Nocturia

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Nocturia: Definition

‘The complaint of interruption of sleep one or more times because of the need to micturate’

‘Each void is preceded and followed by sleep’

Halen et al, 2010
Nocturia: Prevalence

Women (n=1264)

Men (n=1271)

≥1 void per night

≥2 voids per night

Van Djik L et al, 2002
Nocturia: Prevalence

EPIC Study

- Population-based survey; (n=19,165, 5 EU countries)

Overall prevalence in women ≥18 years: of 54.5%

Females
Males

Irwin et al. 2006

Dudley Robinson - BGS Bladders and Bowel Health 2012
Nocturia: Causes

- Nocturnal polyuria
- Detrusor overactivity
- Reduced bladder capacity
- Uncompensated heart disease
- Psychological/sleep problems
- Primary polydipsia
- Oestrogen deficiency
- Untreated diabetes mellitus or insipidus

Fonda, 1999; van Kerrebroeck et al, 2002; Wein et al, 2002
Nocturia

Excessive Urine Production
- Global Polyuria
- Nocturnal Polyuria

Storage Disorder
- Detrusor Overactivity

Behaviour and Sleep Disorders
- Sleep Apnoea
Nocturia: Polyuria
Nocturnal Polyuria: Definition

- Defined as the production of an abnormally large volume of urine during sleep
  - Young: >20% of daily total output
  - Old: >33% of daily total output

van Kerrebroeck et al, 2002

- Major cause of nocturia in 60-80% of patients

Weiss et al, 2009
Nocturnal Polyuria: Causes

Water Diuresis
- Abnormality in secretion of AVP
- Primary Idiopathic
- Secondary – Excessive fluid intake

Solute /Water Diuresis
- Congestive Heart Failure
- Autonomic Nervous System Dysfunction
- Sleep Apnoea
- Renal Failure
- Oestrogen deficiency
Nocturia: Nocturnal Polyuria

Patients with nocturia ≥2 voids per night

<table>
<thead>
<tr>
<th>Age Group</th>
<th>NP in nocturia patients (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>63</td>
<td>845</td>
</tr>
<tr>
<td>65 years and over</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

Abrams et al, 2004
Global Polyuria: Definition

In a 70kg adult is defined as;

24 hr Voided Volume > 2.8 litres

van Kerrebroeck et al, 2002
Global Polyuria: Causes

Diabetes Mellitus
- Insulin dependent
- Non Insulin dependent

Diabetes Insipidus
- Pituitary
- Nephrogenic
- Gestational
- Primary Polydipsia

Psychogenic    Dipsogenic    Iatrogenic
Nocturia: Bladder Storage Disorders
Storage Problems: Causes

Reduced Bladder Capacity
- Extrinsic compression
- Radiotherapy

Bladder Pain Syndrome
- Interstitial Cystitis
- Chronic Cystitis

Overactive Bladder
- OAB – Dry
- OAB - Wet

Detrusor Overactivity
- Idiopathic
- Neurogenic

Voiding Dysfunction
- Urogenital prolapse
- Urethral Stricture

Urogenital Atrophy
- Oestrogen deficiency
- Urogenital Ageing
Overactive Bladder

‘Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious cause’

Haylen et al, 2010
Nocturia: Sleep Disturbance
Sleep Disturbance: Causes

Sleep Disorders
• Insomnia
• Sleep Apnoea
• Arousal Disorders

Medical Disorders
• Cardiac Failure
• COPD

Neurological Conditions
• Parkinsons
• Dementia
• Epilepsy

Psychiatric Conditions
• Anxiety
• Depression

Chronic Pain Disorders
• Rheumatoid Arthritis
• Osteoarthritis

Alcohol / Drugs
• Consumption
• Withdrawal

Medication
• Corticosteroids
• Diuretics
• β Adrenergic Antagonists
Nocturia: Sleep Disturbance

How often do the following disturb your sleep?

