Nocturia Overview

Jerry G. Blaivas, MD

Clinical Professor of Urology
Weill Cornell Medical College

Adjunct Professor of Urology
SUNY Downstate College of Medicine
Nocturia

• Definition: voiding during (nocturnal) sleep time

• Etiology (pathologic & non-pathologic causes):
  • Bladder - doesn’t hold enough
  • Volume - kidneys make too much urine
  • Sleep – insomnia

• Evaluation: bladder diary
Etiology of Nocturia

• Pathologic & non-pathologic causes:

• **Volume** - kidneys make more urine than the bladder can hold
  – Polyuria
  – Nocturnal polyuria

• **Bladder** – bladder doesn’t hold enough
  – Mismatch between bladder capacity & NUV
  – Small capacity bladder

• **Sleep Disorder** – patient awakens for another reason, then voids
## Nocturia Severity & Bother

<table>
<thead>
<tr>
<th>Nocturia episodes</th>
<th>None</th>
<th>Small</th>
<th>Moderate</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>52.2</td>
<td>41.1</td>
<td>5.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Two</td>
<td>29.3</td>
<td>53.8</td>
<td>13.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Three</td>
<td>17.4</td>
<td>26.7</td>
<td>41.9</td>
<td>14.0</td>
</tr>
<tr>
<td>Four or more</td>
<td>11.3</td>
<td>7.0</td>
<td>46.0</td>
<td>35.7</td>
</tr>
</tbody>
</table>

*Bother (%) - Tikkinen et al. Eur Urol 2010;57:488*
Nocturia Bother & Disordered Sleep

• High levels of bother are associated with:
  – difficulty falling asleep
  – difficulty returning to sleep
  – greater morning fatigue
15D (HRQL) dimensions and nocturia

- No nocturia
- 1 void/night
- 2 voids/night
- ≥3 voids/night

**MEN**

- Moving
- Hearing
- Sleeping
- Speech
- Usual activities
- Discomfort
- Distress
- Sexual activity

**WOMEN**

- Seeing
- Breathing
- Eating
- Eliminating
- Mental function
- Depression
- Vitality
15D (HRQL) dimensions and nocturia

- No nocturia
- 1 void/night
- 2 voids/night
- ≥3 voids/night

Level value

MEN

WOMEN

Moving
Hearing
Sleeping
Speech
Usual activities
Discomfort
Distress
Sexual activity

Seeing
Breathing
Eating
Eliminating
Mental function
Depression
Vitality
15D (HRQL) dimensions and nocturia
Consequences

- Daytime sleepiness
- Falls & fractures
- Quality of life
- General health
- Mortality
Nocturia vs sleepiness, naps and sick leave

Nocturnal awakening frequency/week

* p<0.001 vs. awakening <3 nights/week

### Falls in Elderly Patients With Nocturia

<table>
<thead>
<tr>
<th></th>
<th>2–3 voids/night</th>
<th>4–5 voids/night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk of at least 1 fall</td>
<td>5% (RR 1.05, 95% CI, 0.96, 1.16)</td>
<td>23% (RR 1.23, 95% CI 1.08, 1.41)</td>
</tr>
<tr>
<td>Relative risk of at least 2 falls</td>
<td>11% (RR 1.11, 95% CI, 1.08–1.41)</td>
<td>42% (RR 1.42, 95% CI, 1.16, 1.74)</td>
</tr>
</tbody>
</table>

Parsons J. Kellogg et al. BJU Int 2009;104:63–68
Effects on General Health

- Memory
- Diabetes
- Hypertension
- Metabolic syndrome
Effect of Nocturia on Slow Wave Sleep (SWS)

1st nocturia episode

1st nocturia episode**

*Stanley, Eur Urol Suppl 4/7, 17–19, 2005

**van Kerrebroeck P et al. Eur Urol. 2007;52:221-229
Effect of Suppression of SWS on Glucose Metabolism

Data are mean ± SEM (n = 9 ).

\*P = 0.009. \*P = 0.02. \*P = 0.03.

