Tablets were to be taken 1 hour before bedtime.

Diaries and Questionnaires

Patients completed 3-day bladder and sleep diaries immediately before randomization and after randomization at week 1, month 1, month 2 and month 3 to record the time and volume of nocturnal voids. Patients reported on sleep quality using the sleep rating scale (1—poor to 10—excellent). The Nocturia Quality of Life and Work Productivity and Activity Impairment questionnaires were also completed. Patients rated each of the 13 N-QoL statements from 0 (lowest) to 4 (highest), where 1 statement concerns global QoL and 12 statements cover the specific disease. The raw scores were transformed into a standardized score out of 100. The WPAI outcomes were expressed as impairment percentages of 4 scores of absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism) and activity impairment.

End Points

The Food and Drug Administration requested co-primary efficacy end points were change from baseline in mean number of nocturnal voids and 33% responder status during 3 months of treatment using a longitudinal analysis. A 33% responder was defined as a patient with a decrease of at least 33% in the mean number of nocturnal voids at each visit compared to baseline. This end point captures information on the distribution of reductions.

Secondary end points included change from baseline at 3 months in mean number of nocturnal voids, proportion of 33% responders, mean time to first nocturnal void (the time from going to bed with the intention of sleeping to first void) and mean nocturnal urine volume. Exploratory end points included mean self-rated sleep quality, N-QoL scores and WPAI percentages.

Safety and Tolerability

Safety and tolerability were monitored at each visit via observation and assessment of adverse events. AEs were coded by the system organ class and preferred terms using MedDRA, and categorized by severity, seriousness and likelihood of causal relationship to study medication as determined by the investigator.

Serum sodium was measured during screening and on all study visits after treatment. If serum sodium was 130 mmol/L or less the patient was asked to visit the trial site as soon as possible for further evaluation. Patients with a

serum sodium of 125 mmol/L or less were withdrawn from the study immediately.

Additional safety measurements included a standard battery of blood and urine analyses, vital signs and physical examinations. All patients who received 1 or more doses of the study drug or placebo and had 1 or more safety assessments were included in the safety analyses.

Statistical Analysis

The trial was powered to demonstrate superiority to placebo simultaneously on the 2 co-primary end points. Using assumptions on means, variances and correlations of the number of voids at various points based on data from females in a previous trial,[10] simulations demonstrated that a sample size of 130 patients per group yielded at least 95% power to detect 0.5 or more voids constant treatment effect as well as a statistically significant subsequent time averaged odds ratio of 33% responder status.

All end points were analyzed based on the full analysis set that included all randomized and exposed patients with at least 1 efficacy assessment after dosing initiation. Two-sided tests were used for all efficacy end points.

Change from baseline in mean number of nocturnal voids was analyzed longitudinally using a repeated measures ANCOVA (ANCOVA) with change in mean number of nocturnal voids as the dependent variable. The second co-primary end point, proportion of 33% responders, was analyzed using a generalized estimating equation method with the 33% responder status as the dependent variable. For both analyses observed values were used, baseline mean nocturnal voids was a covariate, and treatment, visit (including a treatment by visit interaction term) and age stratification (younger than 65, 65 years old or older) were factors. If the treatment by visit interaction was not significant at the 5% level, it was removed from the model.

All secondary end points were tested using cross-sectional analyses at month 3 using the respective baseline as covariate, and age stratification and treatment as factors. Missing values were imputed using last observation carried forward. Exploratory end points were analyzed in a manner similar to the secondary end points. SAS® version 9.2 was used.

RESULTS

This study was conducted at 39 primary and secondary care centers across the United States and Canada from November 2010 to November 2011. Of 649 screened subjects 268 were randomized to treatment (fig. 1). The most common reason for screening failure was nonfulfillment of the inclusion/exclusion criteria (49%), such as evidence of severe daytime voiding dysfunction, renal impairment and averaging less than 2 nocturnal voids during screening. Overall, 96% of randomized patients took greater than 80% of the planned doses (based on returned medication) and 89% completed the study. An equal percentage of patients prematurely discontinued in the desmopressin and placebo treatment groups (fig. 1). Two patients were randomized to placebo but received desmopressin, and they are included in the placebo group in the full analysis set. Baseline characteristics are summarized in table 1. Overall, treatment groups were well balanced. All patients had a previous diagnosis of nocturia. Daytime frequency of 6 or more voids was reported by 40% to 50% of patients in the treatment groups and 5 patients were included despite having 8 or more voids at baseline. The most common concomitant medications were vitamins, lipid modifying agents, analgesics, anti-inflammatory agents and antirheumatic agents.

