### Aims of course/workshop

This workshop offers a comprehensive overview on the current knowledge on nocturia. We will start with a critical review on terminology, and continue with discussing epidemiology, causes, comorbidities, and consequences of nocturia. Nocturnal polyuria is an important cause of nocturia, but its role in other symptoms, such as incontinence, urinary tract infections and retention, is clearly underestimated. This will be discussed before pointing out the different treatment options for nocturia and specifically nocturnal polyuria. Finally, similarities between nocturia and nocturnal enuresis in children will be explored. The latter has already been studied intensively and offers many hints for further nocturia research.
Terminology and Classification of Nocturia

Jeffrey P. Weiss, MD, FACS
Professor and Chair
Department of Urology
SUNY Downstate College of Medicine
Brooklyn, NY

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

What triggers nocturia*?

Classification of Night-time Voids

- Primary Nocturia
  - Urgency Voids
  - Non-Urgency Voids
- Secondary Nocturia
  - Voids

Diary Assessment
• NPI (Nocturnal polyuria index = NUV/24 hour volume):
  • NPI > 33% = Nocturnal polyuria

Nocturia: Evaluation
• Simple arithmetic analysis of 24 hour voiding diary
  – First AM voided volume included in NUV
  – First AM void diurnal, not nocturnal

• 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

Formulas for evaluation of nocturia

<table>
<thead>
<tr>
<th>Formula</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia index Ni = NUV/ MVV</td>
<td>Ni &gt;1 → nocturia is due to NUV exceeding MVV</td>
</tr>
<tr>
<td>Nocturnal Polyuria index NPI = NUV/ 24hV</td>
<td>NPI &gt;33% → Dx is nocturnal polyuria</td>
</tr>
<tr>
<td>Nocturnal bladder capacity index Ni – 1 = PNV</td>
<td>NBCi &gt;0 → nocturia occurring at volumes &lt; MVV</td>
</tr>
</tbody>
</table>

Nocturia Category

<table>
<thead>
<tr>
<th>Nocturia Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal polyuria</td>
<td>Congestive heart failure, Diabetes mellitus, Obstructive sleep apnea, Peripheral edema, Excessive nighttime fluid intake</td>
</tr>
</tbody>
</table>

Nocturia Category

<table>
<thead>
<tr>
<th>Nocturia Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diminished global/NBC</td>
<td>Prostatic obstruction, Nocturnal detrusor overactivity, Neurogenic bladder, Cancer of bladder, prostate, or urethra, Learned voiding dysfunction, Anxiety disorders, Pharmacologic agents, Bladder calculi, Ureteral calculi</td>
</tr>
</tbody>
</table>
### Nocturia Category and Causes

<table>
<thead>
<tr>
<th>Nocturia Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<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 ≥ 0.9 ml/min (54 ml/hr)
  - Krimpen study (Bosch): Men 50-78: mean NUV=60 ml/hr
  - Suggest NP cutpoint >90 ml/hr
- NUV/24h urine ≥ 0.33 (ICS)
  - <25 years: mean NP=0.14
  - >65 years: mean NP=0.34


### Nocturnal Polyuria: Prevalence
- Investigation of characteristics of patients recruited to a large phase III study for treatment of nocturia
  - Nocturia on average 2 voids/night, mean age 62
  - 1412/934/799 patients screened/eligible to complete diary/randomized
  - 819/1412 (58%) had nocturnal polyuria
  - 478/1412 failed to complete a diary leaving 934 who did
  - 819/934=87.7% of those completing diary had nocturnal polyuria

Nocturnal Polyuria: Prevalence*

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

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

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


---

Findings of the Krimpen study in: Nocturia: Causes, Consequences and Clinical Approaches: Weiss, Branke, van Hemelrijck, Wein; eds. Springer 2002
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: 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%


