Nocturia: Symptom or Disease?

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Nocturia

• What is it?
• Why should we care?
• Evaluating the causes?
• How to treat?
• How not to cause harm?
• Who is in charge?
NOCTURIA is defined as waking at night to urinate, with each voiding episode preceded and followed by sleep.

Clinically Meaningful

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

Prevalent and Undertreated

Prevalence rate: up to 60%\textsuperscript{1,2,*}

Diagnosis rate: 26%\textsuperscript{5}

Treatment rate: up to 18%\textsuperscript{5,†}

\textsuperscript{*}Prevalence rates of men and women older than 70 years old with ≥2 nightly voids (range in men, 29-59%; range in women, 28-62%).\textsuperscript{1,2}

\textsuperscript{†}Desmopressin treatment (melt or tablet) among patients with nocturia only.

The Burden of Nocturia Is Broad and Substantial

- Increased daytime sleepiness
- Reduced daytime energy
- Longer reaction time
- Reduced quality of life\textsuperscript{1,2}
- Poorer overall and mental health\textsuperscript{1}
- Reduced work productivity\textsuperscript{1}
- Increased falls and fractures\textsuperscript{3-6}
- Increased mortality\textsuperscript{5}

**ASSOCIATIONS**

- Increased mortality\textsuperscript{5}
- Reduced quality of life\textsuperscript{1,2}
- Poorer overall and mental health\textsuperscript{1}
- Reduced work productivity\textsuperscript{1}
- Increased falls and fractures\textsuperscript{3-6}
- Depression
- Susceptibility to somatic disease
- Risk of cardiovascular disease
- Risk of car accidents

**Short-Term Consequences\textsuperscript{8}**
- Increased daytime sleepiness
- Reduced daytime energy
- Longer reaction time
- Reduced psychomotor performance
- Decreased concentration/memory/cognitive function
- Poor mood

**Long-Term Consequences\textsuperscript{8}**
- Depression
- Susceptibility to somatic disease
- Risk of cardiovascular disease
- Risk of car accidents

NOCTURIA OR NOCTURNAL POLYURIA

BPH

OAB

Sleep Disorders

Nocturia due to nocturnal polyuria
NOCTURNAL POLYURIA: Multiple Etiologies

OVERCONSUMPTION
- Behavioral
- Environmental
- Disogenic 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 ANTIDIURESIS
- Circadian defect in secretion or action of vasopressin
- Renal conditions
- Cerebrovascular damage
- Central diabetes insipidus
- Nephrogenic diabetes insipidus
How much does the etiology matter?

• The etiology of nocturia is multifactorial but >80% of patients with nocturia have nocturnal polyuria (NP)

• Regardless of the frequency or cause, nocturia results from a production of nocturnal urine that exceeds the capacity of the urinary bladder to comfortably store it
SYMPTOMS DIRECT TREATMENT

BPH
- Alpha Blockers
- 5 ARIs
- PDE 5

OAB
- Antimuscarinics
- Beta 3

Sleep Disorders
- Sleep Clinic

Nocturia due to nocturnal polyuria
- Treat the cause
WITH NOCTURNAL POLYURIA, IF POSSIBLE, TREAT THE CAUSE

<table>
<thead>
<tr>
<th>OVERCONSUMPTION</th>
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</table>
Desmopressin

- Desmopressin is a synthetic analog of AVP and a selective \( V_2 \) receptor agonist.
- It increases water reabsorption in the distal tubule and collecting ducts, concentrates the urine, and decreases urine production.

Desmopressin formulations reduce nocturia but are associated with a risk for hyponatremia\(^1,^2\).
Newer Versions of Desmopressin Have to Be Safer

NOCTIVA™ Is Engineered to Be Different

**High Bioavailability (8%)**
High bioavailability allows for low dosing.\(^2,3\)

**Short Antidiuretic Effect\(^5\)**
The peak plasma concentration results in an antidiuretic effect that lasts 4-6 hours.\(^1\)

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Decreases Nocturnal Urine Production

- **Placebo (n=326)** (pooled data)
  - Week 12: 804.8 mL → 615.3 mL
  - Reduction: -189.5 mL
  - P-value: .0395

- **NOCTIVA 0.83 mcg (n=318)** (pooled data)
  - Week 12: 804.9 mL → 565.9 mL
  - Reduction: -239.0 mL
  - P-value: .0395

- **NOCTIVA 1.66 mcg (n=298)** (pooled data)
  - Week 12: 804.8 mL → 503.0 mL
  - Reduction: -301.8 mL
  - P-value: <.0001
The first 4 hours of sleep are the most important for a restful night.

