Nocturia: Advances in Diagnosis and Management

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Conflicts of Interest:
Consultant

- Ferring
- Pfizer
- Allergan
- Astellas
- Vantia
- Symptelligence
- Elsevier
Nocturia

- **Definition:** voiding during (nocturnal) sleep time
  - Preceded and followed by sleep (ICS guidelines*)

- **Scientific problems:**
  - How to define sleep time
  - Is patient awakened by the need to void, or,
  - Do patients void because they’re awake

*van Kerrebroeck et al Neurourol and Urodyn 21:179-183, 2002
What triggers nocturia*?

Classification of Night-time Voids

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

What triggers nocturia*?

- **UPG 0** => secondary nocturia
- **UPG 1+2** => nocturia nonurgency voids
- **UPG 3+4** => nocturia urgency voids

*Nassau, Avulova, Weiss: Assoc VA Surgeons New Haven April, 2014 abstract 7227022; p=.31 overall for <70 vs ≥ 70
Nocturia

• Medical/Renal?
  – Nocturnal polyuria
  – Polyuria

• Urological/Lower tract dysfunction?
  – Diminished global/nocturnal bladder capacity
Nocturia – at least 1 void/night

**Fig. 1.** Prevalence of nocturia defined as at least 1 void per night by age and sex.
Prevalence of Nocturia in Men

Prevalence of Nocturia in Women

15D (HRQL) dimensions and nocturia

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

MEN

WOMEN
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

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

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

**Levels for MEN and WOMEN**
- Moving
- Hearing
- Sleeping
- Speech
- Usual activities
- Discomfort
- Distress
- Sexual activity
- Eating
- Eliminating
- Mental function
- Depression
- Vitality
Men – Risk factors for Nocturia
FINNO Study

- Sensitivity (Proportion of Nocturics With Exposure)
- Positive Predictive Value (Proportion of Exposed With Nocturia)
Women – Risk factors for Nocturia
FINNO Study

- Sensitivity (Proportion of Nocturics With Exposure)
- Positive Predictive Value (Proportion of Exposed With Nocturia)

Conditions:
- Overweight and Obesity
- Urinary Urgency
- Snoring
- Diabetes
- RLS
- CAD
Conclusions from FINNO Study

• Numerous risk factors for nocturia were identified
  – None of the identified risk factors was associated with nocturia in ≥50% of the affected subjects of both sexes, highlighting the multifactorial etiology

• Health care providers should consider the lower urinary tract, but also beyond it, when treating bothersome nocturia

Nocturia: Consequences

• Mediated by Sleep Deprivation
Survival as function of sleep efficiency

SWS Occurs Early in the Night

REM, rapid eye movement; SWS, slow-wave sleep.

SWS May Be Interrupted by Nocturia

The first nocturia episode occurs within 2 to 3 hours on average.\(^1\)

---


## Nocturia Disrupts SWS (N3): Analysis by Timing of First Void

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>First Void During First 2 Sleep Cycles</th>
<th>First Void After First 2 Sleep Cycles</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep, min (± SD)</td>
<td>306 (54)</td>
<td>330 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>N1/N2 sleep, min (± SD)</td>
<td>170 (41)</td>
<td>171 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>N3 sleep, min (± SD)</td>
<td>37 (24)</td>
<td>56 (22)</td>
<td>0.023</td>
</tr>
<tr>
<td>REM sleep, min (± SD)</td>
<td>95 (35)</td>
<td>103 (25)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Nocturia Disrupts SWS (N3): Analysis by Number of Voids

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>0–1 Voids Per Night</th>
<th>≥2 Voids Per Night</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep, min (± SD)</td>
<td>331 (50)</td>
<td>313 (51)</td>
<td>NS</td>
</tr>
<tr>
<td>N1/N2 sleep, min (± SD)</td>
<td>176 (35)</td>
<td>168 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>N3 sleep, min (± SD)</td>
<td>62 (25)</td>
<td>40 (21)</td>
<td>0.014</td>
</tr>
<tr>
<td>REM sleep, min (± SD)</td>
<td>97 (25)</td>
<td>101 (32)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Nocturia is associated with increased mortality

Hazard Ratio of all-cause mortality: Night time frequency

<table>
<thead>
<tr>
<th>Hours of Nighttime Frequency</th>
<th>Hazard Ratio (95% CI)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 (n=425)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2 (n=219)</td>
<td>1.59 (0.80, 3.17)</td>
<td></td>
</tr>
<tr>
<td>3 (n=99)</td>
<td>2.34 (1.09, 5.00)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥4 (n=41)</td>
<td>3.60 (1.38, 9.35)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, BMI, diabetes, smoking status, history of coronary heart disease renal diseases and stroke, use of tranquilizers, hypnotics, and diuretics.

