Emerging Challenges in Primary Care: 2018

Management of Nocturia: An Unmet Need in LUTS

Faculty

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Disclosures

- Matt T. Rosenberg, MD serves as a consultant for Astellas, Avadel, OPKO, and Ferring. He also serves as a speaker for Astellas, Avadel and OPKO.

- David R. Staskin, MD serves as an investigator for GTX and Urovant. Dr. Staskin also serves as a consultant for Ferring and a speaker, consultant, and investigator for Astellas Pharma.
Learning Objectives

1. Describe the impact of nocturia on affected patients.
2. Evaluate symptoms of nocturia in affected patients.
3. Assess current pharmacologic and nonpharmacologic nocturia management strategies.
4. Differentiate the mechanisms of action and safety and efficacy profiles of available and emerging therapies for nocturia.

PRE-TEST QUESTIONS

Pre-N1: How confident are you in your ability to manage patients with nocturia?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 2

Pre-N2: In a patient with nocturia, which quality of life measure is not affected:

1. Sleep
2. Eating
3. Sex
4. Work

Pre-test ARS Question 3

Pre-N3: A 50 year-old patient with BPH and no other medical problems has persistent nocturia despite a greatly improved urine flow with an alpha blocker. Which of the following is a reasonable intervention?

1. Add an antimuscarinic
2. Add low dose desmopressin
3. Consider a TURP
4. Add a 5-alpha reductase inhibitor

Pre-test ARS Question 4

Pre-N4: Which of the following is a risk factor for developing hyponatremia in a patient treated with desmopressin?

1. Low sodium diet
2. Age
3. Gender
4. Low urine output at baseline
Pre-test ARS Question 5

Pre-N5: How often should you check sodium levels for a patient on low dose desmopressin?

1. At initiation and then every 3 months
2. At initiation and then every 1 month
3. Every 30 days
4. At initiation, day 7, day 30 and then periodically

NOCTURIA is defined as waking at night to urinate, with each voiding episode preceded and followed by sleep

Clinically Meaningful ≥2

NOCTURNAL POLYURIA is defined as nighttime urine production >20% of the total urine output for younger adults and >33% for older adults


The Bottom Line

- When the volume of urine made at night is greater than functional bladder capacity.
- By understanding this, it helps us understand that we can either attempt to increase capacity, or decrease volume.
What Nocturia and Nocturnal Polyuria are Not

- Merely a symptom of other urologic conditions (OAB, BPH)
- Normal part of aging (or is it?)
Nocturia Prevalence by Gender and Age


Obstacles to Clinical Presentation Leads to Undertreatment

- Patients may not recognize nocturia as a medical condition
  - 60.7% of patients assumed it was part of aging process
- Embarrassment and reluctance
  - 66.4% with <3 nocturnal voids perceived it as a minor problem
- Failure of medical professionals to acknowledge and treat
  - Of those who had consulted a doctor, 37.2% were not offered any treatment.
- Delay in diagnosis
  - 12 weeks to make a diagnosis
  - 37 weeks until first prescribed treatment.
  - Time from the onset of symptoms to beginning treatment 105.5 weeks

Consequences of Nocturia and Poor Sleep?

Short-Term
- Increased daytime sleepiness
- Reduced psychomotor performance
- Reduced daytime energy
- Increased reaction time
- Poor mood

Long-Term
- Depression
- Susceptibility to somatic disease
- Risk of cardiovascular disease
- Risk of car accidents

Impact of Nocturia on Bone Fracture and Mortality in Older Individuals

Figure 1: Incidence of all and fall-related fractures in 369 patients with (light blue bars) and in 420 without (dark blue bars) nocturia were significantly higher in former (each χ² = 0.03).

Increasing Nocturnal Voids Decreases Most HRQoL Dimensions

Figure 2: Nocturia Frequency, Both, and Quality of Life

Survival Probability with Nocturia


Risk Factors for Nocturia

Both genders

- Age
- Hispanic and Black ethnicity
- Diabetes mellitus or insipidus
- Arthritis
- Asthma
- High blood pressure
- Anxiety
- Depression
- Childhood bed-wetting

Men

- Prostatitis
- Prostate cancer

Women

- High body mass index
- Heart disease
- Inflammatory bowel disease
- Recurrent UTIs
- Uterine prolapse
- Hysterectomy
- Postmenopausal

