A Personal Retrospective: Past Work on Sleep & Aging and the Possibilities for the Future

alt title: Poor Sleep in the Elderly:
A Role for Nocturia?

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Support and Disclosures

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• Consultant: Ferring Pharmaceuticals; Merck; Respocardia
The Personal Retrospective Thing

1974-1982
Allan Rechtschaffen

1982-1992
William Dement

1987
Art Spielman

Treatment of Chronic Insomnia by Restriction of Time in Bed

Jerry Yesavage

Leah Friedman
OUTLINE

- Epidemiology (Prevalence, Outcomes)
- Mechanistic Issues
- Chicken and Egg Problem
- Treatments
Prevalence of Chronic Insomnia Increases with Age

Epidemiology of Insomnia: Population-based Cross-Sectional Odds Ratios (95% CI) for Co-morbidities (the usual suspects)

(Katz & McHorney, Arch Intern Med 1998; 158: 1099-1107)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Mild Insomnia</th>
<th>Sev Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>2.6 (1.9-3.5)</td>
<td>8.2 (5.7-12.0)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>2.2 (1.7-2.7)</td>
<td>3.4 (2.6-4.6)</td>
</tr>
<tr>
<td>MI</td>
<td>1.9 (1.2-2.9)</td>
<td>0.9 (0.4-1.9)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.6 (1.1-2.2)</td>
<td>2.5 (1.5-3.9)</td>
</tr>
<tr>
<td>Angina</td>
<td>1.3 (1.0-1.7)</td>
<td>1.3 (1.0-1.8)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.6 (1.1-2.2)</td>
<td>1.5 (1.0-2.3)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1.4 (1.1-1.7)</td>
<td>1.5 (1.2-2.0)</td>
</tr>
<tr>
<td>Hip Pain</td>
<td>2.2 (1.3-3.8)</td>
<td>2.7 (1.4-5.1)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.4 (1.0-2.0)</td>
<td>1.6 (1.0-2.5)</td>
</tr>
</tbody>
</table>
Proportion of Elderly Men and Women who State “I Sleep Well at Night” in Relation to Number of Nocturnal Voids

<table>
<thead>
<tr>
<th>Number of Voids</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>89.9</td>
<td>79.9</td>
</tr>
<tr>
<td>1</td>
<td>91.3</td>
<td>75.4</td>
</tr>
<tr>
<td>2</td>
<td>78.3</td>
<td>56.8</td>
</tr>
<tr>
<td>3+</td>
<td>75.5</td>
<td>43.6</td>
</tr>
</tbody>
</table>


2, 3p < .0001
Nocturia Is a Widely Reported Cause of Poor Sleep

Prevalence of poor sleep in 3669 Swedish women aged 40 to 64 years according to nocturia severity

Nocturia Is the Leading Cause of Sleep Disturbance in Older Adults (US data)

How often do the following disturb your sleep?

<table>
<thead>
<tr>
<th>Causes of Sleep Disturbance</th>
<th>Percentage of Self-Reporting by Frequency of Disturbed Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia</td>
<td>N = 1424; aged 55-84 years</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Physical pain</td>
<td></td>
</tr>
<tr>
<td>Money problems</td>
<td></td>
</tr>
<tr>
<td>Caregiving</td>
<td></td>
</tr>
<tr>
<td>Family problems</td>
<td></td>
</tr>
<tr>
<td>Health concerns</td>
<td></td>
</tr>
<tr>
<td>Uncomfortable bed</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
</tr>
<tr>
<td>Nighttime heartburn</td>
<td></td>
</tr>
</tbody>
</table>

Frequency of Disturbed Sleep

Nocturia as the Leading Cause of Disturbed Sleep across All Adult Age Groups (US population)

Multivariate Risk Factors for Insomnia in Elderly Taiwanese Men


- Nocturia: Point Estimate 22.5, Upper Bound of 95% CI 45
- Unmarried: Point Estimate 0, Upper Bound of 95% CI 22.5
- Sleepiness: Point Estimate 0, Upper Bound of 95% CI 22.5
- Psychiatric: Point Estimate 0, Upper Bound of 95% CI 22.5
- COPD: Point Estimate 0, Upper Bound of 95% CI 22.5
- Hypnotics: Point Estimate 0, Upper Bound of 95% CI 22.5