Nakagawa et al. J Urol 2010;183(Suppl):4
≥2 voids/night are associated with worse survival in a population-based sample of 7,455 men and 8,533 women

Nocturia and Mortality: 15 yr Krimpen F/U

- 1114 men age 50-78
- Followed 1995-2010
- Mean followup 13.4 years
- Nocturia assoc with HR 1.63 increased mortality (univariate analysis)
- Age, COPD, smoking, HTN all assoc with increased mortality
- Nocturia unassociated with mortality (multivariate analysis)


THE IMPACT OF NOCTURIA ON MORTALITY: A SYSTEMATIC REVIEW AND METAANALYSIS

"(The authors) found consistent evidence of increased mortality for men or women with nocturia, equivalent to 28% excess risk per year"
Nocturia: Evaluation

• Simple arithmetic analysis of 24 hour voiding diary
  – First AM voided volume included in NUV
  – First AM void diurnal, not nocturnal
Voiding diary: Is it important?

- Actual text message from former SUNY Downstate GU Resident Dr. Brian Marks:

- “I just saved 3 lives today with a voiding diary or at least avoided unnecessary surgeries! Thx, B”
Voiding diary: apologies to Will Rogers

- “I never met a diary
  I didn’t like”
Diary Assessment

- NPi (Nocturnal polyuria index = NUV/24^0 volume):
  - NPi > 33% = Nocturnal polyuria

- Ni (Nocturia index = NUV/MVV):
  - Ni >1: Nocturia occurs because functional bladder capacity (maximum voided volume) is exceeded
Diary Assessment: NBCi

• NBCi (Nocturnal Bladder Capacity index) > 0: Diminished nocturnal bladder capacity

• Higher NBCi >> Nocturia occurs at voided volumes < MVV
Diary Assessment: NBCi

- NBCi = Actual minus Predicted # nightly voids (ANV-PNV)
- PNV = Ni - 1
- Example: Patient with Nocturia (ANV) x7
  - NUV = 750 ml
  - MVV = 250 ml
  - Ni = NUV / MVV = 3
  - PNV = 3-1 = 2
  - NBCi = ANV-PNV = 7-2 = 5
## Formulas for evaluation of nocturia

<table>
<thead>
<tr>
<th>Formula</th>
<th>Analysis</th>
</tr>
</thead>
</table>
| **Nocturia index**  
\[ Ni = \frac{NUV}{MVV} \] | \( Ni >1 \rightarrow \text{nocturia is due to NUV exceeding MVV} \) |
| **Nocturnal Polyuria index**  
\[ NPi = \frac{NUV}{24hV} \] | \( NPi >33\% \rightarrow \text{Dx is nocturnal polyuria} \) |
| **Nocturnal bladder capacity index**  
\[ Ni - 1 = PNV \]  
\[ NBCi = ANV - PNV \] | \( NBCi >0 \rightarrow \text{nocturia occurring at volumes < MVV} \) |
<table>
<thead>
<tr>
<th>Nocturia Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal polyuria</td>
<td>• Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Obstructive sleep apnea</td>
</tr>
<tr>
<td></td>
<td>• Peripheral edema</td>
</tr>
<tr>
<td></td>
<td>• Excessive nighttime fluid intake</td>
</tr>
<tr>
<td>Nocturia Category</td>
<td>Causes</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Diminished global/NBC</td>
<td>• Prostatic obstruction</td>
</tr>
<tr>
<td></td>
<td>• Nocturnal detrusor overactivity</td>
</tr>
<tr>
<td></td>
<td>• Neurogenic bladder</td>
</tr>
<tr>
<td></td>
<td>• Cancer of bladder, prostate, or urethra</td>
</tr>
<tr>
<td></td>
<td>• Learned voiding dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Anxiety disorders</td>
</tr>
<tr>
<td></td>
<td>• Pharmacologic agents</td>
</tr>
<tr>
<td></td>
<td>• Bladder calculi</td>
</tr>
<tr>
<td></td>
<td>• Ureteral calculi</td>
</tr>
<tr>
<td>Nocturia Category</td>
<td>Causes</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Polyuria (global)</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>• Primary polydipsia</td>
</tr>
</tbody>
</table>
Summary

• Classification of nocturia through use of the voiding diary “unlocks” up to 17 significant underlying medical conditions which potentially contribute to its genesis

• Efficacy of nocturia treatment based upon this analysis is unproven
Nocturia: Classification

- Nocturnal polyuria (NP)
- Diminished global/nocturnal bladder capacity (NBC)
- Mixed (NP + ↓ NBC)
- Polyuria
Nocturnal polyuria: “medical” cause for nocturia

