

## W3: Conceptualising Causes, Diagnosis and Therapy of Nocturnal LUTS

Workshop Chair: Karel Everaert, Belgium

06 October 2015 09:00 - 10:30

Start	End	Topic	Speakers
09:00	09:15	Introduction: Conceptualising nocturnal LUTS	Karel Everaert
09:15	09:30	Definitions and terminology	Alan Wein
09:30	09:45	Diagnosing reduced bladder capacity - bladder diaries	Jeff Weiss
09:45	10:00	Diagnosing nocturnal polyuria - renal function profile	Karel Everaert
10:00	10:15	Treatment of nocturnal LUTS - increasing bladder capacity or decreasing nocturnal urine production?	Matthias Oelke
10:15	10:30	Discussion	All

### **Aims of course/workshop**

This workshop offers a comprehensive overview on the current knowledge on nocturnal Lower Urinary Tract Symptoms (LUTS). Nocturnal LUTS are nocturia, nocturnal incontinence and bedwetting. The aim is not merely to discuss these symptoms, their diagnosis and therapy, but to conceptualise their mutual causes, diagnosis and therapy, and simplify the clinical thinking when we encounter these patients. We will start with discussing nocturnal LUTS and make critical review on terminology, and continue with discussing causes (reduced bladder capacity and nocturnal polyuria), diagnosis (bladder diaries and renal function profiles) and their therapies.

### **Learning Objectives**

1. Appreciate that nocturia can be a bothersome symptom, a disease with morbidity and mortality and/or a symptom of a systemic disease that needs to be diagnosed and treated
2. Diagnose and treat nocturia caused by bladder and/or kidney pathology
3. Diagnose and treat nocturnal polyuria caused by water and/or salt diuresis

# **Conceptualising Causes, Diagnosis and Therapy of Nocturnal LUTS.**

K. Everaert

A. Wein

J. Weiss

M. Oelke

# Introduction

# Nocturnal LUTS

Nocturia, Bedwetting, Nocturnal incontinence = Imbalance between the nocturnal bladder capacity, the nocturnal urine production and sleep.

Nocturnal LUTS should include first morning void related symptoms?

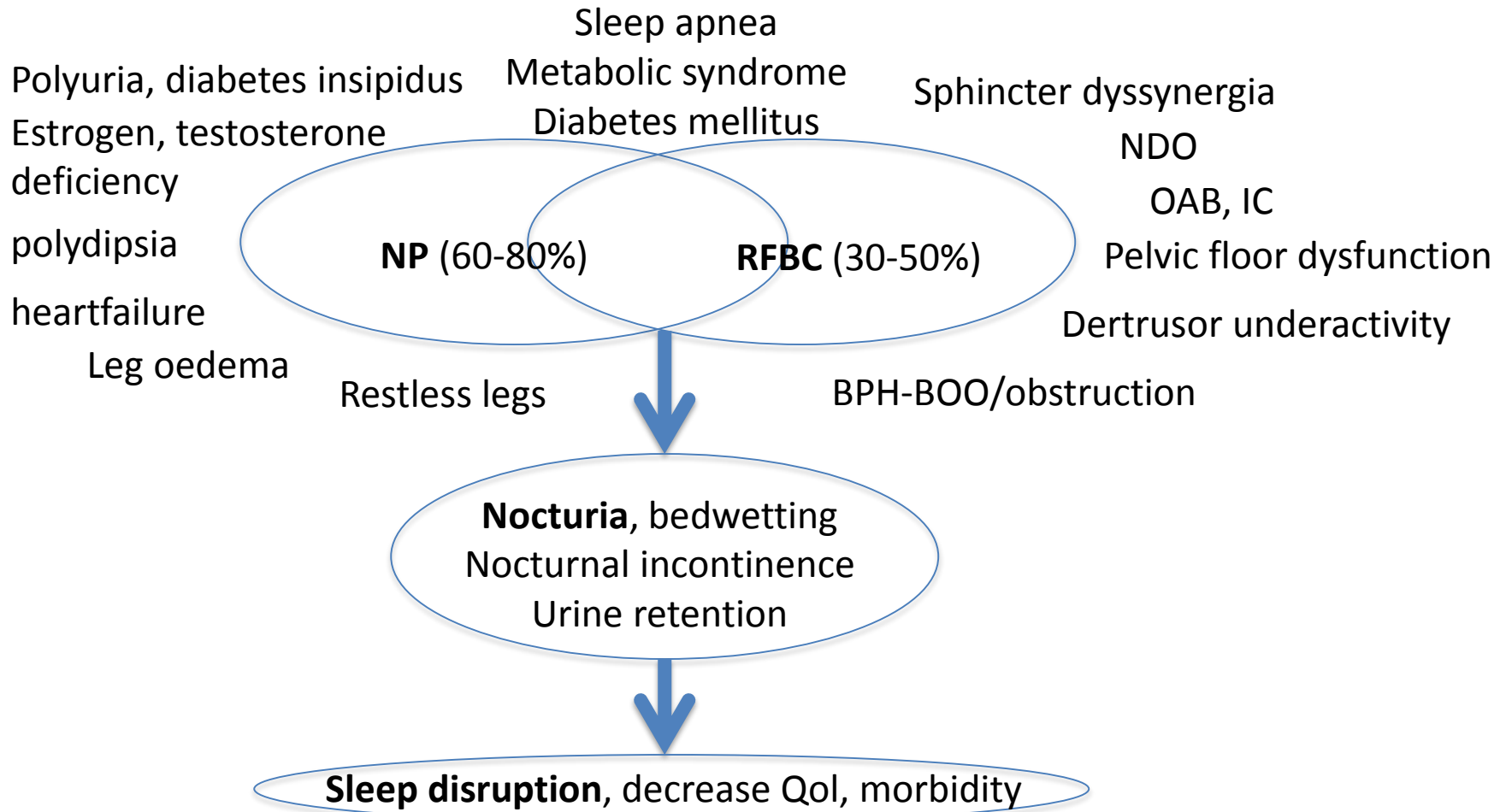
Sleep pathology can cause of a reduced nocturnal bladder capacity and/or nocturnal polyuria.

Sleep pathology can cause nocturia (pee because you can't sleep) without a reduced nocturnal bladder capacity and/or nocturnal polyuria but even though everyone knows such patients this entity is not well defined in the literature.

Loss in QOL and comorbidity is related to the sleep disruption/defragmentation.

Loss in QOL is caused by nocturnal LUTS

# Causes of nocturnal LUTS are generally multifactorial<sup>1-3</sup>



1. Fonda D. *BJU Int.* 1999;84(suppl 1):13-15; 2. van Kerrebroeck P et al. *Neurourol Urodyn.* 2002;21:179-183; 3. Wein AJ et al. *BJU Int.* 2002;90(suppl 3):28-31. 4. Goessaert et al NUU 2014.

## **NOCTURIA: TERMINOLOGY AND DEFINITIONS**

Alan J. Wein MD, PhD (Hon), FACS

*"The beginning of wisdom is to call things by their right names"*

Attributed to Confucius

*"What's in a name? That which we call a rose by any other name would smell as sweet"*

William Shakespeare (Romeo & Juliet)

*"If names are not correct, language will not be in accordance with the truth of things"*

Confucius

## **A. TERMINOLOGY (General) (\*denotes ICS Definition)**

### 1. Symptom

Any subjective evidence of disease apparent to the patient.

The subjective indicator(s) of a disease or change in condition as perceived by the patient, partner or caregiver which may lead him/her to seek help from healthcare professionals. May be volunteered or described during the patient interview. Usually qualitative.

### 2. Sign

Objective. Apparent to patient, physician and others. Any indication of a medical condition that can be objectively observed.

\*Observed by the physician, including by simple means to verify symptoms and quantify them. Includes observations from FVC, pad tests and validated questionnaire.

### 3. Urodynamic Observation

\*Observation made during urodynamic studies.

### 4. Conditions

\*Defined by the presence of urodynamic observations associated with characteristic signs and symptoms and/or non-urodynamic evidence of relevant pathologies.

### 5. Syndrome

\*Describes constellations or varying combinations of symptoms but cannot be used for precise diagnosis. They describe functional abnormalities for which a precise cause has not been established. Examples are bladder pain syndrome, overactive bladder symptom syndrome. The use of "syndrome" can be justified only if there is at least one other symptom in addition to the symptom used to describe the syndrome.

\*Standardization of Terminology in Lower Urinary Tract Function (ICS Subcommittee) 2002, Neurourol Urodyn, 21:167-178

Nocturia is described in the ICS Standardization Document on Nocturia (2002) as a:

- (1) "complaint" (line 1, Introduction)
- (2) "condition" (line 4, Introduction)
- (3) "clinical entity in its own right" (line 4, 5, Introduction)
- (4) sign – (Table 1) – "... as ... derivation is from the frequency volume chart".

Therefore, "nocturia" is (can be) (AW)

- a. sign
- a. condition
- a. symptom

Depending on how the word is utilized, ["symptoms are defined as complaints"].