Cause of Nocturia is Multifactorial and Multidisciplinary

The Evaluation of Nocturia: History, Physical, and Labs are Essential

- Medical and surgical history
- Medications
- Focused physical examination
- Labs
- Voiding diary or awareness of timing and amounts of voids (optional)

Examples in the Patient’s History that may Cause or Worsen LUTS

- Diabetes (new onset or poorly controlled)
  - Causing polyuria/polydipsia
- Congestive heart failure
- Nighttime fluid mobilization
- Recent Surgery
  - Catheterization during surgery, immobilization, constipation from pain medications

A recent onset of the symptoms may provide a clue to the etiology
Examples of Medications Associated with Nocturia or Polyuria

<table>
<thead>
<tr>
<th>Medications</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>Direct blocking of proximal tubular sodium reabsorption or increased atrial natriuretic peptide levels; promote peripheral edema and/or pedal edema</td>
</tr>
<tr>
<td>Excessive vitamins A and D; thiazides</td>
<td>Reduced sodium and bicarbonate reabsorption in proximal tubule</td>
</tr>
<tr>
<td>NSAIDs; thiazolidinedione anti-diabetic agents, GABAergic agents</td>
<td>Promote peripheral edema and/or dependent edema</td>
</tr>
</tbody>
</table>


Treatment Considerations

- Decreasing overall fluid intake and limiting nighttime fluids
- Emptying bladder before going to bed
- Reduction or avoidance of caffeine, alcohol, and salt
- Altering the timing of diuretic medication administration
- Use of compressive stockings
- Leg elevation in the early evening
- Treatment of OSA with continuous positive airway pressure
- Barrier-free access to toilet or toilet chair
- Weight loss and exercise


Behavioral Intervention Considerations

- Decreasing overall fluid intake and limiting nighttime fluids
- Emptying bladder before going to bed
- Reduction or avoidance of caffeine, alcohol, and salt
- Altering the timing of diuretic medication administration
- Use of compressive stockings
- Leg elevation in the early evening
- Treatment of OSA with continuous positive airway pressure
- Barrier-free access to toilet or toilet chair
- Weight loss and exercise

Behavior Therapy is Beneficial Regardless of Etiology of Nocturia

Japanese study of 56 patients
- Restriction of fluid intake
- Restraining from excess hours in bed
- Moderate daily exercise
- Staying warm in bed

Benefits
- Reduction of mean number of nocturnal voids from 3.6 – 2.7 (p<0.0001)
- Reduction in mean nocturnal urine volume from 923 to 768 ml (p<0.0005)
- Elimination of 1 or more voiding episodes per night in 53.1% of patients


Symptoms Direct Therapy

With Nocturnal Polyuria, if Possible, Treat the Cause

OVERCONSUMPTION
- Behavioral
- Environmental
- Dipsogenic diabetes insipidus
- Diabetes mellitus

OVERDIURESIS
- Third-space fluid resorption
- Fluid shifts
- Medications (eg, diuretics)
- Sleep disorders or apnea
- Congestive heart failure
- Renal conditions
- Diabetes mellitus

TOO LITTLE ANTIUREREIS
- Circadian defect in secretion or action of vasopressin
- Renal conditions
- Cerebrovascular damage
- Central diabetes insipidus
- Nephrogenic diabetes insipidus
How much does the Etiology Matter?

- Regardless of the cause, voiding at night results from a production of nocturnal urine that exceeds the capacity of the urinary bladder to comfortably store it.
- Therefore, treatment must be focused on decreasing fluid production, increasing bladder capacity, or improved emptying.

Urine Production Regulated by Arginine Vasopressin

- AVP is produced in the hypothalamus and travels along nerve fibers to the posterior pituitary, where it is stored and released
- AVP promotes reabsorption of water in the distal tubules and collecting duct of nephrons
- As we age we either produce less AVP or it becomes less potent

Pausing Urine Production

Desmopressin

- A synthetic analog of AVP and a selective V2 receptor agonist
- Increases water reabsorption in the distal tubule and collecting ducts
- Concentrates the urine
- Decreases urine production
Available Formulations of Desmopressin

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal spray</td>
<td>Nocturia due to nocturnal polyuria</td>
</tr>
<tr>
<td>Sublingual melt</td>
<td>Nocturia due to nocturnal polyuria</td>
</tr>
<tr>
<td>Tablet</td>
<td>Diabetes insipidus and primary nocturnal enuresis</td>
</tr>
</tbody>
</table>