- NUV > 6.4 ml / kg*
- Nocturnal diuresis $\geq$ 0.9 ml/min (54 ml/hr)
  - Krimpen study (Bosch): Men 50-78: mean NUV=60 ml/hr
  - Suggest NP cutpoint >90 ml/hr, ie, based on urine production rate rather than proportion of 24 hr output**
- NUV/24h urine $\geq$ 0.33 (ICS)
  - <25 years: mean NPi=0.14
  - >65 years: mean NPi=0.34***

Nocturnal Polyuria: Prevalence in Krimpen Study*

- NP prevalence for NUV/24 hr > 33%:
  - Ages 50-54 at baseline: 44% → 51% at 6.5 year followup
  - Ages 65-69 at baseline: 54% → 65% at 6.5 year followup

- NP prevalence for NUP > 90 ml/hr:
  - Ages 50-54 at baseline: 14% → 19% at 6.5 year followup
  - Ages 65-69 at baseline: 23% → 26% at 6.5 year followup

- Thus, it makes a big difference how you define Nocturnal Polyuria

Sleep Disordered Breathing / Nocturia

- Sleep apnea: Sudden cessation of respiration due to airway obstruction during sleep
- Older adults with severe SDB have a greater number of nocturia episodes

Sleep Apnea

Increased airway resistance > hypoxia > pulmonary vasoconstriction > increased right atrial transmural pressure > increased ANP > increased renal sodium & water excretion
Sleep Apnea: Relation to Nocturia Severity

- Sleep apnea incidence:
  - Men: Nocturia x 0, 1, 2, ≥ 3: 10, 13, 17, 20%
  - Women: Nocturia x 0, 1, 2, ≥ 3: 7, 9, 12, 19%

Sleep Apnea: Rx with nasal CPAP (continuous positive airway pressure)

- *Nocturia in 88 men studied with OSA: avg. x3.8 ± 0.4
  - Diminished to x 0.7 ± 0.27 after Rx with nasal CPAP*

- **Nocturia in 196 women: median 3 episodes > 0 episodes per night (p<.001) with CPAP

- “Nocebo” effect of CPAP machine obviates lack of placebo

- Greater contribution to nocturia etiology in younger pts***

Sleep Apnea: Bladder oxidative stress mechanism*

- OSA model in rodents: Intermittent hypoxemia
- CMG changes included detrusor instability, bladder noncompliance
- Electron microscopy revealed ultrastructural damage
- Thus consider lower tract dysfunction in OSA

## Drug effects causing nocturia

<table>
<thead>
<tr>
<th><strong>Increased urine output</strong></th>
<th><strong>Insomnia and CNS effects</strong></th>
<th><strong>Direct LUT effects</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>CNS stimulants (dextroamphetamine, methylphenidate)</td>
<td>Ketamine: Direct toxin</td>
</tr>
<tr>
<td>SSRIs (block ADH secretion)</td>
<td>Antihypertensives (alpha-blockers, beta-blockers, methyldopa)</td>
<td>Tiaprofenic acid (Surgam): Toxic cystitis</td>
</tr>
<tr>
<td>Calcium channel blockers (incr ANP; block Na reabs in PCT)</td>
<td>Respiratory (albuterol, theophylline)</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Tetracycline (attenuates ADH via decr cAMP accum and action)</td>
<td>Decongestants (phenylephrine, pseudoephedrine)</td>
<td></td>
</tr>
<tr>
<td>Lithium (decr AQP2 levels)</td>
<td>Hormones (corticosteroids, thyroid)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychotropics (MAOIs, SSRIs, atypical antidepressants)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dopaminergic agonists (carbidopa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiepileptics (phenytoin)</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacological treatment of nocturnal polyuria

(Timed) Diuretics
- Prevent water accumulation by forcing water out of the system
- May be helpful in patients with lower limb venous insufficiency or congestive cardiac failure
- Level 2 evidence, Grade C recommendation (ICI 2005)
  - Bumetanide 1mg po in afternoon (Pederson PA et al BJU 1988)
  - Furosemide 40mg po in afternoon (Reynard JM et al BJU 1998)

(Timed) Antidiuretics
- Helps retain water until a more appropriate time
- Reduce nocturnal voids and voided volume
- Level 1b evidence, Grade A recommendation (EAU 2013)
  - Desmopressin 60 mcg SL/0.1mg po titrated to 240 mcg SL/0.4mg (van Kerrebroeck PE et al: Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. Eur Urol 2007; 52: 221.)
    - No direct bladder effect
    - No direct cardiovascular actions
    - Hyponatremia main potentially adverse effect
What approach is recommended by the evidence?