(Table 1)

## **B. DEFINITIONS**

ICS Standardization (Terminology in LUT Function) Neurodyn Urodyn, 2002;21:167-178

### 1. LUT Symptoms

- a. Nocturia – complaint that the individual has to wake at night one or more times to void
- b. Enuresis – any involuntary loss of urine. If used to denote incontinence during sleep it should always be qualified with the adjective nocturnal (original)
- c. Nocturnal Enuresis – the complaint of loss of urine during sleep

### 2. Measurements

- a. Daytime Frequency – number of voids recorded during waking hours and includes last void before sleep and the first void after waking in the morning
- b. 24-hour Frequency – total number of daytime voids and episodes of nocturia during a specified 24h period
- c. Nocturia – is the number of voids recorded during a night's sleep; each void is preceded and followed by sleep
- d. 24-hour Production – all urine for 24h. Begin after first void produced after rising in the morning and completed by including first void on rising the following morning
- e. Polyuria – measured production of >2.8 l in 24h in adults. Based on 70Kg person voiding >40ml/Kg



- f. Nocturnal Urine Volume – total amount passed between the time individual goes to bed with the intention of sleeping and the time of waking with the intention of rising. Excludes last void before going to bed at night and includes the first void on rising in the morning. This differs with age >20% (young adults) to 33% (over 65 years)
- g. Nocturnal Polyuria – An increased proportion of the 24h output occurs at night (normally during the 8h while the patient is in bed. NP is offset by lowered daytime production, so 24h production remains within normal limits
- h. Maximum Voided Volume – largest volume of urine voided during a single micturition and is determined from the frequency/volume chart or bladder diary. Some consider this equivalent to functional bladder capacity

### 3. Recording Micturition Events

- a. Micturition Time Chart – records only the times of micturition, day and night, for at least 24 hours
- b. Frequency Volume Chart (FVC) – records volumes voided as well as the time of each micturition, day and night, for at least 24h
- c. Bladder Diary – records the times and voided volumes of micturitions, incontinence episodes, pad usage and other information such as fluid intake, degree of urgency and degree of incontinence.
- d.

(1) On the basis of the FVC can categorize nocturia as:

- (a) Nocturnal Polyuria (NP)
- (b) Low nocturnal bladder capacity despite normal global bladder capacity
- (c) Low global bladder capacity
- (d) Global Polyuria

### **C. MORE DEFINITIONS FROM:**

ICS Standardization of Terminology in Nocturia: Neurourol Urodyn 2002;21:179-183 (van Kerrebroeck et al.)

“Normal” – average 70Kg individual who sleeps 8h a night, ranges  $\pm 2$  SD (STANDARD DEVIATIONS)

Definition of Terms Derived from F/V Chart

Nocturia, Nocturnal Urine Volume, Polyuria, same as ICS 2002 (Abrams et al.)  
Additions / Differences from Abrams et al.

1. Rate of Nocturnal Urinary Production – nocturnal urine volume/time asleep (night) measured in ml/min
2. Night – period of time between going to bed with the intention of sleeping and waking with the intention of rising. Consider only intended sleeping time, not time in bed. Shift workers may have variation in their “night time”
3. Night Time Frequency – number of voids from the time an individual goes to bed with the intention of going to sleep to the time the individual wakes with the intention of rising (note: ≠ symptom or measurement of nocturia). (note: include all voids (i.e. nocturnal enuresis, voiding while awake but not awakened because of the desire to go)).
4. First Morning Void – first void after waking with the intention of rising.
5. Nocturnal Polyuria – In an individual with normal 24h urine volume, the output during sleep can be expressed as a % of the total. NP may be defined in these individuals as >20% of the total in the young and >33% in the elderly with the value for middle age falling somewhere between the two
6. Nocturia Index (Ni) – mean measured nocturnal urine volume/functional bladder capacity (maximal voided volume).  

$$Ni = NUV/MVV$$
 If >1, the NUV exceeds the bladder maximum storage capacity and nocturia or enuresis results
7. Nocturnal Polyuria Index (NPi) – mean measured nocturnal volume/24h urine volume.  $NPi = NUV/24h \text{ volume}$   
 Urine is produced in an age dependent circadian rhythm  
 <25y mean NPi = 0.14  
 >65y mean NPi = 0.34  
 ICS: NP = when 24h volume is wnl,  
 NPi >0.33  
 Other Definitions of NP  
 NUV >6.4ml/Kg  
 Nocturnal Output >54ml/h; ≥90ml/h  
 Makes a big difference!
8. Nocturnal Bladder Capacity Index (NBCi)  
 (Actual number of nightly voids (ANV) (minus) – Predicted number of nightly voids (PNV)  
 The PNV is Ni (NUV/MVV) – 1  

$$NBCi = ANV - PNV$$
 NBCi >0 : nocturia occurs at volumes <MVV

**D. PATIENT REPORTED OUTCOMES (PRO) FOR NOCTURIA**

NQoL – Nocturia Quality of Life Questionnaire  
ICIQ-N – ICI Incontinence Questionnaire for Nocturia  
PSQI – Pittsburgh Sleep Quality Index

**E. ENURESIS – any incontinence, day and night**

1. Nocturnal Enuresis – a normal act of micturition occurring during sleep

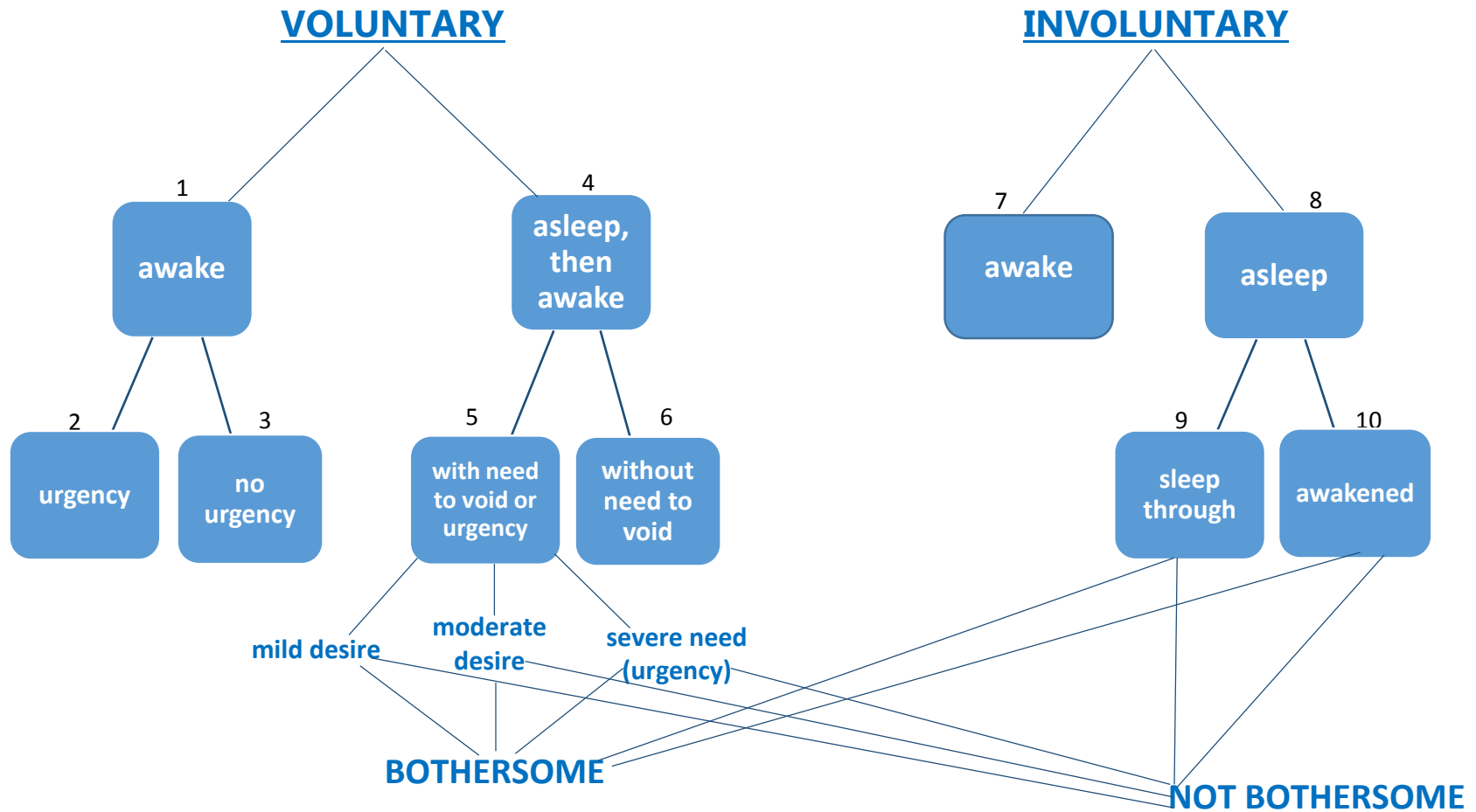
(a) Contributing Factors

- (1) Disturbance of Brain Function – insufficient cortical arousal by bladder distention
- (2) Decreased secretion of AVP
- (3) Renal Tubular Defect
- (4) Reduced sensation
- (5) Detrusor Overactivity
- (6) Reduced Bladder Capacity
- (7) Sleep apnea
- (8) Increased sensation but decreased inhibitory capacity

(b) Modifiers or Contexts

- (1) Severity
- (2) OAB
- (3) BPS
- (4) Urinary Retention
- (5) Neurogenic Bladder Dysfunction
- (6) etc

## URINATION AT NIGHT – Thoughts (1) (AW)



1. nocturnal frequency
2. nocturnal frequency, OAB void
3. nocturnal frequency, normal void
4. nocturia
5. nocturia, normal void or OAB void
6. nocturia, convenience void
7. nocturnal frequency with urgency urinary incontinence (OAB) or no sensory appreciation
8. nocturnal enuresis (can be primary or secondary)

## **URINATION AT NIGHT – Thoughts (2) (AW)**

Each then categorized as to pathophysiology(ies):

- (1) Nocturnal Polyuria
- (2) Global Polyuria
- (3) Diminished Global or Nocturnal Bladder Capacity
- (4) Mixed,
  - (a) NP
    - CHF
    - DM
    - Sleep Apnea
    - Peripheral Edema
    - Excess Nighttime Intake
    - Decreased Nocturnal AVP
    - Other
  - (b) Global Polyuria
    - DM
    - DI
    - Primary Polydipsia
  - (c) Diminished Global or Nocturnal Bladder Capacity
    - Nocturnal DO
    - Nocturnal OAB
    - Neurogenic Bladder
    - Anxiety
    - Any LUT initiative stimulus
    - Other

## **PROBLEMS AND MATTERS FOR DISCUSSION**

"Nocturia" - preceded and followed by sleep?