Nocturia as function of OSA severity

Nocturia: Classification

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

Drug effects causing nocturia

Increased urine output  | Azotemia and CNS effects  | Direct UO7 effects
--- | --- | ---
Sulpiride | CNS stimulants (dopamine, serotonin, methyphenidate) | Ketamine: Direct toxin
SSRIs (block ADH secretion) | Antihypertensives (alpha-blockers, beta-blockers, methyldopa) | Tryptoenic acid (Aureo). Thiolopeptide
Calcium-channel blockers (inhibit ANP) | Reservoir (salbutamol, theophylline) | Cyclophilinase
Tetracycline (alters ADH via NaCl/AMP system and effects) | Deoxoglucantigens (glycerol, fructose, acetaminophen) | Tsumaz (tetracycline, tryptophyl)
Lithium (decreases ADH levels) | Hormones (corticotropin, insulin) | Psychotropics (MAOIs, SSRIs, atypical antidepressants)
Sedative-hypnotics, anxiolytic agents (clobazam, Clonazepam)
Antiepileptics (phenytoin)
Causes of Low global/NBC: **Urologic**
- Infravesical obstruction
- Idiopathic nocturnal detrusor overactivity
- Neurogenic bladder
- Cystitis: bacterial, interstitial, tuberculous, radiation
- Cancer of bladder, prostate, urethra

**Other causes of low global/NBC**
- Learned voiding dysfunction
- Anxiety disorders
- Pharmacologic
  - xanthines (theophylline, caffeine)
  - beta-blockers
  - Other (see next slide)
- Bladder calculi
- Ureteral calculi

**Drug effects**

<table>
<thead>
<tr>
<th>Increased urine output</th>
<th>Acute and CSR effects</th>
<th>Direct LUT effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>CNS stimulants (deoxocortisosterone, methyldopa)</td>
<td>Ketamine: Direct loom</td>
</tr>
<tr>
<td>SSRIs (block ADH secretion)</td>
<td>Antihypertensives (alpha-blockers, beta-blockers, methyldopa)</td>
<td>Tapireronic acid (Surgam) Toxic cystitis</td>
</tr>
<tr>
<td>Calcium-channel blockers (decrease Na/H exchange)</td>
<td>Antidepressants (tricyclics, lithium)</td>
<td>Cytosporic acid</td>
</tr>
<tr>
<td>Tetracaine (similar to ADH via decrease cAMP and action)</td>
<td>Amphetamines (dextroamphetamine, methyldopa)</td>
<td>Tropic spironolactone</td>
</tr>
<tr>
<td>Lithium (decrease ADH levels)</td>
<td>Antihistamines (phenothiazines, hydralazine)</td>
<td>Tropic spironolactone</td>
</tr>
<tr>
<td>Propranolol (block beta receptors)</td>
<td>Opioids (morphine, meperidine)</td>
<td>Tropic spironolactone</td>
</tr>
<tr>
<td>Antidepressants (phenothiazines)</td>
<td>Anticholinergics (hyoscine)</td>
<td>Tropic spironolactone</td>
</tr>
</tbody>
</table>

**FVC Determinants of Nocturia Severity in Men**

<table>
<thead>
<tr>
<th>Nocturia patients (n=88)</th>
<th>Community dwelling older men (n=1082)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual number of nightly voids</td>
<td>Correlation coefficient (Spearman’s rho)</td>
</tr>
<tr>
<td>Nighttime index (N)</td>
<td>-0.777</td>
</tr>
<tr>
<td>Nocturnal polyuria index (NP)</td>
<td>-0.463</td>
</tr>
<tr>
<td>Nocturnal urine volume (NUV)</td>
<td>-0.306</td>
</tr>
<tr>
<td>Hours of sleep</td>
<td>-0.159</td>
</tr>
<tr>
<td>Resting maximum voided volume (MVV)</td>
<td>-0.146</td>
</tr>
</tbody>
</table>