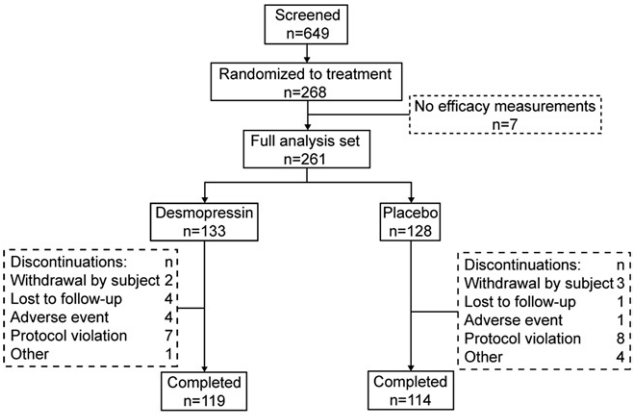

Figure 1. Patient disposition

The trial met its primary objective as statistically significant differences, favoring desmopressin compared with placebo, were shown for the co-primary end points of change from baseline in mean number of nocturnal voids (treatment effect −0.22 voids, $p = 0.028$) and the odds of achieving a 33% or greater responder status (odds ratio 1.85, $p = 0.006$) during 3 months as assessed by longitudinal analysis (table 2). The treatment difference was similar for patients younger than 65 and 65 years old or older (test for interaction $p = 0.25$ and 0.60, respectively). The dose of 25 μg desmopressin ODT rapidly reduced the number of nocturnal voids from baseline and maintained the reduction with a trend for further reduction with time (fig. 2, *A*). Similarly, the proportion of 33% responders increased from baseline by week 1 and was maintained throughout the trial (fig. 2, *B*).

Results of the secondary efficacy end points at 3 months are presented in supplementary table 2 (http://jurology.com/). While a significant difference compared with placebo was seen in the change from baseline in the number of nocturnal voids after desmopressin treatment ($p = 0.01$), the 33% responder rate did not reach statistical significance. A significant increase in time to first void and a reduction in nocturnal urine volume from baseline were seen

Table 1. *Baseline characteristics*

	Desmopressin 25 μg		Placebo	
No. pts	133		128	
Age:				
Mean (SD)	59.5	(14.3)	60.1	(14.1)
Median (min, max)	62	(19, 81)	64	(23, 87)
No. age category (%):				
Younger than 65	71	(53)	65	(51)
65 or Older	62	(47)	63	(49)
Body mass index (kg/m^2):				
Mean (SD)	31.4	(7.03)	29.1	(6.58)
Median (min, max)	30.3	(18.2, 50.5)	28.0	(17.9, 46.6)
No. race (%):				
White	109	(82)	104	(81)
Black/African-American	23	(17)	22	(17)
Other	1	(less than 1)	2	(2)
No. nocturnal voids category (%):				
2–Less than 3	78	(59)	71	(55)
3–Less than 4	45	(34)	44	(34)
4–Less than 5	9	(7)	11	(9)
6–Less than 7	0	(0)	1	(less than 1)
7 or More	1	(less than 1)	1	(less than 1)
Nocturnal voids:				
Mean (SD)	2.84	(0.9)	2.88	(0.8)
Median (min, max)	2.67	(2.0, 9.67)	2.67	(2.0, 7.0)
Mins to first nocturnal void:				
Mean (SD)	147	(57)	143	(58)
Median (min, max)	149	(11, 299)	135	(32, 350)
No. mean daytime voids category (%):				
2–Less than 4	6	(5)	13	(10)
4–Less than 6	57	(43)	62	(48)
6–Less than 8	67	(50)	51	(40)
8 or More	3	(2)	2	(2)
Daytime voids:				
Mean (SD)	5.83	(1.24)	5.45	(1.27)
Median (min, max)	6	(2.0, 9.0)	5.3	(2.3, 8.3)
Nocturnal vol (ml):				
Mean (SD)	627	(328)	607	(338)
Median (min, max)	617	(60; 1,617)	561	(98; 1,742)
24-Hr vol (ml):				
Mean (SD)	1,409	(687)*	1,343	(688)
Median (min, max)	1,372	(165; 3,200)*	1,316	(200; 3,592)
No. NP (%)†	117	(88)	114	(89)
Polydipsia estimate (ml/kg/24-hr):				
Mean (SD)	18.1	(9.6)*	17.9	(9.7)
Median (min, max)	17.0	(2.1, 44.7)*	16.8	(2.4, 52.3)

* In 132 patients.
† Based on a NP index (nocturnal volume/24-hour volume) 33% or greater.

in the desmopressin vs placebo group at 3 months ($p = 0.003$).