"Nocturia" – convenience voids vs "true" nocturia related voids. always

"Sleep Time" – how should this be defined?

Nocturnal Polyuria - Population surveys suggest the 20% and 33% numbers are not in themselves terribly specific. Should the threshold be:

a higher percentage  
an absolute value (ml)

What is(are) the most valuable parameter(s) in measuring response to therapy?

Does "nocturia" need to be a complaint or bothersome?

Is getting up once at night, "nocturia"?

## Use of bladder diaries in diagnosing nocturia

Jeffrey P. Weiss, MD, FACS

Professor and Chair  
Department of Urology  
SUNY Downstate College of Medicine  
Brooklyn, NY



## Nocturia

- Medical/Renal?
  - Nocturnal polyuria
  - Polyuria
- Urological/Lower tract dysfunction?
  - Diminished global/nocturnal bladder capacity

## 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

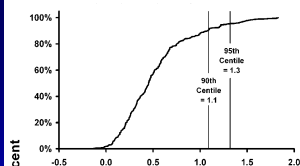
## Diary Assessment: NBCi

- NBCi (Nocturnal Bladder Capacity index) > 0: Diminished nocturnal bladder capacity
- Higher NBCi >> Nocturia occurs at voided volumes < MVV

## Diary Assessment: NBCi

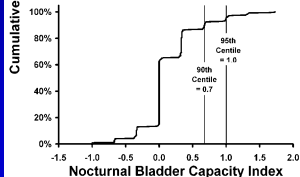
- $NBCi = \text{Actual} - \text{Predicted} \# \text{ nightly voids (ANV - PNV)}$
- $PNV = N_i - 1$
- Example: Patient with Nocturia (ANV) x7
  - NUV = 750 ml
  - MVV = 250 ml
  - $N_i = \text{NUV} / \text{MVV} = 3$
  - $PNV = 3 - 1 = 2$
  - $NBCi = \text{ANV} - \text{PNV} = 7 - 2 = 5$

Unrounded NBCi's



• Cumulative frequency distributions of unrounded and rounded NBC is from the asymptomatic volunteers

Rounded NBCi's



• Suggests cut point where  $NBCi > 1.3$  deserves investigation of low nocturnal bladder capacity\*

\*Burton C, Parsons M, Weiss JP and Coats A. Reference values for the Nocturnal Bladder Capacity Index. NeuroUrol and Urodynamics 30:52-57, 2011

## Formulas for evaluation of nocturia

Formula	Analysis
Nocturia index $N_i = \text{NUV} \div \text{MVV}$	$N_i > 1 \rightarrow$ nocturia is due to NUV exceeding MVV
Nocturnal Polyuria index $NPi = \text{NUV} \div 24hV$	$NPi > 33\% \rightarrow$ Dx is nocturnal polyuria
Nocturnal bladder capacity index $N_i - 1 = \text{PNV}$ $NBCi = \text{ANV} - \text{PNV}$	$NBCi > 0 \rightarrow$ nocturia occurring at volumes < MVV

## Nocturia Category

### Nocturnal polyuria

## Causes

- Congestive heart failure
- Diabetes mellitus
- Obstructive sleep apnea
- Peripheral edema
- Excessive nighttime fluid intake

## Nocturia Category

### Diminished global/NBC

## Causes

- Prostatic obstruction
- Nocturnal detrusor overactivity
- Neurogenic bladder
- Cancer of bladder, prostate, or urethra
- Learned voiding dysfunction
- Anxiety disorders
- Pharmacologic agents
- Bladder calculi
- Ureteral calculi



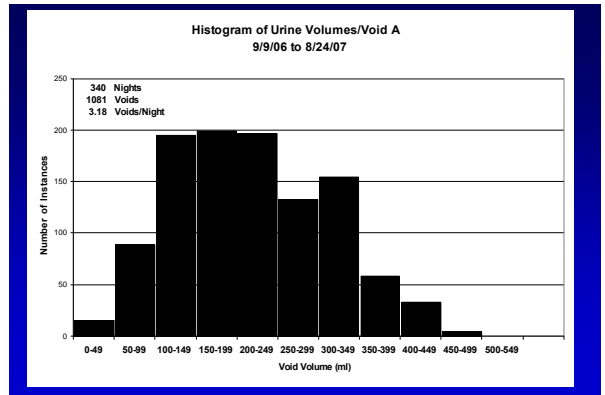
Nocturia Category	Causes
Polyuria (global)	<ul style="list-style-type: none"> <li>•Diabetes mellitus</li> <li>•Diabetes insipidus</li> <li>•Primary polydipsia</li> </ul>

## 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

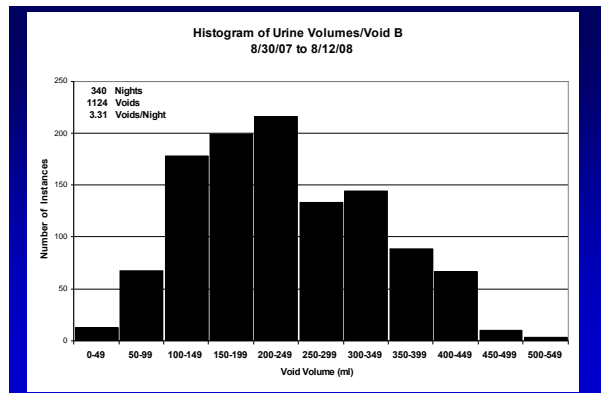
### 68 yo man with nocturia data collected 9/9/06 - 10/28/08 (!!)

- 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

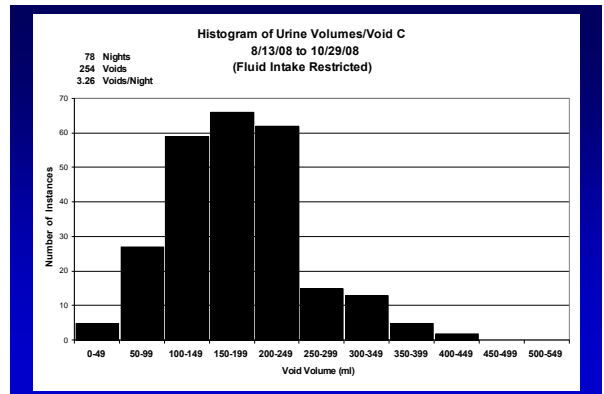
- 340 nights of data 8/30/07 and 8/12/08
- 1124 voids, average number of voids per night = 3.31



## 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

	24 hr vol (ml)	NUV (ml)	ANV	NPi (%)	Ni	MVV (ml)
11/3	2095	800	4	38	4	200
11/4	1230	385	1	31	1.8	210
11/6	2285	890	3	31	2.9	310

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

### 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, ANVx1, 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

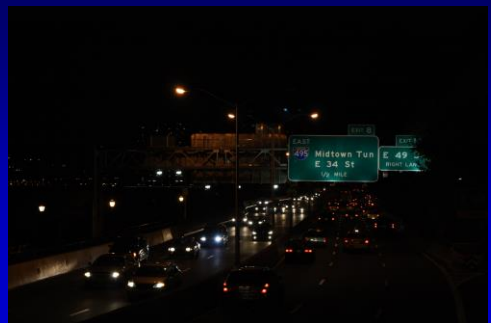
### 52 yo M with nocturia: Key points

- 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

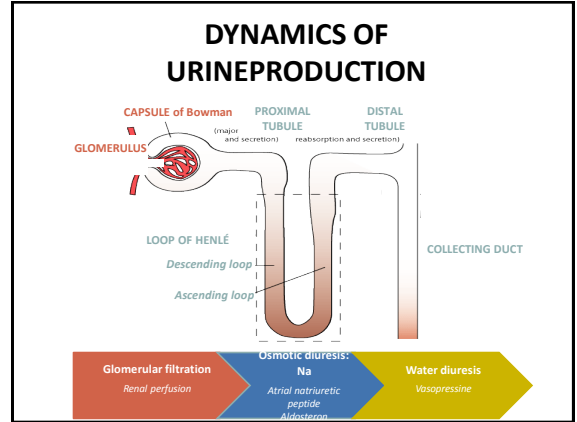
- Currently: two urologists rec TURP/TUIP
- He wants second opinion
- What do you think?

### Discussion/Questions



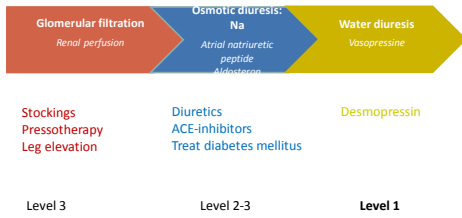
# Nocturnal Polyuria: Conceptualizing diagnosis.