• Directly address nocturnal polyuria
  – Compression stockings
  – Fluid intake- type and amount
  – Afternoon diuretics
  – Anti-diuretic therapy

• Take an indirect approach
  – Treatment of sleep problems
  – Multi-component interventions
  – Drug therapy at other causes
Multicomponent: behavioral and medical
Vaughan et al (2009)

• Behavioral: education
  – Reducing caffeine and alcohol
  – Limiting night-time fluids
  – Improving sleep hygiene (moderate exercise, attention to room temperature, noise, and lighting)

• Algorithm for additional interventions:
  – If edema, early evening leg elevation and compression stockings
  – If sx BPH (AUA-7 SI ≥8, Qmax 4-15 mL/s), then terazosin titrated as tolerated/needed to 10mg daily
  – If ≥8 voids/24hrs, then tolterodine ER 2-4mg daily
  – If needing ≥30min to return to sleep after an awakening, then zaleplon 5mg nightly after first nocturia episode between 23:00 and 03:00 hrs.
Trial Evidence

- Secondary analysis\(^1\) - pelvic floor muscle exercises for women with urge predominant urinary incontinence superior to titrated bladder relaxant

- Controlled clinical trial\(^2\) - multicomponent intervention in men with nocturia efficacious, as was alpha-blocker and combination

<table>
<thead>
<tr>
<th>Change in nocturia</th>
<th>Behavior</th>
<th>Drug</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change</td>
<td>23</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>-1.34 (1.4)</td>
<td>-0.63 (0.9)</td>
<td>-1.06 (1.3)</td>
</tr>
<tr>
<td>P-value(^\dagger)</td>
<td>0.0001</td>
<td>0.0020</td>
<td>0.0008</td>
</tr>
<tr>
<td>Median change</td>
<td>-1.43</td>
<td>-0.71</td>
<td>-1.07</td>
</tr>
<tr>
<td>P-value(^\dagger\dagger)</td>
<td>&lt;0.0001</td>
<td>0.0012</td>
<td>0.0004</td>
</tr>
<tr>
<td>Min., Max.</td>
<td>-6.14, 0.57</td>
<td>-2.14, 1.43</td>
<td>-3.86, 2.55</td>
</tr>
</tbody>
</table>

\(^1\) Johnson et al. J Amer Geriatri Soc 2005  \(^2\) Johnson et al. AUA 2014 Annual Meeting, PD23-10
Normal Circadian Pattern of Urine Production

• Age dependent

• < 25 years
  – NUV/total = 14 %

• > 65 years
  – NUV/total = 34 %
<table>
<thead>
<tr>
<th></th>
<th>men &lt;50 (n=64)</th>
<th>men 50-70 (n=249)</th>
<th>men &gt;70 (n=104)</th>
<th>women &lt;50 (n=142)</th>
<th>women 50-70 (n=209)</th>
<th>women &gt;70 (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age (years)</td>
<td>42</td>
<td>60.7</td>
<td>76.8</td>
<td>40.2</td>
<td>58.8</td>
<td>76.5</td>
</tr>
<tr>
<td>p (age group)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td></td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td># nighttime voids</td>
<td>3.41</td>
<td>3.28</td>
<td>3.26</td>
<td>3.29</td>
<td>3.4</td>
<td>3.11</td>
</tr>
<tr>
<td>p (age group)</td>
<td>0.52</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ni</td>
<td>2.34</td>
<td>2.62</td>
<td>2.81</td>
<td>2.21</td>
<td>2.52</td>
<td>2.53</td>
</tr>
<tr>
<td>p (age group)</td>
<td>0.0008</td>
<td>0.0007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPi</td>
<td>0.33</td>
<td>0.36</td>
<td>0.41</td>
<td>0.33</td>
<td>0.37</td>
<td>0.39</td>
</tr>
<tr>
<td>p (age group)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td></td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBCi</td>
<td>1.75</td>
<td>1.16</td>
<td>0.9</td>
<td>1.53</td>
<td>1.42</td>
<td>1.08</td>
</tr>
<tr>
<td>p (age group)</td>
<td>&lt;.0001</td>
<td>0.0039</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of urine production

AVP concentration is low
• Collecting duct is not permeable to water
• Large volume of urine produced
AVP regulation of water reabsorption from renal tubular cells

- AVP
- V_{2} Receptor
- AQP3
- AQP4
- basolateral membrane
- apical membrane
- GTP (Gs)
- ATP
- cAMP
- PKA
- Recycling vesicle
- Exocytic Insertion
- Endocytic Retrieval
- AVP
- Collecting Duct Cell
- Collecting duct
- Vasa recta
- H_{2}O
Factors causing diuresis via ADH inhibition (inhibits water reabsorption)

- PGE-2
- ANP
- Hypercalcemia
- Hypokalemia
- Lithium
- Tetracyclines
68 yo man with nocturia

data collected 9/9/06 - 10/28/08 (!!)