Odds Ratio
Multivariate Risk Factors for Insomnia in Elderly Taiwanese Women


- **Nocturia**: Odds Ratio 1.6
- **Low Education**: Odds Ratio 23.7
- **Depression**: Odds Ratio 45.8
- **Somatic Pain**: Odds Ratio 67.9
- **Hypnotics**: Odds Ratio 90

Point Estimate and Upper Bound of 95% CI
Proportion of Nightly Awakenings Associated with Nocturnal Voiding Among 119 Elderly Volunteers with Self-reported Insomnia (unselected for nocturia)

(from Bliwise, Friedman et al, Health Psychol 2014: 33: 1362-5)

Median Split at 50%:
No diff: RDI, prostate Hx (men)
Sig Diff: arthritis Hx, urgency

*Figure 1.* Frequency distribution for proportion of nocturnal awakenings accompanied by voids as reported in daily sleep diaries across 119 study participants. Nocturia was defined when at least two-thirds of the awakenings were associated with nocturnal voids for any given case. Proportions represent the mean of all nights for each study participant.
Nocturia Associated with Higher Actigraphically Measured WASO in the Study of Osteoporotic Fractures (SOF) (n = 826) (Fung et al, *JAGS* 2017; in press)

Typical Number of Nocturnal Voids

\[ p < .001 \]
Actigraphic Measurements Confirm Higher WASO and Higher Number of Wake Bouts with Greater # of Voids

(n = 147; 1,774 individual nts)
Frequency Distribution of Time to First Void (also called First Uninterrupted Sleep Period, FUSP) in Untreated Nocturia

(Bliwise et al, J Clin Sleep Med 2015; 11: 53-5)
Short FUSP Associated with Worse Whole-night Sleep in Nocturia Patients

PSQI scores indicate that the shorter the FUSP, the worse the patient’s rating of depth, length, and quality of their sleep for the entire night.


![Graph showing PSQI scores and FUSP quartiles](image-url)
Other Adverse Outcomes Associated with Nocturia
(in addition to poor sleep)
Nocturia and/or Urge Incontinence Increase Risk for Falls

**Nocturia**

**Urge Incontinence**
Nocturia Predicts Fall-related Fractures and Mortality in the Elderly

Kaplan-Meier estimates show significantly lower mortality in patients without nocturia than patients with nocturia (log rank test p=0.0015); CI, confidence interval (Nakagawa H et al. J Urol 2010;184:1413–1418)
Nocturia Associated with Significantly Lower Scores on 14/15 Dimensions of HRQoL

n=1,888 Finnish women (similar results in males)
*P<0.05; **P<0.001 (test for trend)
Mechanistic Issues Underlying the
“...this study and others show that NP [nightly urine overproduction] is present in most patients with nocturia, including those with persistent nocturia despite BPH and OAB therapy. This finding is consistent regardless of gender, age and ethnicity.”
Chronobiology of Age Differences in Urine Production
Controlling for fluid and food intake, posture, sleep and lighting in the Constant Routine protocol
(Normal Subjects: c/o nocturia, sleep apnea)
(from Duffy et al, Current Aging Science 2016: 9: 34-43

Black line = younger (X age = 26)
Red line = older (X age = 69)
Pathophysiology of Nocturia in Sleep Apnea

*Obstructive sleep apnea*

- Intermittent occlusion of the airway
- Episodic, severe hypoxia
- Fluctuations in the intrathoracic pressure
- Hypoxic pulmonary vasoconstriction
- *Secretion of ANP*
- Increased diuresis (natriuresis)
Nocturia and Sleep Disordered Breathing in a Community-Dwelling Elderly Population