### Nocturia (≥2) & General Health

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Outcome</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–59</td>
<td>Diabetes mellitus</td>
<td>1.26 (0.75, 2.11)</td>
<td>1.06 (0.61, 1.85)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1.19 (0.89, 1.59)</td>
<td>1.05 (0.77, 1.43)</td>
</tr>
<tr>
<td></td>
<td>CHD</td>
<td>1.68 (1.13, 2.49)</td>
<td>1.36 (0.87, 2.12)</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>1.32 (0.79, 2.21)</td>
<td>1.31 (0.73, 2.35)</td>
</tr>
<tr>
<td>≥60</td>
<td>Diabetes mellitus</td>
<td>0.85 (0.40, 1.81)</td>
<td>0.74 (0.32, 1.74)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>0.81 (0.57, 1.16)</td>
<td>0.74 (0.51, 1.07)</td>
</tr>
<tr>
<td></td>
<td>CHD</td>
<td>0.95 (0.69, 1.31)</td>
<td>0.92 (0.65, 1.31)</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>1.37 (1.10, 1.70)</td>
<td>1.48 (1.15, 1.91)</td>
</tr>
</tbody>
</table>
### Mortality

**28% excess risk per year**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asplund</td>
<td>1999</td>
<td>1.90 (1.39, 2.60)</td>
<td>10.27</td>
</tr>
<tr>
<td>Kupelian</td>
<td>2011</td>
<td>1.49 (1.25, 1.78)</td>
<td>16.02</td>
</tr>
<tr>
<td>Lightner</td>
<td>2012</td>
<td>1.22 (0.97, 1.54)</td>
<td>13.46</td>
</tr>
<tr>
<td>Van Doorn</td>
<td>2012</td>
<td>1.05 (0.78, 1.42)</td>
<td>10.69</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.38 (1.11, 1.71)</td>
<td>50.43</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asplund</td>
<td>1999</td>
<td>1.30 (0.85, 2.00)</td>
<td>6.99</td>
</tr>
<tr>
<td>Kupelian</td>
<td>2011</td>
<td>1.32 (1.15, 1.51)</td>
<td>18.07</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.32 (1.16, 1.50)</td>
<td>25.06</td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakagawa</td>
<td>2010</td>
<td>1.98 (1.09, 3.59)</td>
<td>4.32</td>
</tr>
<tr>
<td>Bursztyn</td>
<td>2006</td>
<td>0.89 (0.55, 1.43)</td>
<td>6.11</td>
</tr>
<tr>
<td>Galizia</td>
<td>2012</td>
<td>1.02 (0.82, 1.27)</td>
<td>14.08</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.14 (0.79, 1.66)</td>
<td>24.51</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.29 (1.12, 1.48)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.
Factors relating nocturia, sleep, health

Evaluation

• Bladder diary

• “Do the Math” – everything else follows from that

• History +/- questionnaire, +/-:
  – Urinalysis & culture
  – Uroflow and post-void residual urine
24 hour Bladder Diary

• Time and amount of each urination
• Urge perception score for each void
• Voiding difficulties
• Incontinent episodes
• Nocturia episodes
• Reason for nocturia voids
  – Primary nocturia voids
    • Urgency
    • Non-urgency
  – Insomnia voids
Enter urination time and date

03:43 PM

Friday, January 2, 2015

Next
Did you urinate on purpose or did you lose control?

- On Purpose
- Lost Control

Next
Did you just wake up from sleep and urinate? If so, why

- No, this urination was not during sleep hours
- Yes, I was awakened by the urge to void
  - Yes, I was awakened by something else, but once awake I decided to void
  - Yes, I don't know whether the urge to void woke me up or not

Next
Why did you just urinate?

- Out of convenience: no urge or desire.
- Mild urge: can delay urination for over an hour.
- Moderate urge: can delay urination for more than 10 but less than 60 minutes.
- Severe urge: can delay urination for less than 10 minutes.
- Desperate urge: must stop what I am doing and go immediately.

Next
Classification of Night-time Voids

<table>
<thead>
<tr>
<th>Type of Void</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia Urgency Voids</td>
<td>33%</td>
<td>44%</td>
</tr>
<tr>
<td>Nocturia Non-urgency Voids</td>
<td>59%</td>
<td>46%</td>
</tr>
<tr>
<td>Insomnia Voids</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Did you experience any difficulties urinating? Select all that apply

- None
- Difficulties Starting / I had to wait to get it started.
- I had to push or strain.
- I started and stopped multiple times during urination.
- I felt like I did not completely empty.
- It was painful to urinate.

Submit
Diary Assessment

- First AM voided volume included as a nighttime void (part of the NUV)
- First AM void is included as a daytime void
- Ni (nocturia index)
- Npi (nocturnal polyuria index)
- NBCi (nocturnal bladder capacity index)
Nocturia Index (Ni)

- Ni (Nocturia index = NUV/MVV):
  - Eg, NUV = 600 mL; MVV = 325 mL; Ni = 1.8
  - if Ni > 1: Nocturia occurs because functional bladder capacity (maximum voided volume) is exceeded
Nocturnal Polyuria

- NUV/24h urine $\geq 0.33$ (ICS)
  - <25 years: mean NPi=0.14
  - >65 years: mean NPi=0.34*