• Bothersome nocturia, normal H&P

• 340 nights of data 9/9/06 - 8/24/07

• 1081 voids, average number of voids per night = 3.18.
68 yo man with nocturia
data collected 9/9/06 - 10/28/08

• 340 nights of data 8/30/07 and 8/12/08

• 1124 voids, average number of voids per night = 3.31
68 yo man with nocturia
data collected 9/9/06 - 10/28/08

• 78 nights of data 8/13/08 - 10/29/08:

• Fluid intake was restricted for four hours before retiring

• 254 voids: average number of voids per night = 3.26 (no benefit)
Histogram of Urine Volumes/Void C
8/13/08 to 10/29/08
(Fluid Intake Restricted)

- 78 Nights
- 254 Voids
- 3.26 Voids/Night

Number of Instances

Void Volume (ml)

0-49 50-99 100-149 150-199 200-249 250-299 300-349 350-399 400-449 450-499 500-549
## Twenty-four Hour Voiding Diary Analysis

<table>
<thead>
<tr>
<th>Date</th>
<th>24 hr vol (ml)</th>
<th>NUV (ml)</th>
<th>ANV</th>
<th>NPi (%)</th>
<th>Ni</th>
<th>MVV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/3</td>
<td>2095</td>
<td>800</td>
<td>4</td>
<td>38</td>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td>11/4</td>
<td>1230</td>
<td>385</td>
<td>1</td>
<td>31</td>
<td>1.8</td>
<td>210</td>
</tr>
<tr>
<td>11/6</td>
<td>2285</td>
<td>890</td>
<td>3</td>
<td>31</td>
<td>2.9</td>
<td>310</td>
</tr>
</tbody>
</table>

NUV = nocturnal urine volume  
ANV = actual # nightly voids  
NPI = NUV/24 urine volume  
MVV = maximum voided volume  
Ni = NUV/MVV  
PNV = predicted # nightly voids = Ni - 1, rounded up to next integer if not already an integer  
NBCi = nocturnal bladder capacity index = ANV - PNV
68 yo man with nocturia

- Etiology of nocturia varies by the day
- Strategy: expand bladder capacity both day and night.
- Match bladder capacity with nocturnal urine production
  - Fluid restriction failed
    - No peripheral edema, cardiac abnormality
  - Timed diuretic
  - Timed antidiuretic
Nocturia: Classification

- Nocturnal polyuria (NP)
- Diminished global/nocturnal bladder capacity (NBC)
- Mixed (NP + ↓ NBC)
- Polyuria
Causes of Low global/NBC: *Urologic*

- Infravesical obstruction
- Idiopathic nocturnal detrusor overactivity
- Neurogenic bladder
- Cystitis: bacterial, interstitial, tuberculous, radiation
- Cancer of bladder, prostate, urethra
Case Study: Urologic etiology of low nocturnal bladder capacity

- 82 year old male with CaP s/p XRT March 2006, ED on EDEX, uses them rarely. Nocturia x4

- Bladder US suggested bladder stone but not in dependent position therein

- CT revealed that the aforementioned finding is due to a 1 x 0.5 cm stone in a pseudoureterocele of the right distal ureter

- Diary revealed NBCi 3, no nocturnal polyuria
Followup

- Right endoscopic stone extraction
- Nocturia reduced to x1
- NBCi: 3 → 1
Low global/NBC: Treatment

- Dx & Rx of remediable conditions
- Empiric Rx
Nocturia persists despite prostate surgery

– Third National Health and Nutrition Examination Survey (NHANES III) in the USA showed

• Amongst those who undergo TURP, Nocturia (≥2 voids per night) persists for
  » 41% of 60–69 year olds
  » 50% of ≥70 year olds

Platz et al. *Urology* 2002;59;877–883
Surgery (outlet reduction/ablation)

Rationale(s)
1. Lower increased PVR, ↑FBC, reduce frequency
2. Destroy afferents in prostatic urethra and bladder neck
3. Relieve obstruction and the mysterious connection between this and DO/urgency

Does treatment with antimuscarinics alleviate nocturia?

Summary of nocturia therapies targeting bladder and prostate

- 5 ARI: Little success
  - $\alpha (-)$: Occ statistical, not clinically
  - 5 ARI + $\alpha (-)$: Same as $\alpha$-blocker

- Antimuscarinics: Some statistical, minimal clinical
  - AntiM + $\alpha (-)$: Some statistical, minimal clinical

- Optimal group: Large # N episodes, most due to severe urgency
Nocturia: Classification

- Nocturnal polyuria (NP)
- Diminished global/nocturnal bladder capacity (NBC)
- Mixed (NP + ↓ NBC)
- Polyuria
Polyuria

- Polyuria (24 hr urine output > 40 ml/kg)
- Once steady state is reached polyuria is associated with excessive oral intake (polydipsia)
- Results in both day and night urinary frequency due to global urine overproduction in excess of bladder capacity
Common Causes of Polyuria

