W14: Nocturia, what about it?

Workshop Chair: Karel Everaert, Belgium

27 August 2013 09:00 - 12:00

Start	End	Topic	Speakers
09:00	09:30	Terminology and classification of nocturia and nocturnal polyuria	• Jeffrey Weiss
09:30	10:00	Prevalence, incidence, risk factors and impact of nocturia	• Kari Tikkinen
10:00	10:30	Nocturnal polyuria, merely a cause of nocturia?	• Karel Everaert
10:30	11:00	Break	None
11:00	11:30	Nocturia and nocturnal polyuria – what to do?	• Philip Van Kerrebroeck
11:30	12:00	Similarities and differences between nocturnal enuresis and nocturia – what can we learn?	• An-Sofie Goessaert

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

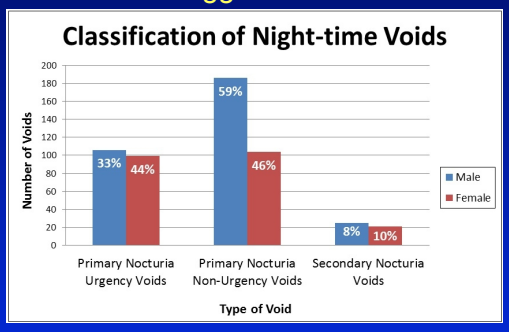
Professor and Chair
Department of Urology
SUNY Downstate College of Medicine
Brooklyn, NY

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

*van Kerrebroeck et al Neurourol and Urodyn 21:179-183, 2002

What triggers nocturia*?



*Weinberger, Weiss, Kashan, Blaivas: Nocturia: Why do people void at night. AUA 2013 abstract

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

Diary Assessment

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

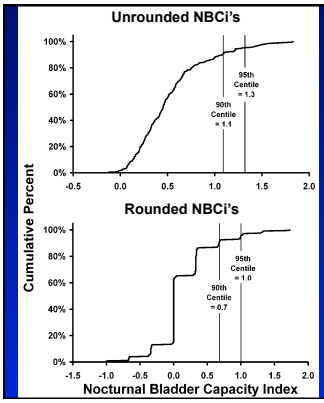
– Ni (Nocturia index = NUV/MVV):
  - Ni >1: Nocturia occurs because functional bladder capacity (maximum voided volume) is exceeded

Diary Assessment: NBCi

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

Diary Assessment: NBCi

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



- Cumulative frequency distributions of unrounded and rounded NBC is from the asymptomatic volunteers
- 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 Ni = NUV ÷ MVV	Ni >1 → nocturia is due to NUV exceeding MVV
Nocturnal Polyuria index NPi = NUV ÷ 24hV	NPi >33% → Dx is nocturnal polyuria
Nocturnal bladder capacity index Ni – 1 = PNV NBCi = ANV – PNV	NBCi >0 → nocturia occurring at volumes < MVV

Nocturia Category	Causes
Nocturnal polyuria	•Congestive heart failure •Diabetes mellitus •Obstructive sleep apnea •Peripheral edema •Excessive nighttime fluid intake

Nocturia Category	Causes
Diminished global/NBC	•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)	•Diabetes mellitus •Diabetes insipidus •Primary polydipsia

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

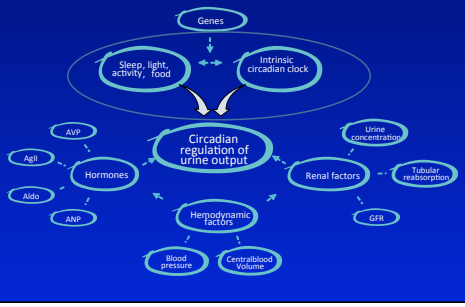
Nocturnal polyuria: "medical" cause for nocturia

- 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 NPi=0.14
  - >65 years: mean NPi=0.34***

*Matthiesen, T.B., et al: J. Urol., 156: 1292, 1996
**Blanker, M. H. et al: J. Urol., 164: 1201, 2000
***Kirkland J.L. et al: Br Med J., 287: 1665, 1983

Mechanisms behind nocturnal polyuria

slide courtesy Dr. Johan Vande Walle, Ghent, Belgium



Nocturnal Polyuria: Prevalence

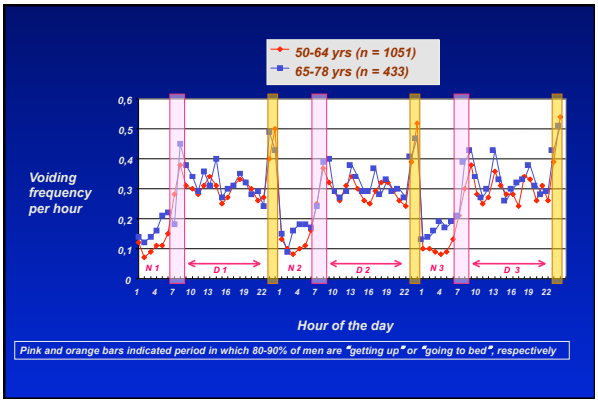
- Investigation of characteristics of patients recruited to a large phase III study for treatment of nocturia
  - Nocturia on average ≥2 voids/night; mean age 62
- 1412/934/799 patients screened/eligible to complete diary/ randomized
- 819/1412 (58%) had nocturnal polyuria
  - **NP defined as nocturnal urine volume >33% 24 hour volume**
- 478/1412 failed to complete a diary leaving 934 who did
- 819/934=87.7% of those completing diary had nocturnal polyuria