Exploratory end points also improved with desmopressin. Analyses of N-QoL scores, reported by patients receiving desmopressin compared with those receiving placebo at 3 months, showed statistical significance in total score as well as in the 2 subdomains. The sleep quality ratings and WPAI percentages were significantly improved with desmopressin in some domains (post hoc analysis, table 3).

Table 2. *Summary of co-primary end point changes from baseline*

	Desmopressin 25 μg	Placebo
No. nocturnal voids:*		
No. pts	133	128
Adjusted mean	−1.46	−1.24
Treatment difference	−0.22	
95% CI	−0.42, −0.02	
p Value	0.028†	
Proportion of 33% responders:‡		
Adjusted probability	0.76	0.64
Adjusted odds	3.23	1.75
Odds ratio	1.85	
95% CI	1.19, 2.86	
p Value	0.006†	

* Repeated measures ANCOVA of change from baseline at week 1, month 1, month 2 and month 3, adjusted for age stratification factor (younger than 65 years, 65 years old or older), visit and baseline nocturnal voids.
† Statistically significant difference vs placebo, $p \leq 0.05$.
‡ Generalized estimating equation logistic regression of 33% responder status at week 1, month 1, month 2 and month 3, adjusted for age stratification factor (younger than 65 years, 65 years old or older), visit and baseline nocturnal voids.

Overall desmopressin was well tolerated (table 4). Treatment emergent AEs with an incidence of 5% or more in either treatment group included urinary

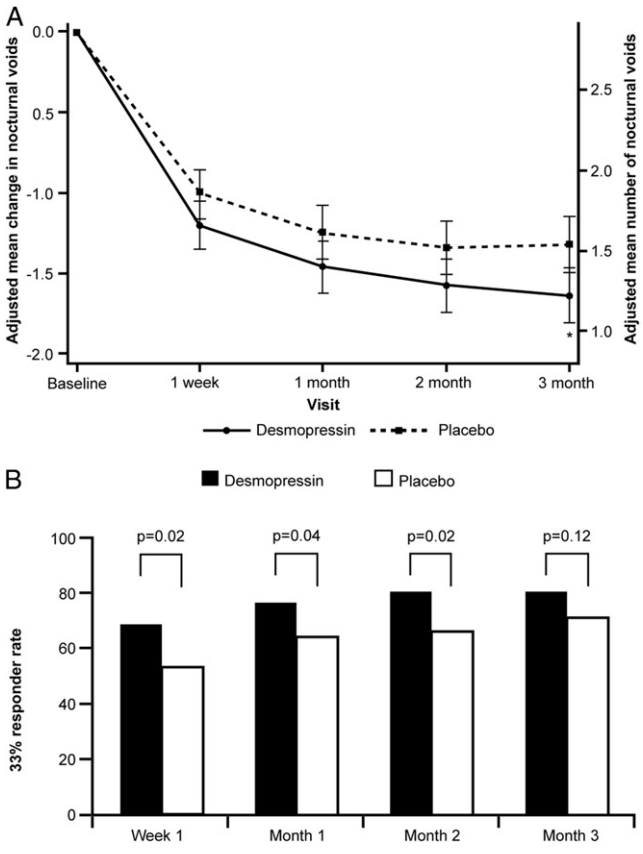

Figure 2. Adjusted mean and change from baseline in mean number of nocturnal voids (*A*) and adjusted 33% responder rates (*B*). Asterisk indicates $p < 0.01$, statistically different from placebo at given point, repeated measures ANCOVA.

Table 3. *Adjusted treatment differences in mean change from baseline in exploratory end points at month 3*

	No. 25 μg Desmopressin*	No. Placebo*	Difference in Adjusted Means (95% CI)	p Value
N-QoL:	133	128		
Total score			5.34 (0.76, 9.92)	0.02†
Bother/concern domain			5.69 (0.72, 10.65)	0.03†
Sleep/energy domain			4.90 (0.06, 9.75)	0.05†
Global quality of life			1.26 (−2.97, 5.49)	0.56
Sleep quality:‡	133	128		
"How do you feel right now?"			0.43 (−0.01, 0.87)	0.06
"Rate how refreshed you feel"			0.46 (0.02, 0.90)	0.04†
"Rate the quality of your sleep last night"			0.53 (0.06, 1.00)	0.03†
WPAI:				
Absenteeism (% work time missed)	32	30	−0.12 (−8.46, 8.23)	0.98
Presenteeism (% impairment at work)	32	31	−2.93 (−13.10, 7.24)	0.57
Work productivity loss	32	30	−3.37 (−14.75, 8.01)	0.56
Activity impairment	124	126	−6.68 (−12.66, −0.70)	0.03†