- Diabetes mellitus
- Diabetes insipidus
- Polydipsia: Primary thirst disorder (dipsogenic, psychogenic)
Diabetes Insipidus (DI)

• Disorder of water balance

• Inappropriate excretion of water leads to polydipsia to prevent circulatory collapse

• Central vs Nephrogenic
Central DI

- Deficient ADH synthesis or secretion
- Causes: Loss of neurosecretory neurons in hypothalamus or posterior pituitary gland
Central DI: Etiology

- Idiopathic
- Trauma
- Primary pituitary tumors (craniopharyngioma)
- Metastatic disease (lung, breast)
- Infiltrative disease (sarcoid, Wegener’s)
- Infarction (Sheehan’s post partum)
- Infection (TB, meningitis)
Nephrogenic DI

• ADH secretion normal

• Kidneys are non-responsive (e.g., chronic renal failure)
Polyuria: Diagnostic algorithm

- Overnight water deprivation (OWD)
- If normal, DDx is polydipsia, either dipsogenic or psychogenic
- If OWD is abnormal, do renal concentrating capacity test (DDAVP)
  - If RCCT normal, Dx = central DI: Tx with DDAVP
  - If RCCT abnormal, Dx = nephrogenic DI: No specific treatment
Renal Concentrating Capacity Test

- 40 mcg desmopressin intranasally (0.4 mg po)
- Bladder emptied; urine sample for osmolality obtained 3-5 hours later
- Water intake restricted for the first 12 hours after drug administration
- Normal > 800 mOsm/kg H2O
Renal Concentrating Capacity Test

- Considerably reduced concentrating capacity indicates renal diabetes insipidus
- Moderately decreased capacity occurs in psychogenic polydipsia
- Central diabetes insipidus: Normal concentrating capacity
Primary polydipsia

• Normal water deprivation studies

• Dipsogenic vs. psychogenic
  – Dipsogenic polydipsia associated with Hx central neurologic abnormality such as Hx of brain trauma, radiation
  – Psychogenic polydipsia is long-term behavioral or psychiatric disorder
Polyuria: Treatment of Remediable Conditions

- Reduce water intake in patients without DI
- Treat diabetes mellitus
- Vasopressin analogues in patients with central DI
- Psychotherapy for compulsive water drinkers
Antidiuretics: Indications

• Antidiuretic hormone vasopressin is important for urinary concentration

• Antidiuretic therapy (desmopressin*) affects urine production. Proven benefit in treatment of polyuric conditions:
  – Pituitary diabetes insipidus
  – Primary nocturnal enuresis (PNE)
  – Nocturia

* vasopressin analogue
Desmopressin: mechanism of action

• Desmopressin is a selective $V_2$-receptor agonist:
  – Retains antidiuretic properties of vasopressin\(^1\)
  – Lacks unwanted pressor activity of vasopressin

• Desmopressin, when bound to $V_2$-receptors in kidney:
  – Increases tubular water permeability
  – Enhances water reabsorption
  – Extracellular fluid = more dilute
  – Urine = more concentrated\(^2\)

Recommendations for desmopressin in nocturia:
ICI: Grade A (Level 1 evidence); EAU: Grade A (Level 1b evidence)

References
Desmopressin formulations*

*no US indication for nocturia

- Intranasal: 10 mcg/spray; Max 40 mcg/day (CDI indication only)
- Oral: 0.1 mg tablets; Max 0.6 mg/day for PNE
- Melt: 60, 120, 240 mcg melt tabs
- Melt in development: 25 mcg (women) and 50 mcg (men)
Desmopressin tablet studies: Long-term reduction in nocturnal voids

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

Lose et al. *J Urol* 2004;172:1021–1025
Summary of recommendations for potential desmopressin patients

- **All patients** – use voiding diary
  - Global polyuria – exclude for further evaluation
  - Low volume per void and no nocturnal polyuria – other Rx?
  - ? Dosing differential between genders
  - Baseline sodium a good idea
    - Where does pediatric "no need" to check Na+ end and adult "need" begin?
    - Hyponatremia risk <1% in <65 yo; 8% >65 yo
  - 5th ICI (p. 633): "Drugs used in Rx of LUTS/OAB/DO": Level I/Grade A
  - EAU Guidelines 2013 Male Non-neurogenic LUTS, Oelke et al: LoE 1b, GoR A
    - For "nocturia based on a polyuric background"