Key Differences of Approved Medications

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Study Population</th>
<th>Onset of action</th>
<th>Available doses</th>
<th>Dosing nuances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal spray</td>
<td>Adult patients ≥50 years of age</td>
<td>Tmax was 15 minutes for 0.83 mcg and 45 minutes for 1.66 mcg</td>
<td>0.83 mcg and desmopressin acetate per 0.1 mL spray</td>
<td>Recommended to start at lower dose in patients ≥65 years of age or at risk for hyponatremia</td>
</tr>
<tr>
<td>Sublingual melt</td>
<td>Patients &gt;18 years of age</td>
<td>30 minutes</td>
<td>27.7 μg for women and 55.3 μg for men</td>
<td>No titration Gender specific dosing</td>
</tr>
</tbody>
</table>

Typical Study Design in Assessing Nocturia

- Patient characteristics were comparable across the placebo and desmopressin groups:
  - Mean age: 62.0 years
  - Gender: 55% men
  - Ethnicity: 80% Caucasian
  - BMI: 29.56 kg/m²
- Overall, 46% of patients experienced >3 voids per night
- Nocturnal polyuria was present in 90.2% of patients
- Approximately 20% of patients (143/799) received concomitant treatment for OAB, BPH or both conditions

BMI, body mass index; BPH, benign prostatic hyperplasia; OAB, overactive bladder
Sublingual Desmopressin Effects Nocturnal Volume

![Graph showing effects of sublingual desmopressin on nocturnal volume](image)

Nasal Desmopressin Decreases Nocturnal Urine Production

![Graph showing the decrease in nocturnal urine volume](image)

Nasal Desmopressin: Mean Decrease in Nocturnal Voids

![Graph showing the mean decrease in nocturnal voids](image)
Sublingual Desmopressin in Women: Mean Decrease in Nocturnal Voids

Sublingual Desmopressin in Men: Mean Decrease in Nocturnal Voids

Sublingual Desmopressin Efficacy is Maintained in the Long Term

<table>
<thead>
<tr>
<th>Number of Nocturnal Voids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>25 µg</td>
</tr>
<tr>
<td>50 µg</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change from baseline to Week 12</td>
</tr>
<tr>
<td>Change from baseline to Week 52</td>
</tr>
</tbody>
</table>
Nasal Desmopressin Extends Time for Bladder Filling and Subsequent Emptying

Sublingual Desmopressin Extends Time for Bladder Filling and Subsequent Emptying

Special Populations: Nocturia Plus OAB or BPH

Low-dose desmopressin plus tamsulosin in men with BPH*
- Reduction of the nocturnal frequency of voids by 84.3% (combo) vs 44.6% (mono) in patients with or without nocturnal polyuria.
- Combination therapy improved the quality of sleep.
- Comparable overall tolerability with monotherapy.

Combination of desmopressin and the antimuscarinic tolterodine in women with OAB and nocturnal polyuria*
- Decrease in nocturnal void volume (P = .034) with combination therapy.
- Increase in time to first nocturnal void (P = .045) over tolterodine monotherapy.
Sublingual Desmopressin  | Nasal Desmopressin
--- | ---
**Drug Interactions**  | Concomitant use of medication and loop diuretics or systemic or inhaled glucocorticoids is contraindicated because of the risk of severe hypernatremia. Medication can be started or resumed 3 days or 5 half-lives after the glucocorticoid is discontinued, whichever is longer.  
  
Medication can be started or resumed 3 days or 5 half-lives after the glucocorticoid is discontinued, whichever is longer.  
  
Drugs such as tricyclic antidepressants, SSRIs, chlorpromazine, opioid analgesics, thiazide diuretics, carbamazepine, famotidine, sulfonylureas (particularly chlorpropamide), and NSAIDs may increase the risk of hyponatremia.  
  
Monitor serum sodium more frequently in patients taking medication concomitantly with these drugs and when doses of these drugs are increased.

**Contraindications**  | Hyponatremia or a history of hyponatremia  
  
Polydipsia  
  
Concomitant use with loop diuretics  
  
Concomitant use with systemic or inhaled glucocorticoids  
  
Renal impairment with eGFR below 50 mL/min/1.73 m²  
  
Known or suspected SIADH  
  
During illnesses that can cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection  
  
Heart failure  
  
Uncontrolled hypertension

**Adverse Reactions**  | Common adverse reactions reported by ≥2% of medication-treated patients and at a higher incidence with either dose than with placebo in patients with nocturia due to NP (in studies 1, 2, and 3) included dry mouth, hyponatremia, headache, and dizziness

**Comparable Package Inserts**


### Sublingual Desmopressin

**Bad Warning**

Medication can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.