* Number of patients completing questionnaire/questionnaire subsection.
† Statistically significant difference vs placebo, repeated measures ANCOVA p ≤0.05.
‡ Mean of scores on 3 consecutive mornings.

tract infection, headache and upper respiratory tract infection. ADRs with an incidence of 2% or more in either treatment group included dry mouth, headache, medication error, somnolence and rash. AEs that led to discontinuation were headache, somnolence and hypertension in the desmopressin group and pulmonary embolism in the placebo group. No serum sodium values of 125 mmol/L or less were observed. All 3 patients whose serum sodium reached less than 130 mmol/L recovered to greater than 130 mmol/L within 2 to 4 days without discontinuing treatment (fig. 3). Of these 3 patients 2 had a serum sodium level of less than 135 mmol/L at baseline.

DISCUSSION

This study confirms the efficacy of 25 μg desmopressin ODT in the treatment of nocturia in adult female patients. It was conducted to confirm the findings of a recently published large trial of 10, 25, 50 and 100 μg desmopressin ODT,[10] where post hoc analyses by gender indicated a difference in the MED as well as safety benefits of targeting the gender specific MED.[22] These findings demonstrate an improved therapeutic window and risk-to-benefit ratio for the more bioavailable desmopressin ODT compared with standard tablet in the treatment of nocturia in female patients.

Table 4. *Summary of treatment emergent AEs and serum sodium values (safety analysis set)*

	No. 25 μg Desmopressin (%)		No. Placebo (%)	
No. pts	135		126	
All AEs	60	(44)	57	(45)
Severe AEs	1 (less than 1)		3	(2)
ADRs*	26	(19)	15	(12)
AEs leading to discontinuation	4	(3)	1 (less than 1)	
ADRs leading to discontinuation*	3	(2)	0	
Serious AEs	0		2	(2)†
Serum sodium (mmol/L):				
125 or Less	0		0	
126–129	3	(2)‡	0	
130–134	11	(8)	2	(2)

* An AE assessed by the investigator as possibly/probably related to study drug.
† Cellulitis and pulmonary embolism.
‡ Two patients were included with baseline serum sodium less than 135 mmol/L.

Compared with baseline, the desmopressin group had a clinically relevant reduction of approximately 1.5 nocturnal voids. Desmopressin demonstrated statistically significant benefits compared to placebo, with reduction in nocturnal voids and nocturnal urine output, and increase in time to first void and proportion of 33% responders. The notable placebo effect is worth discussing. It may be partly linked to advice on fluid restriction given during screening. The regular, extended completion of voiding diaries may increase awareness of drinking and voiding habits and exert similar influences to those reported with behavioral training.[23] Large responses to placebo have been reported for studies in urological indications such as OAB and benign prostatic hyperplasia.[23–25] In a meta-analysis of placebo responses across different disorders, placebo responses were largest in urogenital disorder trials.[23] Participation in a trial may improve patient knowledge to a larger extent than for other conditions that are more widely and openly discussed. Indeed, large placebo effects have been reported even in trials of nonpharmacological interventions for the treatment of OAB, such as pelvic floor training.[23]

In other therapeutic areas the placebo effect tends to decrease with time. However, the placebo effect persisted throughout this study. Durable placebo re-