- **Elderly (>65 years) with nocturnal polyuria**
  - All need baseline serum sodium (no Tx if low)
    - Closely monitor serum sodium <7, and 28 days after starting therapy or increasing dose, then q 3-6 mos
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
<th>Study Design</th>
<th>N</th>
<th>Nocturia Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral therapy + alpha-blocker vs. oxybutynin + alpha-blocker</td>
<td>Johnson 2013 [26]</td>
<td>Planned secondary analysis of randomized trial</td>
<td>127</td>
<td>Among men with ≥1 nocturia episode, behavioral therapy and oxybutynin each reduced nocturia by 0.86 and 0.57 voids per night, respectively (p=0.003).</td>
</tr>
<tr>
<td>Desmopressin + alpha-blocker</td>
<td>Bae 2013 [27]</td>
<td>Prospective cohort</td>
<td>216</td>
<td>After individualized dose-titration and 24-week therapy, desmopressin add-on therapy reduced the number of nocturia episodes from 7 to 5.7 episodes per 3-day period</td>
</tr>
<tr>
<td>Alpha-1a subtype selective antagonist</td>
<td>Eisenhardt 2014 [28]</td>
<td>Pooled analysis of 3 RCTs</td>
<td>n/a</td>
<td>In each individual study and for the pooled cohort, silodosin therapy consistently reduced nocturia as measured by the IPSS (p&lt;0.001)</td>
</tr>
<tr>
<td>5-alpha reductase inhibitor</td>
<td>Tacklind 2010 [29]</td>
<td>Cochrane review</td>
<td>n/a</td>
<td>Doxazosin and terazosin therapy were both significantly more effective than finasteride in improving nocturia</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>Madani 2013 [30]</td>
<td>Prospective cohort</td>
<td>10</td>
<td>For patients who had failed medical therapy and were poor surgical candidates, transurethral intraprostatic botulinum toxin reduced nocturia from 4.1 to 2.4 per night (p&lt;0.001)</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Falahatkar 2008 [31]</td>
<td>RCT</td>
<td>80</td>
<td>After 1 month of celecoxib therapy, the mean nocturnal frequency decreased from 5.17 to 2.5 voids per night in the treatment group, a difference that was statistically superior to placebo (p&lt;0.0001)</td>
</tr>
<tr>
<td>Anti-muscarinic</td>
<td>Weiss 2013 [32]</td>
<td>RCT</td>
<td>963</td>
<td>Flexible dose fesoterodine reduced nocturia by 1.02 voids/night, as compared to 0.85 voids/night for placebo (p&lt;0.01)</td>
</tr>
<tr>
<td>PDE-5 inhibitor</td>
<td>Oelke 2013 [33]</td>
<td>Pooled analysis of 4 RCTs</td>
<td>n/a</td>
<td>Tadalafil therapy led to a decrease of 0.5 voids/night, vs. 0.4 voids/night for placebo (p=0.002)</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Sand 2013 [35]</td>
<td>RCT</td>
<td>261</td>
<td>At the 3-month endpoint, desmopressin significantly reduced the mean number of nocturia episodes vs. placebo, with a treatment effect of -0.22 voids/night</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Weiss 2013 [36]</td>
<td>RCT</td>
<td>385</td>
<td>Desmopressin at 50 and 75 μg significantly reduced the number of nocturnal voids and increased the odds of a ≥33% response vs. placebo</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Yamaguchi 2013 [37]</td>
<td>RCT</td>
<td>111</td>
<td>Nocturia relief followed a dose-response relationship, with female patients requiring a lower dose than men</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Juul 2013 [38]</td>
<td>Pooled analysis of 3 RCTs</td>
<td>n/a</td>
<td>Trials that have extended desmopressin therapy to up to 56 weeks of treatment reveal a durable response</td>
</tr>
</tbody>
</table>
When nocturia improves, what actually gets better?

- Nocturnal urine production parameters decrease
- Nocturnal bladder capacity increases

<table>
<thead>
<tr>
<th></th>
<th>Improved patients (n = 17)</th>
<th>Non-improved patients (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre, mean (STD)</td>
<td>Post, mean (STD)</td>
</tr>
<tr>
<td>Actual number of nocturnal voids (ANV)</td>
<td>4 (1.9)</td>
<td>1.35 (1.37)</td>
</tr>
<tr>
<td>Nocturnal urine volume (NUV)</td>
<td>1100.3 ml (724.1)</td>
<td>607.7 ml (536.1)</td>
</tr>
<tr>
<td>Nocturia index (Ni)</td>
<td>3.2 (1.24)</td>
<td>1.8 (0.987)</td>
</tr>
<tr>
<td>Nocturnal polyuria index (NPI)</td>
<td>0.46 (0.118)</td>
<td>0.31 (0.180)</td>
</tr>
<tr>
<td>24-hr urine volume</td>
<td>2263.8 ml (1180.9)</td>
<td>1907.1 ml (952.3)</td>
</tr>
<tr>
<td>Maximum voided volume (MVV)</td>
<td>335.6 ml (182.7)</td>
<td>307.9 ml (137.0)</td>
</tr>
<tr>
<td>Nocturnal bladder capacity index (NBCI)</td>
<td>1.8 (1.34)</td>
<td>0.510 (0.58)</td>
</tr>
<tr>
<td>Number of voids in 24 hr</td>
<td>12.1 (2.53)</td>
<td>9.7 (1.99)</td>
</tr>
<tr>
<td>Nightly urine production rate (NUP, ml/hr sleep)</td>
<td>131.0 (75.66)</td>
<td>76.6 (55.9)</td>
</tr>
</tbody>
</table>