Medication is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, diseases that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids.

Ensure the serum sodium concentration is normal before starting or resuming medication. Measure serum sodium within 7 days, approximately 1 month after initiating therapy, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia. If hyponatremia occurs, medication may need to be temporarily or permanently discontinued.

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### Sublingual Desmopressin

**Precautions**

- **Hyponatremia**: Limit fluid intake to a minimum from 1 hour before administration until 8 hours after administration. Use of medication without concurrent reduction of fluid intake may lead to fluid retention and hyponatremia. Advise patients to avoid drinks containing caffeine or alcohol before bedtime.

- **Women**: Women are more sensitive to the effects of medication compared to men. The recommended dose for women is lower than for men because women have a higher risk of hyponatremia with the 55.3 mcg dose in clinical trials.

- **Fluid Retention**: Medication can cause fluid retention, which may worsen underlying conditions that are susceptible to volume status. Medication is not recommended for patients at risk for increased intracranial pressure, those with a history of urinary retention and should be used with caution (eg, monitoring of volume status) in patients with NYHA Class I CHF.

### Nasal Desmopressin

**Precautions**

- **Hyponatremia**: Medication can cause fluid retention, which may worsen underlying conditions that are susceptible to volume status. Medication is not recommended in patients at risk for increased intracranial pressure or those with a history of urinary retention.

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**HYponatremia**
## Duration of Action in Key to Safety

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Time with urine production &lt;0.12 mL/kg/min, h</td>
<td></td>
</tr>
<tr>
<td>25 µg, Females</td>
<td>4.86 (4.56)</td>
</tr>
<tr>
<td>50 µg, Males</td>
<td>4.85 (3.42)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Time with urine osmolality &gt;200 mOsm/kg, h</td>
<td></td>
</tr>
<tr>
<td>25 µg, Females</td>
<td>3.00 (3.66)</td>
</tr>
<tr>
<td>50 µg, Males</td>
<td>2.40 (3.08)</td>
</tr>
</tbody>
</table>

## Hyponatremia in Combined Studies with Nasal Desmopressin

### OVERALL

<table>
<thead>
<tr>
<th>Serum Sodium Concentration (mmol/L)</th>
<th>Placebo N=349</th>
<th>Nasal Desmopressin 0.83 mcg N=354</th>
<th>Nasal Desmopressin 1.66 mcg N=341</th>
</tr>
</thead>
<tbody>
<tr>
<td>130-134, n (%)</td>
<td>18 (5.2)</td>
<td>33 (9.3)</td>
<td>42 (12.3)</td>
</tr>
<tr>
<td>126-129, n (%)</td>
<td>0</td>
<td>8 (2.3)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>≤125, n (%)</td>
<td>1 (0.3)</td>
<td>0</td>
<td>5 (1.5)</td>
</tr>
</tbody>
</table>

### BY AGE

#### <65 YEARS

<table>
<thead>
<tr>
<th>Serum Sodium Concentration (mmol/L)</th>
<th>Placebo N=144</th>
<th>Nasal Desmopressin 0.83 mcg N=148</th>
<th>Nasal Desmopressin 1.66 mcg N=146</th>
</tr>
</thead>
<tbody>
<tr>
<td>130-134, n (%)</td>
<td>7 (4.9)</td>
<td>14 (9.6)</td>
<td>28 (14.4)</td>
</tr>
<tr>
<td>126-129, n (%)</td>
<td>0</td>
<td>0</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>≤125, n (%)</td>
<td>0</td>
<td>0</td>
<td>0 (0.5)</td>
</tr>
</tbody>
</table>

#### ≥65 YEARS

<table>
<thead>
<tr>
<th>Serum Sodium Concentration (mmol/L)</th>
<th>Placebo N=205</th>
<th>Nasal Desmopressin 0.83 mcg N=206</th>
<th>Nasal Desmopressin 1.66 mcg N=195</th>
</tr>
</thead>
<tbody>
<tr>
<td>130-134, n (%)</td>
<td>11 (5.4)</td>
<td>25 (12.1)</td>
<td>28 (14.4)</td>
</tr>
<tr>
<td>126-129, n (%)</td>
<td>6 (2.9)</td>
<td>7 (3.6)</td>
<td></td>
</tr>
<tr>
<td>≤125, n (%)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>5 (2.6)</td>
</tr>
</tbody>
</table>
### Hyponatremia in Combined Trials with Sublingual Desmospressin