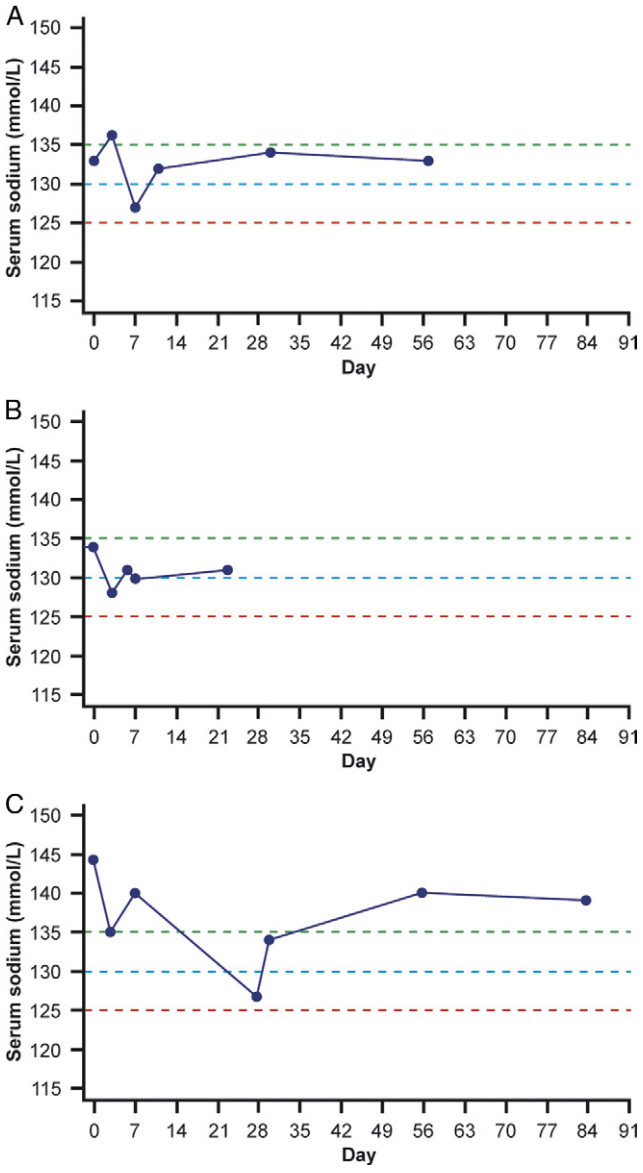

Figure 3. Serum sodium profiles of 3 patients receiving 25 μg desmopressin with post-baseline serum sodium less than 130 mmol/L. *A,* in 58-year-old patient baseline serum sodium was in violation of inclusion criterion (133 mmol/L). *B,* in 71-year-old patient baseline serum sodium was in violation of inclusion criterion (134 mmol/L). Exclusion criteria also violated due to polydipsia and medical history of hyponatremia. Patient discontinued study due to AE of somnolence. *C,* in 72-year-old patient baseline serum sodium was 144 mmol/L and no AEs were reported.

sponses up to 1 year have been recorded in trials for bladder outlet obstruction with tamsulosin.[26] Placebo responses are also hypothesized to be due to regression to the mean when more severe disease is studied.[27] Stringent inclusion criteria such as the greater than 2 nocturnal voids during screening used in this study may lead to a larger placebo response due to this phenomenon.

The treatment difference in time to first void between placebo and desmopressin was 49 minutes at month 3. This corresponds with the post hoc analysis showing significant treatment differences in both domains of the N-QoL questionnaire and in 2 of the 3 sleep quality scales. This suggests that reduction in number of voids might not be the best way of measuring change in nocturia[8] and that an increase in undisturbed sleep and increases in QoL may be the important measures for the patient.

Among productivity instruments the psychometric properties of the WPAI questionnaire[28] have been assessed most extensively.[29] It is generalizable across occupations and disease areas, and is also available in disease specific versions. Using WPAI a significant productivity loss by nocturia has been documented.[30] In our study the WPAI results were less consistent than the QoL and sleep quality results. Insufficient power may have contributed as only approximately 20% of the population was working. General activity impairment was significantly improved with desmopressin compared to placebo.

Desmopressin was well tolerated. The risk of a clinically relevant serum sodium reduction (less than 130 mmol/L) has been shown to be fivefold higher for women compared to men receiving 50 μg desmopressin.[22] No incidences of serum sodium 125 mmol/L or less were seen in this study, even in patients 65 years old or older, supporting an improved therapeutic profile for low dose desmopressin therapy for women compared to higher doses. The importance of confirming a normal serum sodium before treatment was highlighted in this study as 2 of the 3 patients with a serum sodium less than 130 mmol/L during treatment had baseline levels less than 135 mmol/L. The incidence of individual AEs was low and comparable across desmopressin and placebo groups. All AEs were mild or moderate, and most, except reduction in serum sodium, were considered unrelated to desmopressin.

In summary, results from this phase III trial demonstrate the efficacy and safety of 25 μg desmopressin ODT in women with nocturia, providing an improved therapeutic window and confirming the results of an earlier trial in this population.[10] Our findings support recommendations for future gender specific desmopressin doses for the treatment of nocturia.

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