| Mean nocturnal urine production (NUP)** | n/a | n/a | 0.351 | <0.001 |

**Low bladder compliance is a risk factor in nocturia severity**

<table>
<thead>
<tr>
<th>Cohort Based on Bladder Compliance (n)</th>
<th>Average ANV</th>
<th>SD</th>
<th>P-value</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder Compliance (20 cm/mH2O) (15)</td>
<td>3.6</td>
<td>1.24</td>
<td>0.0486</td>
<td>0.019-2.839</td>
</tr>
<tr>
<td>Bladder Compliance (20-30 cm/mH2O) (17)</td>
<td>3.6</td>
<td>1.73</td>
<td>0.0486</td>
<td>0.019-2.839</td>
</tr>
<tr>
<td>Bladder Compliance (30-40 cm/mH2O) (18)</td>
<td>3.5</td>
<td>1.64</td>
<td>0.0015</td>
<td>0.455-7.634</td>
</tr>
<tr>
<td>Bladder Compliance (40-50 cm/mH2O) (24)</td>
<td>3.4</td>
<td>1.64</td>
<td>0.0015</td>
<td>0.455-7.634</td>
</tr>
<tr>
<td>Bladder Compliance (50-60 cm/mH2O) (33)</td>
<td>3.3</td>
<td>1.76</td>
<td>0.0002</td>
<td>0.629-3.819</td>
</tr>
<tr>
<td>Bladder Compliance (60 cm/mH2O) (39)</td>
<td>3.0</td>
<td>1.52</td>
<td>0.0002</td>
<td>0.629-3.819</td>
</tr>
</tbody>
</table>

**Nocturia: Classification**
- Nocturnal polyuria (NP)
- Diminished global/nocturnal capacity (NBC)
- Mixed (NP + ↓ NBC)
- Polyuria

---

“Mixed” Nocturia etiology

- Review of 194 consecutive patients with nocturia
- 13 (7%) had NP, 111 (57%) ↓ NBC, 70 (36%) had “mixed” etiology
- Forty-five (23%) also had polyuria
- NP = a significant component of nocturia in 43% of the patients
- Conclude: Etiology of nocturia multifactorial and often unrelated to underlying urologic condition

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 (eg chronic renal failure)

Extrarenal Causes of Nephrogenic DI
(block action of ADH)
- PGE-2
  - NSAIDS reported to improve nocturia possibly due to block in PGE-2 – mediated diuresis*
- ANP
- Hypercalcemia
- Hypokalemia
- Lithium
- Tetracyclines

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

Water deprivation test
- No drinking overnight
- Normal: first AM urine osmolality > 600-800 mOsm/kg H2O
- Normal means that there is normal AVP secretion and normal renal response

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

Nocturia: Practice Examples
Diary analysis: Nocturnal polyuria
- NUV = 750 ml
- 24 hour volume = 1500 ml
- NPI = NUV / 24hr = 0.5 (>0.33)

Diary analysis: Diminished nocturnal bladder capacity
- NUV = 750 ml
- MVV = 150 ml
- Ni = NUV / MVV = 5
- PNV = Ni-1 = 5-1 = 4
- ANV = 8
- NBCi = ANV – PNV = 8-4 = 4
- NBCi > 2: Nocturia strongly related to low NBC
- MVV=150 ml: Nocturia strongly related to poor global bladder capacity

Diary analysis: Global polyuria
- 24 hour volume = 5000 ml
- NUV = 1500 ml
- MVV = 500 ml
- Ni = NUV/MVV = 3
- PNV = Ni-1= 3-1 = 2
- ANV = 2
- NBCi = ANV – PNV = 2-2 = 0 (nocturic voids at capacity)
- NPI = 1500/5000 = 30% (normal)

Diary analysis: Mixed
- 24 hour volume = 2500 ml (no polyuria)
- NUV = 1500 ml
- MVV = 500 ml
- Ni = NUV/MVV = 3
- PNV = Ni-1= 3-1 = 2
- ANV = 6
- NBCi = ANV – PNV = 6-2 = 4
- Thus low nocturnal bladder capacity -cf- MVV
- NPI = 1500/2500 = 60% (nocturnal polyuria)
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)
### Twenty-four Hour Voiding Diary Analysis