Karel Everaert

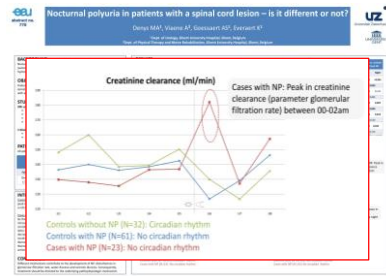


## Conceptualizing diagnosis of nocturnal LUTS, does it matter?

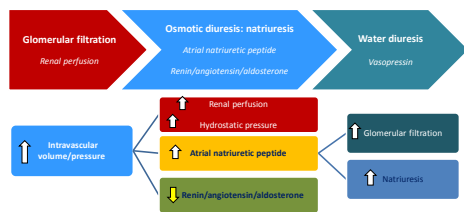
Does this really matter?



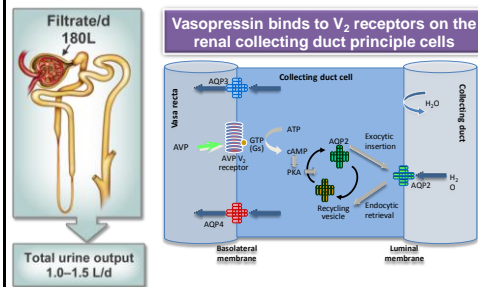
## Conceptualizing diagnosis of nocturnal LUTS, does it matter?



## Conceptualizing diagnosis of nocturnal LUTS, does it matter?



## Pathophysiology of water metabolism



Adapted from Mayinger & Hensen. Exp Clin Endocrinol Diabetes 1999 107:157-165

## Conceptionalizing diagnosis of nocturnal LUTS, does it matter?

### Desmopressin

Decreases excretion of "free water" during the night

Evidence of long term effect available

AE 1-10%:

- Headache
- GI disorder
- Fatigue
- Abdominal pain
- Nausea
- Rhinitis
- Conjunctivitis
- Edema eyes
- Lacrimation disorder



**Hyponatremia < 5%** (<65y, mid-long term)

Increases with:

Age

Women

Renal failure)

### Furosemide

Increases excretion of "salt with water" during the day

No evidence of long term effect available

AE 1-10%:

- Imbalance electrolytes: dry mouth, tiredness, muscle pain, feeling sick, cramps, fast heart rate
- Stomach irritation
- Nausea
- Low blood pressure
- Rash
- Hyperuricemia and gout

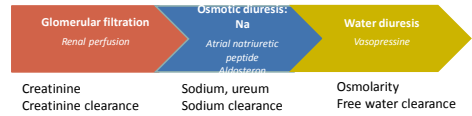


**Hyponatremia 1/15** (<60y, long term)

Increases with age)

## Diagnosing nocturnal polyuria: the renal function profile, how to do it?

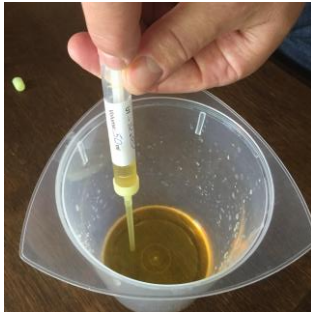
Start	8 urinesamples: 1 / 3h							
Voids	U1	U2	U3	U4	U5	U6	U7	U8
	8-10h	11-13h	14-16h	17-19h	20-22h	23-01h	2-4h	5-7h



Creatinine, Creatinine clearance, Sodium, ureum, Sodium clearance, Osmolarity, Free water clearance

Gossaert et al Eur Urol 2014

## Diagnosing nocturnal polyuria: the renal function profile, how to do it?



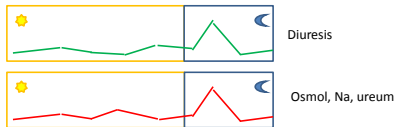
## Diagnosing nocturnal polyuria: the renal function profile, how to do it?

Void	Time	(n between void)*	(n between void)*	Volume void at sample time	Urinary incontinence	Total volume (during 3h period)
1 <sup>st</sup> morning void (in void)	.....					
U1	.....	.....	.....	.....g	.....g	= ..... ml
U2	.....	.....	.....	.....g	.....g	= ..... ml
U3	.....	.....	.....	.....g	.....g	= ..... ml
U4	.....	.....	.....	.....g	.....g	= ..... ml
U5	.....	.....	.....	.....g	.....g	= ..... ml
U6	.....	.....	.....	.....g	.....g	= ..... ml
U7	.....	.....	.....	.....g	.....g	= ..... ml
U8	.....	.....	.....	.....g	.....g	= ..... ml

Time you went to bed to go sleeping .....  
Time you woke up in the (next) morning .....

## Interpretation of the renal function profile

Use the circadian rhythm principle



- Use urinary osmolality, ureum, sodium / creatinine ratio's
- Plot peaks against diuresis
- Day versus night values are less accurate
- No blood samples needed

## Interpretation of the renal function profile

Use existing cutoffs

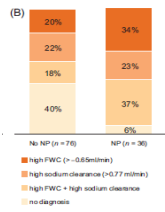
Cutoff values based on free water clearance and sodium clearance based on 4 NP definitions

		AUC	Cutoff	Sens	Spec
NPI>33	FWC (12-2am)	49% (39%-60%)	-0.75	54%	50%
	SC (3-5am)	71% (61%-81%)	0.75	67%	63%
NUP>90	FWC (12-2am)	63% (52%-74%)	-0.65	71%	62%
	SC (3-5am)	66% (55%-77%)	0.77	60%	60%
NUP>10	FWC (12-2am)	50% (38%-62%)	-0.65	53%	53%
	SC (3-5am)	71% (60%-83%)	0.77	73%	63%
NI>1.5	FWC (12-2am)	54% (43%-65%)	-0.65	54%	57%
	SC (3-5am)	65% (55%-76%)	0.76	62%	61%

Parameters based on ROC-curve

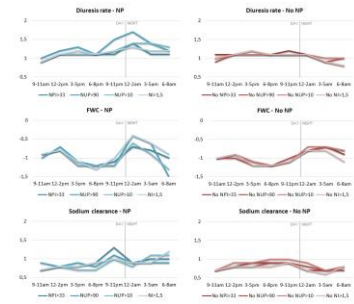
- Bloodsamples needed
- based on small series
- low accuracy

### Interpretation of the renal function profile



Water diuresis is main (> 50% regardless of definition) mechanism of nocturnal polyuria

### Diagnosing nocturnal polyuria: the renal function profile based on 4 definitions



### Conceptualizing diagnosis of nocturnal LUTS: conclusion

Diagnose when bothersome + check for underlying systemic disease

Questionnaires LUTS, sleep disruption and bother

Diagnose RBC / nocturnal polyuria with FVC

Diagnose mechanism of nocturnal polyuria with RFP  
Diagnose RBC with urodynamics,....

## Nocturia: state of the art and critical analysis of current assessment and treatment strategies

Matthias Oelke · Erika Adler · Daniela Marschall-Kehrel ·  
Thomas R. W. Herrmann · Richard Berges

Published online: 13 September 2014  
© Springer-Verlag Berlin Heidelberg 2014



Matthias Oelke

**Abstract** This editorial of the topic issue of the *World Journal of Urology* provides a state of the art on nocturia which includes descriptions of the terminology, epidemiology, health-related quality of life, medical and financial consequences, pathophysiology, assessment tools and treatment strategies of nocturia. This summary also includes a flowchart on the pathophysiology of nocturia with illustration of the various causes of reduced bladder capacity, increased fluid intake or increased diuresis; a flowchart with the key findings of frequency–volume charts to determine the underlying pathophysiology; and a flowchart on

the treatment of the various causes of nocturia. The editorial critically discusses current assessment and treatment strategies in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) and nocturia. The outcome of nocturia remains hidden in drug trials of patients with LUTS/BPH because nocturia-specific measures were not included. The authors recommend using frequency–volume charts, measurement of the hours of undisturbed sleep, and nocturia-specific quality of life questionnaires (e.g., ICIQ-N or N-QoL) in all future studies in patients with LUTS/BPH and nocturia.

**Keywords** Nocturia · Lower urinary tract symptoms · Benign prostatic hyperplasia · Outcome assessment

### Terminology

The terminology of and around nocturia may be unknown or confusing; therefore, the terminology is briefly presented and discussed once more because it has implications on the results of studies presented in this topic issue on nocturia of the *World Journal of Urology*. Nocturia has been defined by experts of the International Continence Society (ICS) as the general complaint that the individual (independent of age, gender, cause(s) and associated bother) has to wake at night one or more times to void [1, 2]. The definition also includes that nocturnal voids are preceded and followed by sleep. In contrast, nighttime frequency or nocturnal voiding frequency is the term used to describe the number of nocturnal voids without specially excluding sleep before or after emptying the bladder [2]. Therefore, nocturia and nighttime frequency may be identical but the terms are not interchangeable, unless specific information about sleep is available. These specific definitions imply that the vast

---

M. Oelke (✉) · E. Adler · T. R. W. Herrmann  
Department of Urology, OE 6240, Hannover Medical School,  
30625 Hannover, Germany  
e-mail: oelke.matthias@mh-hannover.de

D. Marschall-Kehrel  
Urology Consultancy, Frankfurt-Main, Germany

R. Berges  
Department of Urology, PAN-Klinik, Cologne, Germany



majority of published trials on nocturia are actually trials on nighttime frequency because sleep before or after voiding during the night was rarely documented.