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Sodium ≤130 mmol/L</th>
<th>Sodium ≤125 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>N</td>
<td>Affected, n(%)</td>
<td>N</td>
</tr>
<tr>
<td>N</td>
<td>Affected, n(%)</td>
<td>N</td>
</tr>
<tr>
<td>Placebo</td>
<td>113 (0)</td>
<td>32 (0)</td>
</tr>
<tr>
<td>10 µg desmospressin</td>
<td>35 (0)</td>
<td>63 (2)</td>
</tr>
<tr>
<td>25 µg desmospressin</td>
<td>37 (0)</td>
<td>62 (3)</td>
</tr>
<tr>
<td>50 µg desmospressin</td>
<td>34 (0)</td>
<td>50 (0)</td>
</tr>
<tr>
<td>75 µg desmospressin</td>
<td>63 (2)</td>
<td>59 (7)</td>
</tr>
<tr>
<td>100 µg desmospressin</td>
<td>32 (0)</td>
<td>53 (14)</td>
</tr>
</tbody>
</table>

**Incidence of Hyponatremia in Women and Men Long-Term (Up to 3 Years)**

<table>
<thead>
<tr>
<th>Post baseline</th>
<th>Serum Sodium (mmol/L)</th>
<th>Women (25 µg)</th>
<th>Men (50 µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 135</td>
<td></td>
<td>52 (78)</td>
<td>45 (58)</td>
</tr>
<tr>
<td>130-134</td>
<td></td>
<td>12 (18)</td>
<td>24 (31)</td>
</tr>
<tr>
<td>126-129</td>
<td></td>
<td>3 (4)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>≤ 125</td>
<td></td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Risk Factors for Hyponatremia

- Age (single best predictor)
- Lower serum sodium at baseline
- Higher basal 24-hour urine at baseline per body weight
- Weight gain at time of serum sodium concentration
- Higher dose
- Decreased GFR

Monitoring Sodium

**FDA Recommendations**
- Prior to initiation
- 7 days
- 30 days
- Periodically thereafter

**Expert Opinion**
- Prior to initiation
- 7 days
- 30 days
- 60 days
- 90 days
- Every 3 months

A PERFECT OPPORTUNITY FOR SHARED CARE
Urologists and Primary Care Must Work Together on This

- Must be able to effectively evaluate and differentiate other diseases.
- Must be able to safely treat and monitor.

Conclusions

- Nocturia may have a complicated etiology but simply results from a production of nocturnal urine that exceeds the functional bladder capacity.
- The prevalence is significant.
- Behavioral therapy and treating underlying medical conditions is essential but may fall short.
- Short acting versions of desmopressin reduce nocturia by decreasing urine production during sleeping hours.
- Attention to contraindications and monitoring recommendations regarding serum sodium are critical.

POST-TEST QUESTIONS
Post-test ARS Question 1

Post-N1: After completing this activity, how confident are you now in your ability to manage patients with nocturia?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

Post-test ARS Question 2

Post-N2: In a patient with nocturia, which quality of life measure is not affected:

1. Sleep
2. Eating
3. Sex
4. Work

Post-test ARS Question 3

Post-N3: A 50 year old patient with BPH and no other medical problems has persistent nocturia despite a greatly improved urine flow with an alpha blocker. Which of the following is a reasonable intervention?

1. Add an antimuscarinic
2. Add low dose desmopressin
3. Consider a TURP
4. Add a 5-alpha reductase inhibitor
Post-test ARS Question 4
Post-N4: Which of the following is a risk factor for developing hyponatremia in a patient treated with desmopressin?

1. Low sodium diet
2. Age
3. Gender
4. Low urine output at baseline

Post-test ARS Question 5
Post-N5: How often should you check sodium levels for a patient on low dose desmopressin?

1. At initiation and then every 3 months
2. At initiation and then every 1 month
3. Every 30 days
4. At initiation, day 7, day 30 and then periodically

Post-test ARS Question 6
Approximately how many patients with complaints of nocturia do you see on a weekly basis:

1. 0-1
2. 1-5
3. 6-10
4. 11-15
5. 16-20
6. >20
Questions

Emerging Challenges in Primary Care

We are Taking a Break

The Program Will Resume Shortly

If the program does not resume after the break please refresh your page

For technical support, please post a message with your question in the Q&A box on your screen and our tech support specialist will assist you.