<table>
<thead>
<tr>
<th>Date</th>
<th>24 hr vol (ml)</th>
<th>NUUV (ml)</th>
<th>ANV</th>
<th>NPy (%)</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>36</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>

- NUUV = nocturnal urine volume
- ANV = actual # nightly voids
- NPy = NUUV/24 urine volume
- MVV = maximum voided volume
- Ni = NUUV/MVV
- PN = predicted # nightly voids = Ni-1, rounded up to next integer if not already an integer
- NBC = nocturnal bladder capacity index = ANV/PN

### 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: Discussion
Nocturnal polyuria, merely a cause of nocturia?

K. Everaert
Functional Urology
Ghent University Hospital, Belgium

Introduction
Although the problem of nocturnal polyuria has been recognized, its pathophysiological mechanism remain unclear. Since urine output depends on water intake, distribution and excretion, it is evident that abnormalities in each of these components could affect urinary output (1). First, it is considered that the circadian rhythmicity in the secretion of the anti-diuretic hormone, arginine vasopressin (AVP), is disturbed in the same way as in children with enuresis and aged persons with nocturnal polyuria. Healthy individuals produce smaller volumes of concentrated urine during the night due to the increased nocturnal vasopressin secretion but this would be inadequate or even absent in para- and tetraplegics and elderly and therefore contribute to an increased water diuresis (2;4). Second, it is known that patients with spinal cord lesions experience fluid retention in the lower extremities during daytime because of the absence of the pumping action of the leg muscles and the vessel tone loss that is attributed to the chronic autonomic failure. Changing position during the night to a recumbent position, increases intravascular volume and causes a surplus of fluid that is presented to the kidney and leads to a higher nocturnal diuresis (2;4). This increased intravascular volume also stimulates secretion of the atrial natriuretic peptide (ANP) which contributes to an increased solute diuresis by increasing natriuresis (1;5).

Nocturnal polyuria in young adults
Besides nocturnal enuresis and nocturia, nocturnal polyuria can present as nocturnal incontinence, bilateral flank pain in the early morning, hydronephrosis and urinary retention. Typical examples are patients with lazy bladder syndrome and Fowler syndrome.

Nocturnal polyuria in elderly people
Nocturnal polyuria is a highly age-dependent condition, affecting up to 85% of the elderly population (>65 years old). A decrease in renal concentrating ability appears to be a normal ageing process, which might already lead to a higher nocturnal urine production, but a decrease of nocturnal ADH secretion with an increased diuresis at one hand and/or an increase of nocturnal ANP secretion with
an increased natriuresis at the other hand seem to lay at the base of excessive nocturnal urine production.(7,8) Anyhow, it is a multifactorial condition, especially in the elderly, who often have an extended medical history and accompanying medical therapy list.

A review from 2007 published that 44% of women and 29% of men suffer from UI once they are older than 65 years. Over 80 years, the prevalence rates are respectively 57% and 42%. For elderly who are institutionalized, the prevalence rates increases up to 77%. It affects more women and is an important indicator of institutionalization (9,10). With the global population aging, the absolute numbers of elderly people, also those who suffer from UI, will increase exponentially in the future.

We currently recognize 3 ethiopathogenetic causes for UI that can exist as a solitary condition or co-exist with each other:

1. Incontinence associated with decreased urethral resistance (stress urinary incontinence)
2. Incontinence associated with detrusor overactivity (overactive bladder syndrome)
3. Incontinence associated with overdistention of the bladder (related to polyuria, loss in bladder sensation and/or voiding difficulties).

Nocturnal polyuria is a highly prevalent condition in the elderly population of a nursing home. This excessive nocturnal urine production cannot be attributed to a longer sleep duration or a higher drinking volume, so it must be related to hormonal disturbances during nighttime.