<table>
<thead>
<tr>
<th>RDI Level</th>
<th>0-9 (n=26)</th>
<th>10-24 (n=21)</th>
<th>25+ (n=11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.9 (6.0)</td>
<td>79.7 (6.9)</td>
<td>76.5 (7.2)</td>
<td>.26</td>
</tr>
<tr>
<td>BMI</td>
<td>24.5 (3.8)</td>
<td>23.4 (3.0)</td>
<td>28.0 (5.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>99.9 (11.5)</td>
<td>91.9 (11.3)</td>
<td>105.2 (14.7)</td>
<td>.015</td>
</tr>
<tr>
<td># NOC Voids (3-day voiding diary)</td>
<td>1.7 (1.1)</td>
<td>1.6 (0.9)</td>
<td>2.6 (1.4)</td>
<td>.028</td>
</tr>
</tbody>
</table>

Note: Subjects with CHF, uncontrolled diabetes and men with post-void residual volumes > 100 cc excluded; loop diuretics excluded.

From: Endeshaw et al, JAGS 2004; 52: 957-60
Polysomnographic (PSG) Measures and Nocturia
Sleep Heart Health Study (n = 6342)

*NOTES: Nocturia defined as at least 1 awakening to use the bathroom ≥ 5 nts/month; Values represent median (IQR) or %’s (Parthasarathy et al PLoS One 2012: 7:e30969)

<table>
<thead>
<tr>
<th>PSG Measure</th>
<th>Nocturia</th>
<th>No Nocturia</th>
<th>Comparison (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Duration</td>
<td>365 (317, 404)</td>
<td>367 (322, 408)</td>
<td>.06</td>
</tr>
<tr>
<td>Sleep</td>
<td>82.8 (75.4,</td>
<td>85.1 (77.4,</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>WASO</td>
<td>55.5 (34.0,</td>
<td>43.5 (26.5,</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>N1%</td>
<td>4.6 (2.8, 7.2)</td>
<td>4.5 (2.8, 7.1)</td>
<td>.32</td>
</tr>
<tr>
<td>N2%</td>
<td>57.5 (49.3,</td>
<td>57.2 (49.3,</td>
<td>.30</td>
</tr>
<tr>
<td>N3%</td>
<td>16.7 (8.2,</td>
<td>17.0 (8.2,</td>
<td>.36</td>
</tr>
<tr>
<td>REM%</td>
<td>19.8 (15.4,</td>
<td>20.5 (16.5,</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>AHI &gt; 15 (%)</td>
<td>23.2</td>
<td>17.4</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Nocturia Episodes Reduced by CPAP

No Effect of CPAP on Nocturia: The PREDICT Trial


![Graph showing the number of voids over baseline and 3 months for CPAP and control groups.]

- **CPAP**
  - Baseline: 1.7
  - 3 Month: 1.6

- **CONTR**
  - Baseline: 1.8
  - 3 Month: 1.7
Nocturnal Urine Volume is Reduced by 3 Months of CPAP Usage
(Miyazato et al, Neurourol Urodynam 2017; 36: 376-9)
What About the Chicken and the Egg?
Chicken and Egg

• Do patients awaken because of the need to void?  OR...

• Do patients awaken from other causes and then appreciate bladder sensations that prompt the bathroom trip?
Nocturia in the Sleep Lab

Only half of 121 awakenings to void attributed to urinary urgency

(Pressman et al, Arch Int Med 1996: 156: 545-60)
Bidirectionality in a Longitudinal Study of Nocturia and Poor Sleep

5-year follow up of the BACH Cohort

(Araujo et al, *J Urol* 2014; 191: 100-6)

Controlling for baseline sleep (or nocturia) and controlling for age, sex, race, SES, diabetes, heart disease, alcohol, physical Activity, smoking, anti-depressants, sedative/hypnotics, stimulants
Proximate Causation (Part I):
Detrusor Overactivity (DO) during Sleep in Patients with Overactive Bladder (OAB)

7 of 9 OAB pts also had nocturnal polyuria; control groups show neither DO nor NP

DO defined as pressure of $\geq 2 \text{ cm H}_2\text{O}$ for $\geq 1 \text{ sec}$

(Krystal et al, *J Urol* 2010; 184: 623-8)
Proximate Causation (Part II)  
Sleep Apnea and Incontinence in the Nursing Home

Wetness Episodes Can Begin during Apneic Events:  
Negative Pressure Breathing Causing Incontinence

Nocturia and Restless Legs

Attributable Fraction (%) of Nocturia Cases Eliminated If Exposure (i.e., Restless Legs) was Eliminated (Finland):
Awakening Because of Urge vs. Voiding When Awake

Treatment Issues with Nocturia
Nocturia is in the News!