- NUV > 6.4 ml / kg**

- Nocturnal diuresis $\geq 54$-90 ml/hr***

**Matthiesen, J. Urol., 156: 1292, 1996
***Hofmeester, BJUI., 2014
• 77 year old man
• c/o nocturia x 5, urinary frequency & urgency, voiding symptoms
## 24 Hour Bladder Diary

**Sleep time:** 10:00 PM; **Wake time:** 6:30 AM

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Urgency</th>
<th>Stream Strength</th>
<th>Difficulty Urinating</th>
<th>Nocturia</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 AM</td>
<td>100 ml</td>
<td>2: moderate urge</td>
<td>1: very weak</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>8:50 PM</td>
<td>300 ml</td>
<td>2: moderate urge</td>
<td>1: very weak</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>11:05 PM</td>
<td>250 ml</td>
<td>2: moderate urge</td>
<td>1: very weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:20 PM</td>
<td>275 ml</td>
<td>2: moderate urge</td>
<td>1: very weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:00 PM</td>
<td>300 ml</td>
<td>2: moderate urge</td>
<td>1: very weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:15 PM</td>
<td>200 ml</td>
<td>2: moderate urge</td>
<td>1: very weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:50 PM</td>
<td>400 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td>Yes</td>
<td>Due to Urge</td>
</tr>
<tr>
<td>10:50 PM</td>
<td>310 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td>Yes</td>
<td>Due to Urge</td>
</tr>
<tr>
<td>11:39 PM</td>
<td>300 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td>Yes</td>
<td>Due to Urge</td>
</tr>
<tr>
<td>01:20 AM</td>
<td>400 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td></td>
<td>Due to Urge</td>
</tr>
<tr>
<td>04:10 AM</td>
<td>225 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td></td>
<td>Due to Urge</td>
</tr>
<tr>
<td>05:00 AM</td>
<td>150 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td>Yes</td>
<td>Due to Urge</td>
</tr>
<tr>
<td>06:10 AM</td>
<td>150 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td>Yes</td>
<td>Due to Urge</td>
</tr>
<tr>
<td>07:15 AM</td>
<td>175 ml</td>
<td>2: moderate urge</td>
<td>2: moderately weak</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Diary Summary

<table>
<thead>
<tr>
<th><strong>Voided Volume (ml)</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>3,535</td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>1,917</td>
<td></td>
</tr>
<tr>
<td>Nighttime</td>
<td>1,618</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong># Voids</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Nighttime</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Maximum Voided Volume</strong></th>
<th>400</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong># Incontinent Episodes</strong></th>
<th>0</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong># Urgency Episodes</strong></th>
<th>0</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong># Difficulty Voiding Episodes</strong></th>
<th>1</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Nocturnal Polyuria Index</strong></th>
<th>0.46</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Nocturia Index</strong></th>
<th>4.05</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Spearman’s Rho</strong></th>
<th>0.51</th>
</tr>
</thead>
</table>
• 77 year old man
• c/o nocturia x 5, urinary frequency & urgency, voiding symptoms
• Dx: polyuria, nocturnal, “prostatism”
• Rx:
  • behavior modification (fluid management)
  • Alpha adrenergic blocker
# Diary Summary

<table>
<thead>
<tr>
<th></th>
<th>Pre Rx</th>
<th>Post Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voided Volume (ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>3,535</td>
<td>1,950</td>
</tr>
<tr>
<td>Daytime</td>
<td>1,917</td>
<td>1,350</td>
</tr>
<tr>
<td>Nighttime</td>
<td>1,618</td>
<td>600</td>
</tr>
<tr>
<td><strong># Voids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Daytime</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Nighttime</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum Voided Volume</strong></td>
<td>400</td>
<td>450</td>
</tr>
<tr>
<td><strong># Incontinent Episodes</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong># Urgency Episodes</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong># Difficulty Voiding Episodes</strong></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nocturnal Polyuria Index</strong></td>
<td>0.46</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Nocturia Index</strong></td>
<td>4.05</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Spearman’s Rho</strong></td>
<td>0.51</td>
<td>0.31</td>
</tr>
</tbody>
</table>
VOID

Pre-treatment
18/381/331/2

Post-treatment
10/179/95/2
Etiology of Nocturia

• Pathologic & non-pathologic causes:

• **Volume** - kidneys make more urine than the bladder can hold
  – Polyuria
  – Nocturnal polyuria

• **Bladder** – bladder doesn’t hold enough
  – Mismatch between bladder capacity & NUV
  – Small capacity bladder

• **Sleep Disorder** – patient awakens for another reason, then voids
Regulation of urine production

**Daytime:**
Complex homeostatic mechanisms regulate salt & water metabolism.

**Night-time:**
- ↑AVP concentration
- Collecting duct permeable to water
- Diuresis
Polyuria

- Polyuria – increased 24 hr urine output:
  - => 40 ml/kg or
  - => 2500 – 3000 mL