- Nocturia
- Physical pain
- Caregiving
- Health concerns
- Cough
- Night-time heartburn

n=1424; aged 55–84 years

Bliwise et al, 2009
Consequences of sleep deprivation

Impaired Daytime Functioning
- Reduced daytime energy, psychomotor performance, concentration, memory and cognitive function
- Reduced mood and depression
- Reduced quality of life
- Increased number of traffic accidents (RR=3–6)

Increased morbidity/mortality
- Increased risk of cardiovascular disease due to metabolic and immune suppression and increased glucose tolerance
- Increased mortality

Roth, 2005
"Right now, the best way to please me in bed... is to let me SLEEP!"
Nocturia: QoL Impairment

Tikkinen et al, 2010

3597 subjects; *p<0.05, **p<0.001

Dudley Robinson - BGS Bladders and Bowel Health 2012
Nocturia: Productivity

- Productivity, vitality, and QoL were assessed in 203 Swedish adults with ≥ 1 void/night.
- Nocturia patients had significantly:
  - Increased work impairment
  - Increased impairment in non work activities
  - Reduced vitality (SF-36)
  - Reduced overall QoL (EQ-5D)
- Work impairment increased with nocturia severity \((p<0.05)\)
- Vitality decreased with nocturia severity \((p<0.01)\)

Kobelt et al, 2003
Nocturia: Survival

Asplund, 1999
Nocturia: Mortality

Nakagawa et al, 2010

Hazard Ratio of all-cause mortality: Night time frequency

<table>
<thead>
<tr>
<th></th>
<th>≤1 (n=425)</th>
<th>2 (n=219)</th>
<th>3 (n=99)</th>
<th>≥4 (n=41)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>1.59 (0.80, 3.17)</td>
<td>2.34 (1.09, 5.00)</td>
<td>3.60 (1.38, 9.35)</td>
<td>&lt;0.01</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.
‘Don’t be alarmed — loss of bladder control is a side effect of receiving my bill.’
International Consultation on Nocturia 2002

Nocturia

Is it bothersome?

No

Advice

Yes

Establish cause

Sleep disturbance

Bladder storage problems

Polyuria

Psychological

Behavioural

Nocturnal polyuria

24-hour polyuria
Nocturia: Investigation

History
- Urinary Symptoms
- Fluid Intake

Examination
- Urogenital Prolapse
- Urogenital atrophy
- Pelvic mass

Bladder Diary
- Nocturnal Polyuria

Urodynamic Studies

Cystoscopy
Nocturia: Management

Identify and treat underlying pathology

Conservative

- Modification of fluids
- Posture
- Evening diuretics
- Improve Sleeping environment
- CPAP

Drug Therapy

- Anti-diuretics
- Antimuscarinics
- Diuretics
<table>
<thead>
<tr>
<th>Drug</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
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<tr>
<td>Darifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propiverine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Trospium</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>1</td>
<td>A</td>
</tr>
</tbody>
</table>
OAB: Nocturnal Polyuria

- In EPIC 12.8% of women responders had OAB
  Irwin et al, 2006
- Amongst women with OAB 74% had nocturia
  Irwin et al, 2008
- Overall 62% of patients with OAB + nocturia have nocturnal polyuria (NP)
  Brubaker et al, 2007
- Rate of NP in women with OAB + nocturia increases with age
  Drake et al, 2005
OAB: Nocturnal Polyuria

Even in patients without nocturnal polyuria, reduction in nocturia is not large

Brubaker & Fitzgerald, 2007
Nocturia: Desmopressin

- Desmopressin - Synthetic analogue of antidiuretic hormone arginine vasopressin (AVP)
- No effect on $V_1$ receptors
- Greater effect on renal $V_2$ receptors than vasopressin
- Avoids undesirable vasopressor and uterotonic effects
- Increases reabsorption of water, concentrating urine and decreasing urine production

Urine osmolarity (mosm/L)

<table>
<thead>
<tr>
<th>Osmolarity</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>200</td>
<td>200</td>
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<td>700</td>
<td>700</td>
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<td>800</td>
<td>800</td>
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</tbody>
</table>

Plasma vasopressin (pg/mL)

<table>
<thead>
<tr>
<th>Flow (mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

Nørgaard et al, 2007
Robertson and Norgaard, 2002
Rationale for desmopressin use in nocturia

- Overall 76% of women with nocturia have NP
  - Swithinbank et al, 2003

- 62% of women with OAB and nocturia have NP
  - Brubaker & Fitzgerald, 2007

- NP, if present, must be addressed to achieve clinically significant improvement in nocturia

- Desmopressin: antidiuretic agent capable of effectively reducing night-time urinary output

Useful treatment for nocturia in patients whose nocturia is caused by nocturnal polyuria, including OAB patients refractory to antimuscarinic therapy
Desmopressin: Short-term study

- 3-week double-blind placebo-controlled study of desmopressin treatment in women with nocturia