The definition of nocturia also suggests consciousness of a full bladder and a compelling desire to void which motivates the individual to wake and voluntarily use the toilet during the night. In contrast, nocturnal enuresis is also nighttime voiding, but the individual is not aware of a full bladder, does not awake and empties urine involuntarily in the bed during the nighttime; therefore, nocturia and nocturnal enuresis are distinguishable by the alertness of a full bladder and waking up to void [2]. Nighttime is defined as the period of going to bed with the intention of sleeping and waking up with the intention of arising [2]. There may appear confusion with the definition of nighttime in shift-workers who work at night and sleep during the day. In this particular group, sleep during the day is considered nighttime and any void during this sleeping period is considered nocturia [2].

Nocturia specifically is the number of voids recorded during the nighttime [2]. The first morning void is excluded from the count because it is not followed by sleep. Nocturnal urine volume describes the amount of urine excreted during the nighttime and also includes the volume of the first morning void because this urine has been produced during the nighttime [2]. Nocturnal polyuria is an abnormally large urine volume produced during the nighttime. The ICS classifies nocturnal polyuria as the nocturnal urine volume divided by the 24-h urine volume (i.e., nocturnal polyuria index, NPi) [2]. NPi increases with aging and is approximately 14 % in healthy individuals aged 21–35 years (95 % confidence interval 10–19 %) and approximately 34 % in adults aged >65 years (95 % confidence interval 30–36 %). To simply matter, the ICS defines nocturnal polyuria as NPi > 20 % in young individuals and >33 % in elderly [2].

## Epidemiology

Epidemiological trials in different countries have drawn attention to high prevalence rates of nocturia/nighttime frequency in community-dwelling men and women worldwide. In general, nocturia (independent on cause(s) and associated bother) increases with aging and affects both men and women equally [3, 4]. In an analysis of 43 trials, 11.0–35.2 % of men aged 20–40 years reported about nocturia  $\geq 1$  times per night and 2.0–16.6 % of men about nocturia  $\geq 2$  times per night [4]. In men >70 years of age, the prevalence rates of nocturia  $\geq 1$  times per night rose to 68.9–93.0 % and  $\geq 2$  times per night to 29.0–59.3 %. This topic issue of the *World Journal of Urology* on nocturia also contains the first report on nocturia in German

community-dwelling men in which 87 % of men aged 50–80 years reported about nocturia  $\geq 1$  times per night and 43 % of men  $\geq 2$  times per night [5]. This study confirmed the high prevalence rates in Germany and is in line with the results of other epidemiological studies.

## Health-related quality of life

The definition of nocturia does not contain any information on bother or deterioration of health-related quality of life (HRQoL). However, this information is crucial as it could explain health-care seeking behavior and medical consultations of the affected people. Several studies have shown that nocturia is not only the most frequently reported symptom of all lower urinary tract symptoms (LUTS) in men but is also perceived as (one of) the most bothersome. Although the perception of bother associated with nocturia largely depends on the individual, the FINNO study reported bother from nocturia when the individual has to void at least 2 times per night (i.e., clinically relevant nocturia) [3]. The German epidemiological study on nocturia, first presented in this topic issue, confirmed this threshold value in adult men and showed that  $\geq 2$  voids per night significantly reduces HRQoL (as measured by the SF-12 questionnaire and the IPSS-QoL index) and is the only symptom of all LUTS captured on the IPSS questionnaire that triggers medical consultations in the 2-year follow-up period [5]. The higher the nocturnal voiding frequency was, the more deteriorated the HRQoL became. Because the participants evaluated in this study are representative of the German male population, the authors were able to calculate the total number of affected people: there are an estimated number of 5.83 million German men with  $\geq 2$  nocturnal voids of which approximately 1.8 million men seek professional help for nocturia. These numbers in only one country and only in adult men demonstrate the proportion of the medical problem associated with nocturia in Germany and worldwide.

## Medical and financial consequences of nocturia

Nocturia is not only bothersome for the individual but can also have a profound impact on health and health care. Nocturia has been identified as the leading cause for sleep disturbance and sleep fragmentation, causes daytime fatigue, impacts daily activities, and deteriorates psychomotor performance, cognitive function and mood [6–9]. Nocturia can also cause depression, immune suppression, increases vulnerability for cardiovascular diseases and the development of diabetes mellitus [7, 10–12]. Additionally, nocturia ( $\geq 2$  times per night) significantly increases accidents, falls and

fractures [13–17]. The costs associated with nocturia are tremendous and alarming. Nocturia can cause direct, indirect and intangible costs [18]. Only the direct annual costs of (hip) fractures were estimated to be approximately \$1.5 billion in the US and approximately € 1 billion in the 15 largest countries of the European Union [18]. Indirect costs of nocturia are for example loss or impairment of work productivity, and those numbers are even more alarming. It was calculated that the annual loss of work productivity due to nocturia amounts for approximately \$62.5 billion in the US and approximately € 29 billion in the 15 largest countries of the European Union [18]. Therefore, societies must have a fundamental interest to diagnose and treat nocturia to reduce morbidity and costs.

### Pathophysiology

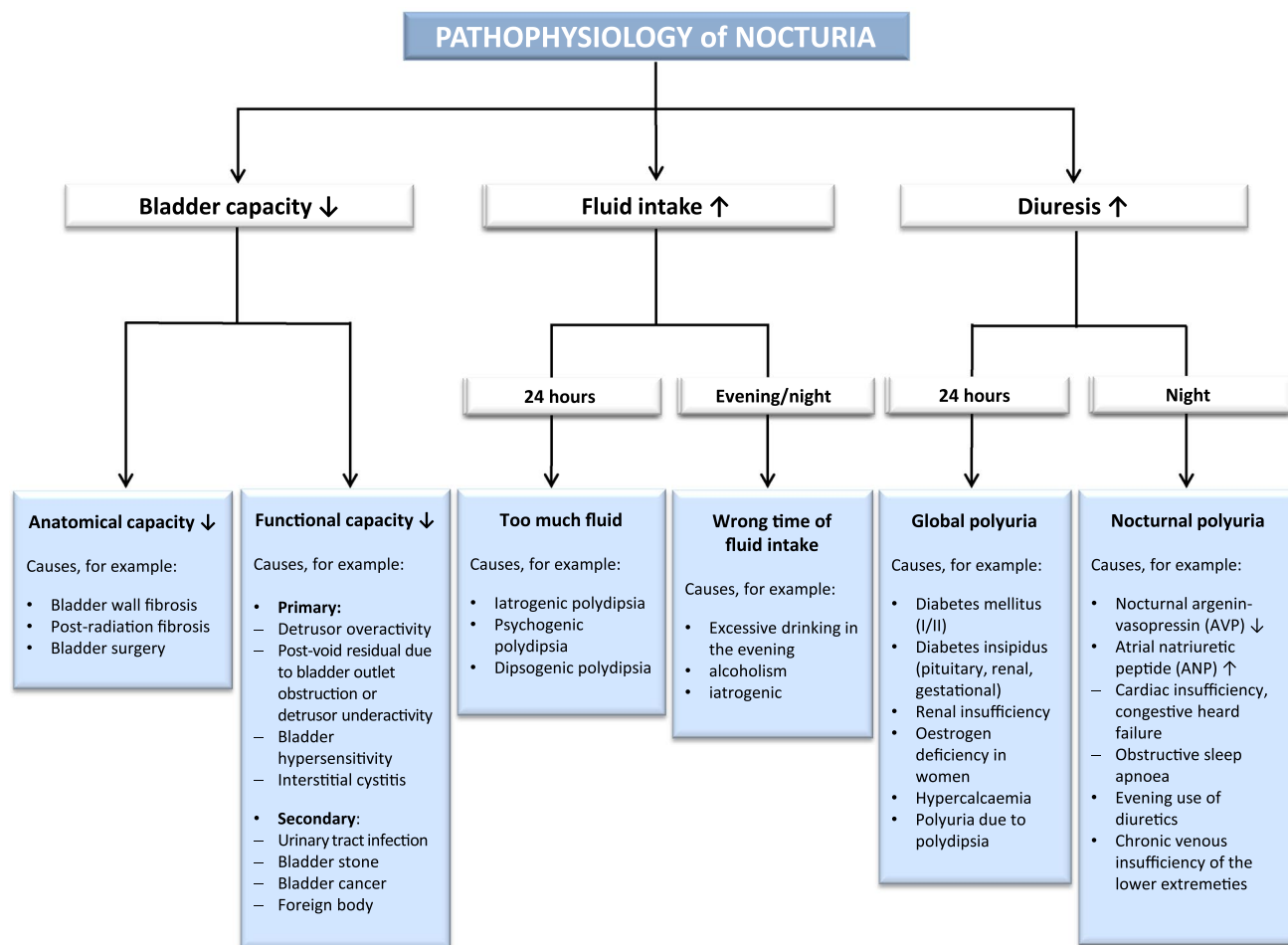
Nocturia has a multifactorial etiology, and the various causes often overstep the borders of individual medical specialties. Therefore, a broad spectrum of medical professionals deal with nocturia patients, including, besides others, urologists, gynecologists, nephrologists, cardiologists, pulmonologists, angiologists, psychiatrists, general practitioners and family care physicians. As many doctors tend to assess symptoms only within their medical specialty and not beyond the scope of their specialization, this may cause doubt or uncertainty about the underlying pathophysiology in the individual patient and, consequently, underdiagnosis and undertreatment of patients with nocturia. It becomes evident that a medical specialty or specialized doctors within this specialty need to focus on nocturia, follow generally accepted assessment paths and initiate nocturia-specific treatments based on the underlying pathophysiology. Once the pathophysiology has been clarified and a diagnosis established, it is acceptable to consult other medical specialties for support thereafter.