52 yo man with nocturia x4-5

- Onset age 32
- Cystoscopy revealed “Hunner’s Ulcers”
  - Dx interstitial cystitis; treatment to no avail
- Age 40 onset gynecomastia
- Diagnosis pituitary adenoma
- Treated medically
  - Dostinex → Cabergoline → Clomid to reduce PL and increase T
52 yo man with nocturia

- Age 37:
- Capacity 500 ml
- “tight sphincter”
- “tremendous inflammation of prostate”
- 13/320/40 = Qmax/voided vol/PVR
- Now Dx Primary BNO
  - Tx terazosin → orthostatic
  - Oxybutynin no help
52 yo man with nocturia

- Age 44 UDS:
- Capacity 600 ml
- Qmax=5 ml/sec, no involuntary contrs
  - Plateau flow tracing
- pdetQmax=40 cm H2O
- Dx BOO: Prostatic vs BNO
- Rx: tamsulosin
52 yo man with nocturia

- Age 46 FVC:
- No DDAVP
  - NUV=1050, ANV x5 (100-300 vv)
  - NUV=975, ANV x6 (75-300 vv)
- + DDAVP
  - NUV=300, ANV x2
  - NUV=75, ANV x1, 2 AM
  - NUV=350, ANV x1, 6 AM
  - NUV=200, ANV x1, 4:15 AM
  - NUV=400, ANV x3, 12:45 AM, 2:40 AM, 5:30 AM
52 yo man with nocturia

- Age 46 FVC 3 mos later:
- No DDAVP
  - NUV=735, ANV x4 (110-225 vv)
  - NUV=1275, ANV x5 (200-325 vv)
  - Day volume=775; NUV=1250; ANV x6
  - Day volume=1210; NUV=1050; ANV x6
- + DDAVP
  - Day volume=950; NUV=550; ANV x4
52 yo man with nocturia

- Age 49 UDS:
- Capacity 309 ml
- Qmax=6 ml/sec, no involuntary contrs
- pdetQmax=58 cm H2O
- Dx BOO
- Rx: Klonopin HS mainly for the nocturia
52 yo M with nocturia: Key points

• Anterior pituitary tumor
  – ? Causing posterior pituitary dysfunction and primary nocturnal polyuria syndrome
  – Responds to DDAVP

• Bladder outlet obstruction
  – Prostatitis
  – Strong bladder
  – Intolerance to meds

• Sleep apnea
  – Responds to CPAP
52 yo man with nocturia

• Currently: two urologists rec TURP/TUIP
• He wants second opinion

• What do you think?
Nocturia

Frequency-volume chart

Low nocturnal/global bladder capacity
Nocturnal polyuria: NPI >33%
Diabetes mellitus
Congestive heart failure
Obstructive sleep apnea suspected (snoring, obesity, short neck)
Peripheral edema due to venous disease
Excessive PM fluid intake
Overnight water deprivation
Polyuria: 24-hour volume >40 ml/kg
Urine >800 m0sm/kg
Urine <800 m0sm/kg
Primary polydipsia
Renal concentrating capacity test
Normal
Dx central diabetes insipidus
Abnormal
Dx nephrogenic diabetes insipidus
Chronic renal failure, lithium, tetracycline, hypercalcemia, hypokalemia

Refer to endocrinology

Multiple incremental etiologies as per individual nocturia categories

Mixed

Look for urological cause:
• prostatic obstruction
• nocturnal detrusor overactivity
• neurogenic bladder
• pharmacologic agents
• bladder/ureteral calculi

Refer to cardiology

Nocturia: Future Considerations

• Treatment of Nocturia irrespective of bother?
  – Is nocturia itself morbid or just a symptom of a morbid underlying condition?
    • Analogous to
      – HTN
      – Hypercholesterolemia

• Nocturia and Sleep
  – Will we ever show that diminishing nocturia results in improved sleep?
    – Does it matter what phase of sleep gets better?
    – Does less nocturia directly result in improvement of the many aspects of function known to decline in sleep-deprived patients?
      » Cardiovascular disease
      » HTN
      » DM
      » Life expectancy

• We need better treatments for nocturia!
Nocturia: Discussion/Questions