About 40% of the subjects with nocturnal polyuria present with nocturia, whereas 52% presents with incontinence; the latter group has significantly higher nocturnal urine volumes and experiences a more pronounced influence on quality of life compared to those who can get up at night to void. And although the need for incontinence material might not only depend on bladder related problems, it seems that reducing the nocturnal urine volume might improve quality of life within the subgroup of patients wearing incontinence material because of nocturnal enuresis by reducing the need for incontinence material.

**Nocturnal polyuria and neurogenic bladder disease**

Nocturnal polyuria is related to edema in the lower limbs in elderly. Wheelchair bound patients encounter the same phenomenon. This leg-edema related nocturnal polyuria results in nocturnal overdistention of the bladder, elevated bladder pressures, hydronephrosis, incontinence and the need for nocturnal bladder emptying which is more time consuming than in people with normal bladder function. Nocturnal polyuria decreases quality of life of the neurogenic patients and their partners.

The effect of detrusor pressure on complications or prevention or treatment of complications in neurogenic bladder disease is generally accepted. Clinical studies relate detrusor pressure to reflux, hydronephrosis and UTI (11-12). Renal tubular damage is related to detrusor pressure and not to the...
presence of bacteria in patients with vesico-ureteral reflux without fever (13). When the interval between catheterisation increases due to low frequency of catheterisation, the incidence of bacteriuria may increase. Adding a moment of bladder-emptying decreases symptomatic UTI in patients with menigomyelocele. In conclusion bladder overdistention in neurogenic bladder disease is responsible for increasing prevalence of UTI due to increasing pressure, the time urine lasts in the bladder and trauma to the urothelium. Nocturnal polyuria is therefore a contributing factor for UTI in neurogenic bladders.

Autonomic dysreflexia (14) is seen in 19-70% of the spinal cord injured patients with lesions at or above sixth thoracic neurogenic level (T6). It is less frequently seen in incomplete lesions or lesions below T6 (T10-T6), in multiple sclerosis or medullar tumours. Mild chronic forms of AD are used by patients as signal for bladder or bowel emptying but can be very disturbing during the night. Also the higher blood pressure during these episodes is potentially long term risk for cardiovascular complications. UTI and bladder overdistention are the main cause of the more acute clinical presentation of autonomic dysreflexia with sometimes life-threatening hypertension.

Conclusion:
Nocturnal polyuria is more than nocturnal enuresis and nocturia but can cause important decrease in quality of life due to nocturnal incontinence, flank pain, urinary retention and can be complicated by severe and even life-threatening situations (hydronephrosis, autonomic dysreflexia) sometimes demanding for major surgery like bladder augmentation and urinary diversion.


Both nocturnal enuresis and nocturia have following characteristics:

1) A genetic factor is suspected
2) Reduced bladder capacity and nocturnal polyuria are the main underlying bladder related conditions, on which treatment is based
3) There is a clear link with sleep disorders
4) Physical and mental health is comprised in both conditions, however, in other ways:
   a. NE:
      - constipation and attention deficit/hyperactivity disorder are the most important comorbidities
      - effect on mental health and quality of life is mainly through the negative impact on self-esteem
   b. nocturia:
      - cardiovascular disease and fall injuries are important comorbidities, which mainly affect the older nocturia population
      - personal distress and depression can be a consequence of poor sleep quality
5) treatment is often inadequate