Decreased Urine Production Equals Decreased Bladder Filling

Baseline: 2.4 hours

- **NOCTIVA 1.66 mcg**: Change from baseline +108 minutes
- **NOCTIVA 0.83 mcg**: Change from baseline +96 minutes
- **Placebo**: Change from baseline +66 minutes

210 minutes
240 minutes
252 minutes

The first 4 hours of sleep are the most important for a restful night.
HISTORICAL FEARS ABOUT DESMOPRESSIN

- DECREASING SODIUM
- DECREASING SODIUM
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- DECREASING SODIUM
## Hyponatremia* Incidence: 12-Week Clinical Trials

### Overall Hyponatremia

<table>
<thead>
<tr>
<th>Serum Sodium Concentration (mmol/L)</th>
<th>Placebo N=349</th>
<th>Noctiva™ 0.83 mcg N=354</th>
<th>Noctiva™ 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>

### Hyponatremia by Age

<table>
<thead>
<tr>
<th>Serum Sodium Concentration (mmol/L)</th>
<th>&lt;65 years</th>
<th>≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=144</td>
<td>Noctiva 0.83 mcg N=148</td>
<td>Noctiva 1.66 mcg N=146</td>
</tr>
<tr>
<td>130-134, n (%)</td>
<td>7 (4.9)</td>
<td>8 (5.4)</td>
</tr>
<tr>
<td>126-129, n (%)</td>
<td>0</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>≤125, n (%)†</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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*Hyponatremia was defined as serum sodium level ≤125 mmol/L with or without symptoms or serum sodium level between 126 and 129 mmol/L with clinical symptoms associated with hyponatremia.2

†Of the 5 patients with serum sodium ≤125 mmol/L, all were ≥65 years old, 4 were men, and onset ranged from 6 days to 12 weeks after start of dosing; 4 patients were taking concomitant systemic or inhaled glucocorticoid, and 3 patients were taking a nonsteroidal anti-inflammatory drug (NSAID).1

CONTRAINDICATIONS

- Hyponatremia or a history of hyponatremia
- Polydipsia
- Primary nocturnal enuresis
- Concomitant use with loop diuretics or systemic or inhaled glucocorticoids
- Estimated glomerular filtration rate below 50 mL/min/1.73 m²
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- During illnesses that can cause fluid or electrolyte imbalance
- New York Heart Association (NYHA) Class II-IV congestive heart failure
- Uncontrolled hypertension

WARNINGS AND PRECAUTIONS

- Fluid retention: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention. Monitor volume status in patients with NYHA Class I congestive heart failure.
- Nasal conditions: Discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved.

Please see the full Prescribing Information for Noctiva at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/201656lbl.pdf.
Monitor Serum Sodium Concentration

<table>
<thead>
<tr>
<th>Prior to initiating</th>
<th>Within 7 days of starting treatment</th>
<th>Approximately 1 month after initiating treatment or increasing the dose</th>
<th>Periodically after treatment as clinically appropriate</th>
</tr>
</thead>
</table>

More frequent serum sodium monitoring is recommended for patients ≥65 years of age and for those at increased risk of hyponatremia.

If the patient develops hyponatremia
- NOCTIVA™ may need to be **temporarily or permanently discontinued**, and treatment for the hyponatremia instituted, depending on the clinical circumstances, including the duration and severity of the hyponatremia.
DOES ANY SPECIALTY OWN URINE?
DOES ANY SPECIALTY OWN URINE? **NO**

A PERFECT OPPORTUNITY FOR SHARED
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
What This Family Doctor Believes

• Adequate treatment of nocturia requires shared care
• Regardless of the frequency or cause, nocturia results from a production of nocturnal urine that exceeds the capacity of the urinary bladder to comfortably store it
• Therefore, whether nocturia is a symptom or disease is of little relevance in choosing to treat
What do you believe is the future direction for the treatment of NOCTURIA?