**JAMA Online First** (April 06, 2017)

**JAMA** 2017; 317, 1518  (April 18, 2017)
Improvement in Nocturia is Associated with Improvements in Sleep Quality

One hour increase in FUSP was associated with a significant improvement in 7 out of 8 components of the PSQI

<table>
<thead>
<tr>
<th>PSQI Scale Component</th>
<th>n</th>
<th>Parameter estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>607</td>
<td>-0.488</td>
<td>0.054</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>633</td>
<td>-0.106</td>
<td>0.012</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>609</td>
<td>-0.079</td>
<td>0.015</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>632</td>
<td>-0.068</td>
<td>0.013</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>632</td>
<td>-0.102</td>
<td>0.018</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>634</td>
<td>-0.044</td>
<td>0.012</td>
<td>≈0.0002</td>
</tr>
<tr>
<td>Sleep Medication</td>
<td>634</td>
<td>-0.016</td>
<td>0.016</td>
<td>≈0.30</td>
</tr>
<tr>
<td>Daytime Dysfunction</td>
<td>634</td>
<td>-0.075</td>
<td>0.014</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Bliwise et al, *Sleep Medicine* 2014; 15: 1276-8
TURP has Limited Effect on Nocturia

- 118/138 (85.5%) BPO patients had nocturia before TURP
- After treatment, 91 of these (77.1%) still reported nocturia
- Improvement in nocturia score (1.0) significantly inferior to improvements for all other IPSS symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients scoring ≥2 score before TURP</th>
<th>Patients scoring ≥2 score after TURP</th>
<th>Rate of response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emptying</td>
<td>102</td>
<td>27</td>
<td>54.3</td>
</tr>
<tr>
<td>Voiding frequency</td>
<td>116</td>
<td>63</td>
<td>38.4</td>
</tr>
<tr>
<td>Intermittency</td>
<td>101</td>
<td>33</td>
<td>49.3</td>
</tr>
<tr>
<td>Urgency</td>
<td>103</td>
<td>70</td>
<td>37.0</td>
</tr>
<tr>
<td>Weak stream</td>
<td>122</td>
<td>35</td>
<td>63.0</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>84</td>
<td>18</td>
<td>47.8</td>
</tr>
<tr>
<td>Nocturia</td>
<td>118</td>
<td>91</td>
<td>19.6</td>
</tr>
</tbody>
</table>

TURP not the answer – are other mechanisms involved?

Solifenacin-related Improvements in Sleep Quality: Assessment with Wrist Actigraphy


<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>8 WEEKS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLEEP LATENCY</strong></td>
<td>13.8 (13.9)</td>
<td>13.1 (10.8)</td>
<td>.683</td>
</tr>
<tr>
<td>(mins)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL SLEEP</strong></td>
<td>352.2 (46.4)</td>
<td>368.8 (44.4)</td>
<td>.030</td>
</tr>
<tr>
<td><strong>TIME (mins)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SLEEP EFFICIENCY</strong></td>
<td>73.0 (7.2)</td>
<td>75.7 (6.2)</td>
<td>.007</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WAKE AFTER</strong></td>
<td>98.0 (40.0)</td>
<td>89.6 (35.5)</td>
<td>.096</td>
</tr>
<tr>
<td><strong>SLEEP ONSET</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NUMBER OF</strong></td>
<td>30.8 (7.7)</td>
<td>29.6 (7.7)</td>
<td>.272</td>
</tr>
<tr>
<td><strong>AWAKENINGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sleep Deprivation in Humans Increases Urine Production

24 hrs sleep deprivation vs normal sleep with H₂O and Na intake controlled

Water-loaded, wild-type rats show dose-dependent, zolpidem-induced decreases in urine volume the 1st hour after oral administration.