- Mean reduction in number of voids from baseline:
  - 2.9 to 1.6 with desmopressin
  - 2.9 to 2.4 with placebo

- Significant reduction in bother (p=0.01)

- Clinical response defined as ≥50% reduction in mean number of nocturnal voids

Lose et al, 2003

*Clinical response defined as ≥50% reduction in mean number of nocturnal voids
Desmopressin: Short-term study

- 33% of desmopressin group had >5 hours undisturbed initial sleep period per night (Vs 6% with placebo)

\[ \text{Mean increase in sleep period (minutes):} \]
\[ \text{Desmopressin: 130 Vs Placebo: 37} \] \[ (p<0.0001) \]

Lose et al, 2003
Desmopressin: Long-Term Study

Mean reduction in night-time voids: 55–59%

Lose et al, 2004
Desmopressin: Long-term Study

Mean increase in first sleep period: 54%

- Baseline
- Start of long-term
- 10 months
- 12 months
- 1 month treatment-free follow-up

Women: n=117, n=56, n=85, n=79, n=83

Lose et al, 2004
Desmopressin: Adverse Effects

- Frequency and type of adverse events similar in short- and long-term studies
- Majority of adverse events mild or moderate
- Higher incidence of adverse events in women ≥65 years: (41% vs 19%)
- 10% withdrew due to adverse events
- Fluctuations in serum sodium low:
  - 13 females had asymptomatic borderline hyponatremia (130mmol/L or above)
  - Only 1 symptomatic (between 125–130 mmol/L)

Lose et al, 2004
Desmopressin: Hyponatremia

- **Risk increased in:**
  - Patients > 65 years
  - Low baseline serum sodium

<table>
<thead>
<tr>
<th>Age</th>
<th>Basal s-sodium</th>
<th>n</th>
<th>No. of patients with significant hyponatremia</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>Normal</td>
<td>336</td>
<td>3</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>Normal</td>
<td>260</td>
<td>22</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>8</td>
<td>6</td>
<td>75%</td>
</tr>
</tbody>
</table>

Check serum sodium at baseline and at day 5 - 7

Rembratt et al, 2006
Desmopressin: Gender Differences

- Study of diurnal variation of ADH in 69 volunteers
- Two fold higher level of ADH in men when compared to women

Aspund and Aberg, 1991

- Urine osmolality is similar in men and women

Hvistendahl et al, 2007

- Suggests higher renal sensitivity in women
- Oestrogen lowers the plasma osmotic threshold for ADH and increases renal sensitivity

Stachenfeld et al, 1998
Desmopressin: Gender Differences

• Significantly more V2 receptor mRNA in female rats when compared to male rats
  
  Liu et al, 2008

• Mutations in the AVPR2 gene located on the X chromosome may cause polyuric, polydipsic and antidiuretic disorders
  
  Migeon, 2008

• Clinically less severe in the female phenotype when compared to the male phenotype probably due to female carriers “escaping” X inactivation

  Carrell and Willard, 2005
Desmopressin: Gender Differences

- 4 week prospective double blind randomised study of desmopressin melt in 757 subjects
  Placebo or oral desmopressin (10, 25, 50 or 100µg)

- Co-primary endpoints:
  Mean change in nocturnal voids from baseline
  Proportion of subjects with >33% reduction in mean nocturnal voids

- Clear evidence of dose effect

- Significantly greater decrease in nocturnal urine volume in women at the lower doses of 10µg and 25µg when compared to men

Weiss et al, 2012
Desmopressin: Gender Differences

- ED$_{50}$ lower in women when compared to men
  - 16.1µg vs 43.2µg
- Significantly higher sensitivity to desmopressin in women
- Fivefold higher risk of hyponatremia (Na<130mmol/l) in women over 50 years old at the 50µg dose when compared to men

Weiss et al, 2012

- 50-100µg is an efficacious dose in men
- 25µg is equally efficacious in women and there were no reported cases of hyponatremia

Juul et al, 2011
Conclusions

- Nocturia in women is multifactorial
- Significant effect on QoL and mortality
- Nocturnal polyuria is a frequent underlying factor
- Underlying causes of nocturia need to be excluded
- Nocturia in OAB patients may not be treated with antimuscarinic therapy
- Desmopressin reduces nocturnal voids
- Shown to increase sleep and reduce patient bother
- May be used in combination therapy with an antimuscarinic
- Should be used with caution in the elderly
- Significant gender difference in response