The main difference between nocturnal enuresis and nocturia seems to be the difference in arousal to bladder stimuli, suggesting that sleep characteristics might be a key factor in these conditions.
<table>
<thead>
<tr>
<th>Definition:</th>
<th>NE in children</th>
<th>Nocturia in adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>involuntary urinary incontinence at night while being asleep</td>
<td>the need to wake up once or more at night to void with each void preceded and followed by sleep</td>
</tr>
<tr>
<td>Prevalence:</td>
<td>10% in 7-year-olds, 0,5% in adults</td>
<td>50% in &gt;50-year-olds, 4-7% in healthy schoolchildren</td>
</tr>
<tr>
<td>Genetics:</td>
<td>Familial occurrence, 66% has a first degree relative affected</td>
<td>Familial occurrence proven in twin studies, Prevalence differs according to ethnicity, but no related genotypes have been unraveled</td>
</tr>
<tr>
<td></td>
<td>chromosomels 12q, 13q and 22q are involved, phenol- and genotype are not closely linked</td>
<td></td>
</tr>
<tr>
<td>Underlying condition:</td>
<td>OAB due to delayed maturation of the CNS; lazy bladder syndrome; dysfunctional elimination syndrome</td>
<td>OAB, obstruction (BPH, strictures), cancer of the bladder or prostate, bladder hypersensitivity, calculi, vesicoureteral reflux, bladder diverticula and infection</td>
</tr>
<tr>
<td></td>
<td>nocturnal urine output exceeding 130% of the expected bladder capacity for age; due to water- or solute-handling disturbances</td>
<td>a nocturnal urine volume greater than 20-33% of the total 24-hour urinary volume (cut-off 65 years old); due to an abnormal secretion of arginine vasopressin, nighttime fluid intake, diuretics, heart or kidney failure, sleep apnea</td>
</tr>
<tr>
<td>Comorbidities / Consequences:</td>
<td>superficial, fragmented sleep with inappropriate arousal; PLMD, RLS, sleep apnea</td>
<td>fragmented sleep; insomnia, sleep apnea</td>
</tr>
<tr>
<td></td>
<td>constipation, dysfunctional elimination syndrome; psychological problems: Low self-esteem, behavioral problems, concentration disorders and aggressive behavior, ADHD</td>
<td>hypertension, obesity, diabetes, cardiovascular events, falls and fractures; daytime fatigue, personal distress, decreased cognitive function and even depression</td>
</tr>
<tr>
<td>Treatment:</td>
<td>Antimuscarinics</td>
<td>reduction of nocturia episodes with max. 50%, only when underlying OAB</td>
</tr>
<tr>
<td></td>
<td>second-line treatment, combination therapy</td>
<td>first-line treatment when due to nocturnal polyuria, effective in 33-67%, side effects in 7%</td>
</tr>
<tr>
<td></td>
<td>first-line treatment when due to nocturnal polyuria; effective in 1/3, low prevalence of side effects</td>
<td>lifestyle changes, surgery</td>
</tr>
<tr>
<td></td>
<td>urotherapy, enuresis alarm, neurostimulation</td>
<td></td>
</tr>
</tbody>
</table>
Long-term follow-up of enuretic patients

Aim:
- What is the prevalence of nocturia in former enuretics?
- What are the characteristics in nocturics compared to non-nocturics?

Materials&Method:

1265 former enuretic patients were asked to fill out a questionnaire on current status on urinary incontinence (ICIQ-UI), nocturia and overactive bladder symptoms (ICIQ-OAB).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nocturics</th>
<th>Non-nocturics</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean,SD)</td>
<td>18 ± 3.7</td>
<td>17 ± 2.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>Sex: male (N, %)</td>
<td>101 (56%)</td>
<td>230 (69%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>female (N, %)</td>
<td>81 (44%)</td>
<td>103 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; UI = urinary incontinence; *N=134; **N=255

Results:

Questionnaires from 516 patients (41%): mean age 17 (SD 3.2), 331 male (64%) and 184 female (36%) participants; 35% reports nocturia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nocturics</th>
<th>Non-nocturics</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaks before getting to the toilet</td>
<td>27 (15%)</td>
<td>29 (9%)</td>
<td>0.029*</td>
</tr>
<tr>
<td>Leaks when asleep</td>
<td>21 (12%)</td>
<td>15 (4%)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Conclusion:
Approximately 1 out of 3 enuretic patients develops nocturia, which is often accompanied by other urinary symptoms.

Some of the nocturic patients might benefit from continuous treatment for the underlying urologic condition, such as overactive bladder syndrome or nocturnal polyuria.