Nocturia in principle can be caused by reduced bladder capacity (anatomical, functional), increased fluid intake (during the 24-h period or in the evening/night) or increased diuresis (during the 24-h period or during nighttime only) [2]. An overview of the various causes is shown in Fig. 1. It was shown in adult urological patients with nocturia that more than 80 % of men had nocturnal polyuria (NPi > 33 %) of whom 20 % had nocturnal polyuria alone and more than 60 % had nocturnal polyuria in combination with a decreased functional bladder capacity due to LUTS suggestive of benign prostatic hyperplasia (LUTS/BPH) or benign prostatic obstruction [19]. Physicians need to be aware that a single person may have more than one cause of nocturia. Therefore, thorough assessment of nocturia and its various causes is mandatory before treatment initiation.

### Assessment

The key diagnostic tool to capture, quantify and evaluate the origin (pathophysiology) of nocturia is the frequency–volume chart for 24–72 h. Frequency–volume charts objectively document the time of each void, voided volume per micturition, time of going to bed with the intention of sleeping and the time of waking up with the intention of starting the day; optional assessments are the ingested fluid volume, type of fluid and pad use in case of urinary incontinence (bladder diaries). Frequency–volume charts can distinguish between global polyuria (i.e., 24-h urine volume >40 ml/kg bodyweight), nocturnal polyuria (i.e., nighttime urine volume >20 % in younger and >33 % in older adults in relation to 24-h urine volume) and reduced (anatomical or functional) bladder capacity (i.e., frequent voiding with low voided volumes) [2]. These quick and cheap tests can therefore discriminate between the major causes of nocturia and can identify the underlying pathophysiology (Fig. 2). The basic diagnostic workup for urological patients with nocturia further includes patient history and documentation of currently used drugs, physical investigation with digito-rectal examination in men, validated symptom questionnaires, urinalysis and measurement of post-void residual volume. However, additional tests may be necessary in individual patients to evaluate the exact origin of LUTS and nocturia, such as uroflowmetry, computer-urodynamic evaluation of bladder function, cystoscopy, bladder biopsies, blood analyses, sleep lab evaluation or specific cardiology tests (e.g., electrocardiography, echocardiography, magnetic resonance imaging of the chest or coronary angiography).

Nocturia-specific instruments may be useful to clarify the time of undisturbed sleep and degree of HRQoL reduction. These disease-specific instruments are particularly useful for the research, for example for the evaluation of drug effects on nocturia. However, these nocturia-specific instruments have had a limited role in routine patients until now. The hours of undisturbed sleep can be measured with a chronograph either by the patient or spouse. Reduction of the first sleep period, which consists of deep restorative slow wave sleep (SWS) and usually occurs during the first 3–4 h of sleep, has a negative effect on sleep quality. Disruption of SWS, even without a reduction in total sleep quantity, can result in daytime fatigue and somnolence, and a reduction in cognitive ability and overall functioning [6, 9]. Quality of sleep can be measured with disease-specific questionnaires of which the Leeds Sleep Evaluation Questionnaire (LSEQ) has frequently been used [20]. Other disease-specific HRQoL questionnaires for nocturia are the International Consultation on Incontinence Questionnaire–Nocturia (ICIQ-N [21]) and the Nocturia-Quality of Life questionnaire (N-QoL, [22]). Generic QoL-questionnaires



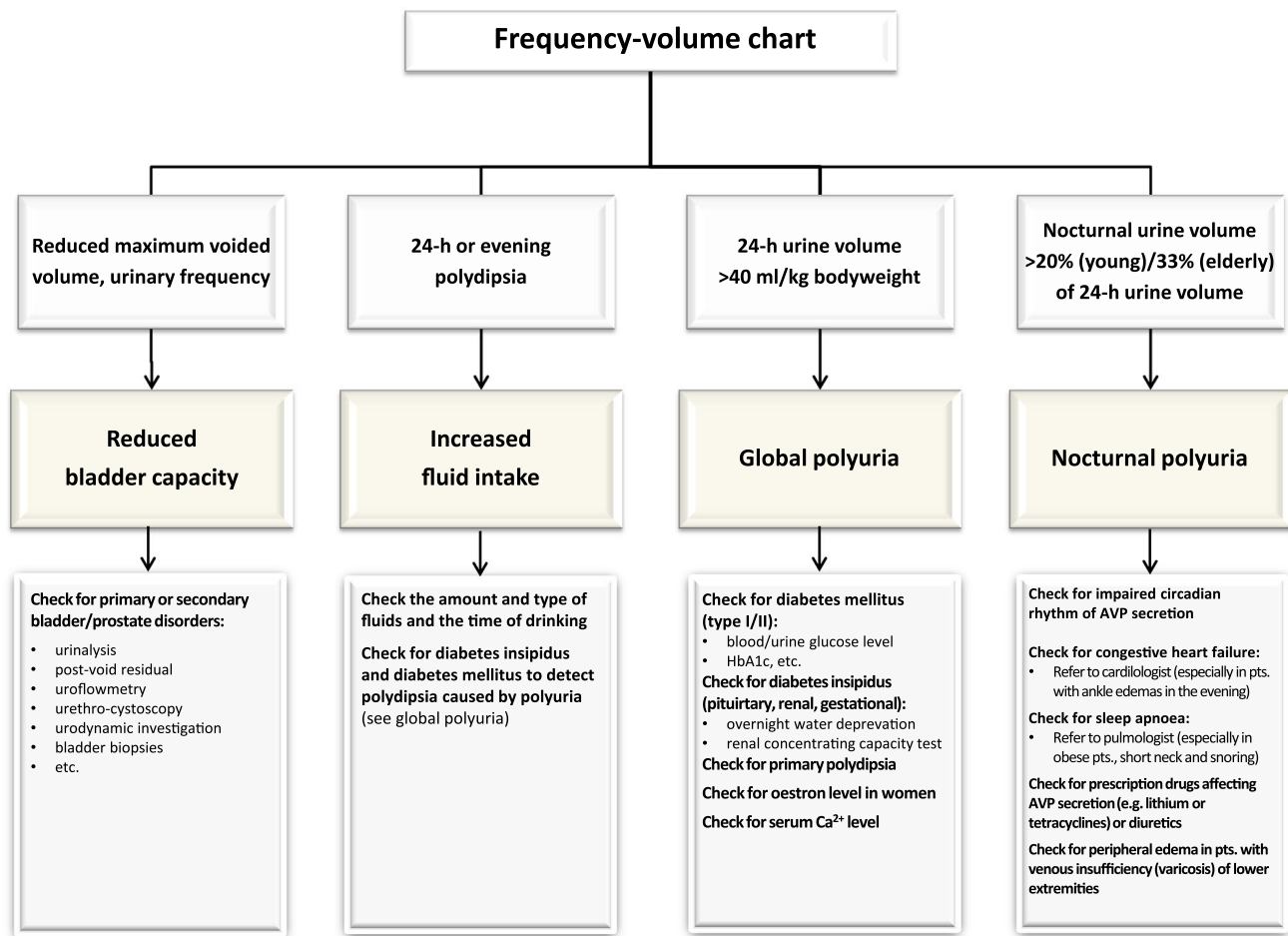
**Fig. 1** Pathophysiology of nocturia (in line with the ICS standardization report [2]). Note that one or more causes may be present in the individual patient

can measure the deterioration of HRQoL due to nocturia in general, and results can be compared with patient groups without nocturia or other diseases (e.g., prostate cancer or diabetes mellitus). Generic QoL-questionnaires include the SF-36 or SF-12 questionnaires and the EQ-5D questionnaire.