- Once steady state, polyuria > polydipsia

- Etiology:
  - Acquired dysfunction
  - Diabetes mellitus
  - Diabetes insipidus
  - Primary polydipsia
Treatment of Polyuria

• Reduce water intake (in patients without DI)

• Rx remediable conditions:
  – Optimize treatment of diabetes mellitus,
  – Vasopressin analogues in patients with central DI
  – Psychotherapy for compulsive water drinkers
Etiology of Nocturnal Polyuria

- Excessive nighttime fluid intake
- Diabetes mellitus
- Obstructive sleep apnea
- Peripheral edema
- Congestive heart failure
- Medications (SSRI’s, tetracycline)
## Sleep Apnea: Rx with nasal CPAP

<table>
<thead>
<tr>
<th></th>
<th>Nocturia Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Rx</td>
</tr>
<tr>
<td><strong>Men (n=88)</strong></td>
<td>3.8 ± 0.4</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
</tr>
<tr>
<td><strong>Women (n=196)</strong></td>
<td>3</td>
</tr>
<tr>
<td>(median: p&lt;.001)</td>
<td></td>
</tr>
</tbody>
</table>


Treatment of Nocturnal Polyuria

• **Rx remediable conditions:**
  – Optimize treatment of OSA, diabetes mellitus, CHF, peripheral edema

• **Empiric decrease of urine production**
  – Compressive stockings for pedal edema
  – Timed diuretics
  – Timed antidiuretics
Timed Diuretics

• Short acting diuretics given 6 hours HS
  – Furosemide 40 mg, bumetanide 1mg po
  – Level 2 evidence, grade C recommendation (ICI 2005)
• Mobilizes third space fluid > diuresis
• Prevents postural fluid resorption that causes nocturnal polyuria, eg, lower limb venous insufficiency or congestive cardiac failure

Pederson, BJU 1988; Reynard, BJU 1998
Timed Antidiuretics

• Taken before bed-time
• Decreases urinary output during sleep hours
• Reduces nocturnal voids and voided volume
• Increase urine output after med has worn off
• Level 1b evidence, Grade A recommendation
  —eg, desmopressin* No direct bladder or cardiovascular effect, hyponatremia main AE

*van Kerrebroeck, Eur Urol 2007; 52: 221
Desmopressin tablet studies: Long-term reduction in nocturnal voids

Mean reduction in night-time voids:
men = 48–58%; women = 55–59%

Etiology of Small Bladder Capacity

- Prostatic obstruction
- Idiopathic detrusor overactivity
- Neurogenic bladder
- Acquired voiding dysfunction
- Cancer of bladder, prostate, or urethra
- Pharmacologic agents
- Bladder calculi
- Ureteral calculi
# Effect of TURP vs Tamsulosin on Nocturia

<table>
<thead>
<tr>
<th>TURP/Tamsulosin</th>
<th>Baseline</th>
<th>3 mo</th>
<th>1 yr</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia</td>
<td>2.4/2.0</td>
<td>1.5/1.5</td>
<td>1.4/1.4</td>
<td>&lt;0.001/&lt;0.001</td>
</tr>
<tr>
<td>Hours of uninterrupted sleep</td>
<td>1.7/2.2</td>
<td>2.3/2.8</td>
<td>2.3/2.7</td>
<td>&lt;0.001/&lt;0.013</td>
</tr>
</tbody>
</table>

Relation of nocturia with OAB

MEN

WOMEN

Sleep Disorders
Nocturia etiology

Incidence of Nocturia

- Forty-five (23%) also had polyuria
- Does not include sleep disorders
- NP = a significant component of nocturia in 43% of the patients
Empiric Treatment

• Behavioral:
  – Reduce caffeine and alcohol
  – Limit night-time fluids
  – Improve sleep hygiene (attention to room temperature, noise, and lighting)

• Additional interventions:
  – Edema: leg elevation and compression stockings
  – LUTS: alpha blockers
  – OAB: anticholinergics
  – Difficulty falling back asleep: zaleplon 5mg nightly after first nocturia episode between 23:00 and 03:00 hrs.

Vaughan et al (2009)
Summary

• Nocturia is common
• Increases with advancing age
• Bother and quality of life correlate with:
  • Severity of nocturia
  • Difficulty falling back asleep
• May impact general health
• Nocturia > 2 per night correlates with increased mortality
Summary

• Nocturia is classified based on bladder diary by “doing the math”
• There is a plethora of underlying conditions which contribute to its genesis
• Many conditions are remediable and/or harmful to health
• So, should nocturia be evaluated and treated even when asymptomatic like hypertension?