*An effect of sleep?*

(Yokoyama et al, *Neurourol Urodynam* 2010; 29: 587-91)
GABAergic Medication May Enhance Efficacy of Nocturia Rx

Song & Ku, *Int Urol Nephrol* 2007; 39: 1147-52
Can Treating Insomnia Behaviorally Benefit Nocturia in the Elderly?

*Brief Behavioral Treatment for Insomnia (BBTI) vs Information Control (IC)*

Nocturia Moderates Relative Effect Sizes (d) for Treatment Efficacy in Behavioral Insomnia Treatment: Brief Behavioral Treatment for Insomnia (BBTI) vs Information Control (IC)

Sleep Efficiency (SE) (in mins) and PSQI Global Score

(Tyagi et al, *Sleep* 2014: 37: 681-7)

<table>
<thead>
<tr>
<th></th>
<th>Nocturia Pre/Post-Baseline Adjusted Group Differences</th>
<th>No Nocturia Pre/Post-Baseline Adjusted Group Differences</th>
<th>Nocturia (Cohen’s d)</th>
<th>No Nocturia (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SE (%)</strong>&lt;br&gt;<strong>self</strong></td>
<td>2.16 (4.13)</td>
<td>6.72 (1.64)</td>
<td>0.25</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>SE (%)</strong>&lt;br&gt;<strong>actigraphy</strong></td>
<td>3.48 (1.91)</td>
<td>2.59 (1.57)</td>
<td>0.43</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>PSQI Global</strong></td>
<td>-2.27 (0.92)</td>
<td>-3.41 (0.72)</td>
<td>0.53</td>
<td>0.82</td>
</tr>
</tbody>
</table>
What about Desmopressin?

*(trade names: Noctiva, Nocdurna)*

*JAMA* Online First (April 06, 2017)

*JAMA* 2017; 317, 1518 (April 18, 2017)
Increase in FUSP With Desmopressin Melt (25 µg) in Women Over 3 Months’ Nightly Administration

Mean Change From Baseline in Initial Period of Undisturbed Sleep, h

- Desmopressin ODST 25 µg (n = 132)
- Placebo (n = 128)

Significance levels:
- P = 0.09
- P = 0.02
- P = 0.02
- P = 0.003

Increase in FUSP With Desmopressin Melt (50 µg) in Men Over 3 Months’ Nightly Administration


Mean Change From Baseline in Initial Period of Undisturbed Sleep, h

- Desmopressin ODST 50 µg (n = 119)
- Placebo (n = 142)

*P* = 0.0004

*P* = 0.0017

*P* < 0.0001

*P* = 0.0064
Baseline Subtracted Increments in FUSP with Oral Melt Formulation of Desmopressin Relative to Placebo: Average = 32-76 Mins \(^1-3\)

<table>
<thead>
<tr>
<th>Sedative-Hypnotic</th>
<th>Treatment Difference (Active vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eszopiclone (Lunesta)® 3mg(^4)</strong></td>
<td>25.0</td>
</tr>
<tr>
<td><strong>Doxepin (Silenor)® 6mg(^5)</strong></td>
<td>22.2</td>
</tr>
<tr>
<td><strong>Zolpidem-MR (Ambien-MR)®(^6)</strong></td>
<td>16.0</td>
</tr>
</tbody>
</table>

1. Weiss et al. *Neurourol Urodyn* 2012; 31: 441-7
Caudal-to-Rostral Fluid Shifts as Potentially Impacting Upper Airway Caliber

Could Fluid Retention Exacerbate Sleep Apnea?
SUMMARY

• Epidemiology (Prevalence, Outcomes)
• Mechanistic Issues involving Circadian Rhythms and Features of Sleep (including sleep apnea)
• Chicken and Egg Problem
• Treatments for Nocturia
Thank you for your attention
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Colleagues/Collaborators

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**EMORY DIVISION OF GERIATRIC MEDICINE**
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