## Treatment

At the beginning, it is necessary to define the treatment goals. In patients with nocturia, the decrease of the number of nocturnal voiding episodes is relevant, but the decrease to <2 nocturia episodes/night, the prolongation of undisturbed sleep to >4 h and the improvement of disease-specific QoL (such as sleep quality and the feeling after awakening) seem to be more important. There is not one single treatment which can cure all forms of nocturia. Treatment rather has to focus on the underlying pathophysiology (Fig. 1). For example, it appears unlikely that

a patient with obstructive sleep apnoea will profit from bladder- or prostate-specific drugs, such as  $\alpha$ -blockers or antimuscarinics. Consequently, specific treatments have to be applied after careful assessment of the patient with nocturia (Figs. 2, 3). Nevertheless, behavioral treatments and lifestyle modifications appear beneficial in all patients despite differences in the underlying pathophysiology. Behavioral treatments and lifestyle interventions have not been subject of thorough clinical investigations and are rarely applied in routine practice, but they are cheap and easy and, therefore, should be included in every treatment strategy. Behavioral treatments include restriction of fluids a couple of hours before going to sleep, avoidance of caffeinated or alcoholic beverages in the evening, emptying the bladder before going to bed, leg elevation in case of edema of the lower extremities, moderate physical exercise and keeping warm in bed. It was shown in a prospective study on lifestyle interventions that more than 50 % of patients reported improvement of nocturia when fluid restriction in the evening, limited time in

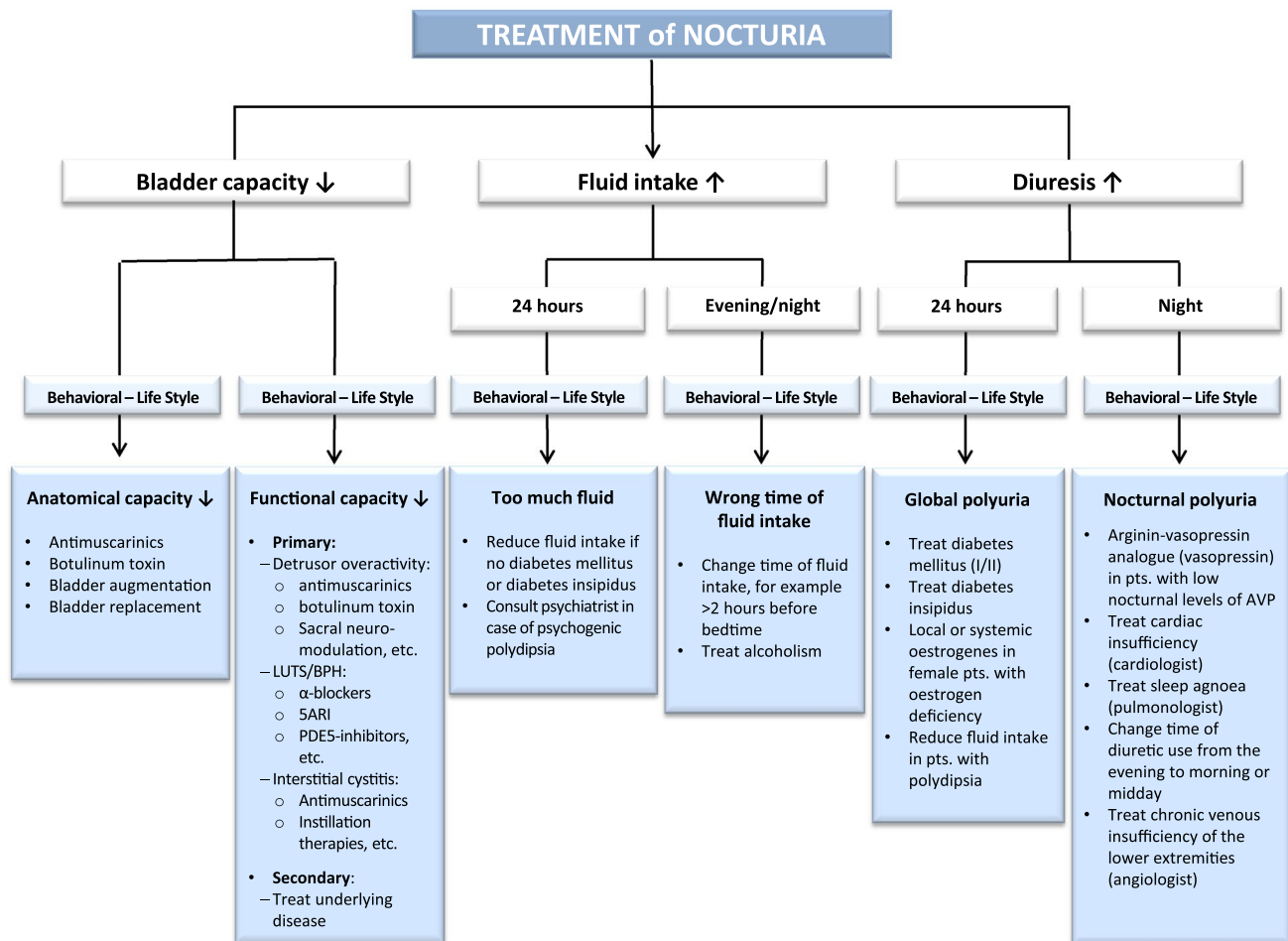


**Fig. 2** Relevant information of frequency–volume charts (*first line*) which allows gross classification of the causes of nocturia (*second line*). Special investigations have to clarify the exact underlying pathophysiology of nocturia (*third line*)

bed, moderate exercise and keeping warm in bed were employed [23].

This topic issue of the *World Journal of Urology* on nocturia aims to analyze the effects of LUTS/BPH drugs on nocturia and, therefore, follows the common belief of urologists that nocturia is primarily caused by bladder or prostate disorders. The dedicated teams of authors analyzed all major drug classes used in urology to treat LUTS/BPH, i.e.,  $\alpha$ -blockers (silodosin [24]),  $5\alpha$ -reductase inhibitors (dutasteride [25]),  $\alpha$ -blocker +  $5\alpha$ -reductase inhibitor combination therapy (tamsulosin + dutasteride [26]), phosphodiesterase type 5 inhibitors (tadalafil [27]) and plant extracts (*sabal serrulata* + *urtica dioica*, PRO 160/120 [28]). Additionally, the effects of the arginine-vasopressin analogue desmopressin were analyzed in a cohort of LUTS/BPH patients with clinically relevant nocturia due to nocturnal polyuria [29]. For the purpose of this topic journal, databases of controlled, randomized phase II/III drug trials were used and evaluated homogeneously post hoc by using the same efficacy parameters to judge the effects on

nocturia (e.g., number of nocturnal voids before vs. after treatment, number of patients with  $<2$  nocturnal voids at treatment end and percent improved stable-worsened nocturia frequency). The results of the various LUTS/BPH drug classes on nocturia of this topic issue of the *World Journal of Urology* are summarized in Table 1. It became evident that (1)  $>95$  % of patients with LUTS/BPH report about nocturia (nighttime voiding) with a frequency of  $\geq 1$  and  $>73$  % with a frequency  $\geq 2$  times per night. Therefore, nocturia is an essential part of LUTS/BPH and appears more frequently than in community-dwelling men [4]. (2) The mean number of nocturnal voids per night in patients with the clinical diagnosis LUTS/BPH is between 2.3 and 3.0. This nocturia frequency indicates that the majority of patients with LUTS/BPH experience bother and reduced HRQoL from nocturia [3, 5]. (3) The reduction of the nighttime voiding frequency with LUTS/BPH drugs is only modest compared to placebo or active comparator, and the difference is approximately 0.2 voids per night, regardless of the drug class. (4) There is a high placebo effect when



**Fig. 3** Treatment path of nocturia based on the underlying pathophysiology (in line with the ICS standardization report [2]). Note that a patient may need more than one treatment of nocturia

treating nocturia in patients with LUTS/BPH, indicating that behavioral and lifestyle modifications under controlled study situations substantially add to treatment effects. (5) Despite the low mean reduction of nocturnal voids, 38–69 % of patients report about nocturia improvement of  $\geq 1$  void/night, and 26–44 % of men with  $\geq 2$  voids/night at baseline have  $< 2$  voids/night at study end, indicating a clinically relevant improvement of and only a minor amount of bother from nocturia [3, 5].

### Critical analysis of current assessment and treatment strategies

This topic issue of the *World Journal of Urology* also elucidates relevant gaps in the assessment and treatment of patients with LUTS/BPH and nocturia. All trials were specifically designed to evaluate LUTS/BPH, and therefore, all trials only used assessment tools to evaluate the

key parameters of LUTS/BPH (e.g., IPSS questionnaire, prostate volume, uroflowmetry) but, however, lack of specific instruments for the evaluation of nocturia (e.g., frequency–volume charts, measurement of hours of undisturbed sleep, quality of sleep or HRQoL questionnaires). Therefore, it is possible that the magnitude of the problem has not been correctly addressed in drug trials on LUTS/BPH; nocturia has been shown to be a relevant and bothersome part of LUTS/BPH and is mainly responsible for decreased HRQoL and health-care seeking behavior in these men [5]. During the recruitment of patients in drug trials on LUTS/BPH, no specific attempt was made to look for other causes of LUTS, and therefore, other origins of nocturia beyond the bladder or prostate remained undetected in patients during LUTS/BPH checkup and study inclusion. It was shown in previous studies that nocturnal polyuria frequently appears together with LUTS/BPH [19]; consequently, it appears likely that only bladder or prostate disorders were correctly treated

**Table 1** Nocturia results with drugs used to treat lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH)

Parameter	$\alpha$ -Blocker [24]		5ARI [25]		$\alpha$ -blocker + 5ARI [26]			PDE5 inhibitor [27]		Plant extract [28]	
	Silodosin	Placebo <sup>†</sup>	Dutasteride	Placebo <sup>†</sup>	Combina- tion	Tamsulo- sin <sup>†</sup>	Dutas- teride <sup>†</sup>	Tadalafil	Placebo <sup>†</sup>	PRO 160/120	Placebo <sup>†</sup>
Study participants ( <i>n</i> )	837	642	2,121	2,123	1,569	1,575	1,578	752	748	147	145
Study duration (weeks)	12	12	24	24	48	48	48	12	12	24	24
Mean IPSS at base- line	21	21	17	17	16	16	16	18	17	18	18
Nocturia preva- lence at baseline (%)	99.2	99.4	97.3	97.6	96.8	96.9	96.7	96.6	97.4	99.3	98.6
$\geq 2$ noc- turnal voids at baseline (%)	85.3	86.0	76.2	75.5	75.3	75.3	75.9	73.3	74.2	85.7	81.4
Mean nocturia frequency at base- line ( <i>n</i> )	3.0	3.0	2.4	2.4	2.4	2.4	2.4	2.3	2.3	2.4	2.4
Mean nocturia frequency at study end ( <i>n</i> )	2.2*	2.4	2.1*	2.3	1.8	2.1	2.0	1.7*	1.9	1.6*	1.8
Reduction nocturia frequency ( <i>n</i> )	-0.8*	-0.6	-0.28*	-0.11	-0.5*	-0.3	-0.4	-0.5*	-0.4	-0.8*	-0.6
$\Delta$ nocturia frequency vs. com- parator	0.2*		0.17*		0.1*/0.2*			0.2*		0.2*	
Improve- ment nocturia (% pts)	53*	43	38*	32	48*	39	43	48*	41	69*	52
Stable frequency nocturia (% pts)	38	43	41	43	38	38	39	41	45	26	41
Worsening nocturia (% pts)	9*	14	21*	26	15*	24	18	12	14	5	8

**Table 1** continued

Parameter	$\alpha$ -Blocker [24]		5ARI [25]		$\alpha$ -blocker + 5ARI [26]			PDE5 inhibitor [27]		Plant extract [28]	
	Silodosin	Placebo <sup>†</sup>	Dutasteride	Placebo <sup>†</sup>	Combina- tion	Tamsulo- sin <sup>†</sup>	Dutas- teride <sup>†</sup>	Tadalafil	Placebo <sup>†</sup>	PRO 160/120	Placebo <sup>†</sup>
<2 Noctur- nal voids at study end in pts. with $\geq 2$ voids at baseline (% pts)	29*	19	26*	19	34*	26	30	36*	26	44*	40

The individual studies are presented in this topic issue on nocturia

<sup>†</sup> Comparator; \* Drug versus comparator  $p \leq 0.05$

with LUTS/BPH drugs, but nocturnal polyuria (and other causes) remained untreated. The observational study on desmopressin in patients with LUTS/BPH and nocturia due to nocturnal polyuria, which has also been included in this topic issue on nocturia, is in line with these statements [29]. It is therefore not surprising that nocturia is the most frequently reported (bothersome) symptom after prostate treatment, remaining in 68 % in a series of dissatisfied, symptomatic patients after transurethral resection of the prostate [30].

The treatment results of LUTS/BPH drugs presented in this topic issue on nocturia do not answer the question whether trial participants were satisfied with the nocturia outcome. Although the average reduction of nocturia episodes per night was low and the effects versus placebo only modest, 50–70 % of patients reported about a nocturnal voiding frequency <2 episodes per night with drug treatment (26–44 % of all patients with a baseline nighttime frequency  $\geq 2$ ), suggesting only a minor or no problem with nocturia (anymore). It may also be that drugs used for LUTS/BPH prolong the hours of undisturbed sleep beyond the magical border of 4 h and, therefore, can substantially increase sleep quality without substantially decreasing the amount of nocturnal voids. Again, these clinical questions can only be answered by using nocturia-specific instruments. Future studies of patients with LUTS/BPH and nocturia should therefore also include nocturia-specific instruments to correctly classify the underlying pathologies for nighttime voiding and, hence, provide a rationale for the treatment of all LUTS causes. The author of this editorial comment recommend using, besides others, frequency–volume charts, measurement of the hours of undisturbed sleep, sleep evaluation questionnaires such as the LSEQ, and HRQoL questionnaires such

as ICIQ-N or N-QoL in all future trials of LUTS/BPH patients with nocturia.

Matthias Oelke,  
on behalf of the authors

## References

- Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A (2002) The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-Committee of the International Continence Society. *Neurourol Urodyn* 21:167–178
- van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, Jennum P, Johnson T, Lose G, Mattiasson A, Robertson G, Weiss J (2002) The standardisation of terminology in nocturia: report from the Standardisation Sub-Committee of the International Continence Society. *Neurourol Urodyn* 21:179–183
- Tikkininen KA, Johnson TM 2nd, Tammela TL, Sintonen H, Huakka J, Huhtala H, Auvinen A (2010) Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol* 57:488–496
- Bosch JL, Weiss JP (2012) The prevalence and causes of nocturia. *J Urol* 189:S86–S92
- Oelke M, Wiese B, Berges R (2014) Nocturia and its impact on health related quality of life and health care seeking behaviour in German community-dwelling men aged 50 years or older. *World J Urol*. doi:10.1007/s00345-014-1374-6
- Stanley N (2005) The physiology of sleep and the impact of ageing. *Eur Urol Suppl* 3:17–23
- Abrams P (2005) Nocturia: the effect on sleep and related health consequences. *Eur Urol Suppl* 3:1–7
- Asplund R (2005) Nocturia: consequences for sleep and daytime activities and associated risks. *Eur Urol Suppl* 3:24–32

9. Dijk DJ, Groeger JA, Stanley N, Deacon S (2010) Age-related reduction in daytime sleep propensity and nocturnal slow wave sleep. *Sleep* 33:211–223
10. Akerstedt T, Nilsson PM (2003) Sleep as restitution: an introduction. *J Intern Med* 254:6–12
11. Asplund R (1999) Mortality in the elderly in relation to nocturnal micturition. *BJU Int* 84:297–301
12. Bonnet MH, Arand DL (2003) Clinical effects of sleep fragmentation versus sleep deprivation. *Sleep Med Rev* 7:297–310
13. Stewart RB, Moore MT, May FE, Marks RG, Hale WE (1992) Nocturia: a risk factor for falls in the elderly. *J Am Geriatr Soc* 40:1217–1220
14. Vaughan CP, Brown CJ, Goode PS, Burgio KL, Allman RM, Johnson TM II (2010) The association of nocturia with incident falls in an elderly community-dwelling cohort. *Int J Clin Pract* 64:577–583
15. Nakagawa H, Niu K, Hozawa A, Ikeda Y, Kaiho Y, Ohmori-Matsuda K, Nakaya N, Kuriyama S, Ebihara S, Nagatomi R, Tsuji I, Arai Y (2010) Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. *J Urol* 184:1413–1418
16. Asplund R (2006) Hip fractures, nocturia, and nocturnal polyuria in the elderly. *Arch Gerontol Geriatr* 43:319–326
17. Temml C, Ponholzer A, Gutjahr G, Berger I, Marszalek M, Madersbacher S (2009) Nocturia is an age-independent risk factor for hip-fractures in men. *NeuroUrol Urodyn* 28:949–952
18. Holm-Larsen T (2014) The economic impact of nocturia. *NeuroUrol Urodyn* 33:S10–S14
19. Chang SC, Lin AT, Chen KK, Chang LS (2006) Multifactorial nature of male nocturia. *Urology* 67:541–544
20. Parrott AC, Hindmarch I (1980) The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations—a review. *Psychopharmacology* 71:173–179
21. McKown S, Abraham L, Coyne K, Gawlicki M, Piault E, Vats V (2010) Linguistic validation of the N-QOL (ICIQ), OAB-q (ICIQ), PPBC, OAB-S and ICIQ-MLUTS sex questionnaires in 16 languages. *Int J Clin Pract* 64:1643–1652
22. Abraham L, Hareendran A, Mills IW, Martin ML, Abrams P, Drake MJ, MacDanagh RP, Noble JG (2004) Development and validation of a quality-of-life measure for men with nocturia. *Urology* 62:481–486
23. Soda T, Masui K, Okuno H, Terai A, Ogawa O, Yoshimura K (2010) Efficacy of nondrug lifestyle measures for the treatment of nocturia. *J Urol* 184:1000–1004
24. Eisenhardt A, Schneider T, Cruz F, Oelke M (2014) Consistent and significant improvements of nighttime voiding frequency (nocturia) with silodosin in men with LUTS suggestive of BPH—pooled analysis of three randomized, placebo-controlled, double-blind phase III studies. *World J Urol*. doi:10.1007/s00345-013-1228-7
25. Oelke M, Roehrborn CG, D’Ancona C, Wilson TH, Castro R, Manyak M (2014) Nocturia improvement with dutasteride in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): a pooled analysis of three phase III studies. *World J Urol*. doi:10.1007/s00345-014-1316-3
26. Oelke M, Roehrborn CG, D’Ancona C, Wilson TH, Castro R, Manyak M (2014) Nocturia improvement in the combination of Avodart® and tamsulosin (CombAT) study. *World J Urol*. doi:10.1007/s00345-014-1296-3
27. Oelke M, Weiss JP, Mamoulakis C, Cox D, Ruff D, Viktrup L (2014) Effects of tadalafil on night-time voiding (nocturia) in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: analyses of pooled data from four randomized, placebo-controlled clinical studies. *World J Urol*. doi:10.1007/s00345-014-1255-z
28. Oelke M, Berges R, Schläfke S, Burkart M (2014) Fixed dose combination of sabal and urtica improves nocturia in men with LUTS suggestive of BPH—re-evaluation of four controlled clinical studies. *World J Urol*. doi:10.1007/s00345-014-1338-x
29. Berges R, Höfner K, Gedamke M, Oelke M (2014) Impact of desmopressin on nocturia due to nocturnal polyuria in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). *World J Urol*. doi:10.1007/s00345-014-1381-7
30. Seaman EK, Jacobs BZ, Blaivas JG, Kaplan SA (1994) Persistence or recurrence of symptoms after transurethral resection of the prostate: a urodynamic study. *J Urol* 152:935–937





## Notes