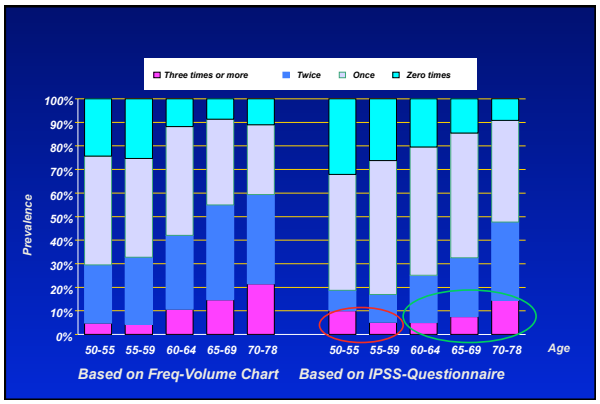
Weiss, JP: Prevalence of nocturnal polyuria in nocturia. J Urol 181 [4]: 538, 2009

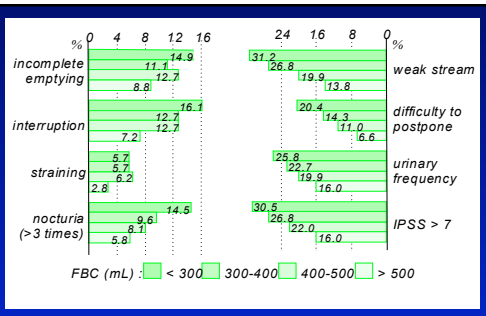
Nocturnal Polyuria: Prevalence*

- NP prevalence for NUV/24 hr > 33%:
  - Ages 50-54 at baseline: 44% → 51% at 6.5 year followup
  - Ages 65-69 at baseline: 54% → 65% at 6.5 year followup
- NP prevalence for NUP > 90 ml/hr:
  - Ages 50-54 at baseline: 14% → 19% at 6.5 year followup
  - Ages 65-69 at baseline: 23% → 26% at 6.5 year followup
- Thus, it makes a big difference how you define Nocturnal Polyuria

*Blanker, M. H. et al: J. Urol., 164:1201, 2000







Bosch JLHR and van Doorn B: Diary-based population analysis of nocturia in older men: Findings of the Krimpen study in: *Nocturia: Causes, Consequences and Clinical Approaches*. Weiss, Blaivas, van Kerrebroeck, Wein, eds. Springer 2012.

A. Prevalence of nocturia 2 times or more

	Baseline		2.1-year follow up		4.2-year follow up	
Baseline age strata	Prevalence (n= 1201)	(95% C.I.)	Prevalence (n = 929)	(95% C.I.)	Prevalence (n = 409)	(95% C.I.)
50-54 yrs	20,1%	(14,7-25,5)	19,7%	(13,8-25,6)	41,5%	(29,2-53,8)
55-59 yrs	23,8%	(19,4-28,6)	29,2%	(23,4-35,1)	44,4%	(35,1-53,6)
60-64 yrs	34,1%	(28,7-39,6)	44,0%	(37,8-50,3)	61,3%	(52,1-70,5)
65-69 yrs	45,9%	(39,5-52,4)	45,5%	(38,1-52,9)	66,3%	(55,7-76,8)
70-78 yrs	54,9%	(46,9-62,9)	57,5%	(47,3-67,6)	65,8%	(50,0-81,6)

B. Prevalence of nocturia 3 times or more

	Baseline		2.1-year follow up		4.2-year follow up	
Baseline age strata	Prevalence (n= 1201)	(95% C.I.)	Prevalence (n=929)	(95% C.I.)	Prevalence (n= 409)	(95% C.I.)
50-54 yrs	2,8%	(0,6-5,0)	3,7%	(0,7-6,1)	7,7%	(1,0-14,4)
55-59 yrs	4,2%	(1,9-6,4)	5,1%	(2,3-7,9)	14,8%	(8,2-21,4)
60-64 yrs	7,9%	(4,8-11,1)	9,9%	(6,1-13,7)	17,1%	(10,0-24,2)
65-69 yrs	12,5%	(8,2-16,7)	16,5%	(12,8-24,3)	26,3%	(16,4-36,1)
70-78 yrs	17,0%	(11,0-23,0)	27,7%	(18,5-36,9)	28,9%	(13,8-44,1)

C.I. : confidence interval

a. Prevalence of nocturnal polyuria defined as NUP33%/24h

	Baseline		2.1 year-follow up		4.2-year follow up		6.5-year follow up	
baseline age strata	Prevalence (n=1532)	(95% C.I.)	Prevalence (n = 1080)	(95% C.I.)	Prevalence (n = 803)	(95% C.I.)	Prevalence (n = 739)	(95% C.I.)
50-54 yrs	41,8%	(36,2-47,4)	44,3%	(37,4-51,2)	52,2%	(44,4-59,9)	51,4%	(44,0-58,9)
55-59 yrs	44,3%	(39,3-49,3)	44,2%	(38,4-50,1)	48,9%	(42,3-55,5)	48,8%	(42,1-55,6)
60-64 yrs	47,5%	(42,4-52,5)	48,8%	(42,9-54,6)	50,0%	(43,2-56,9)	62,5%	(55,4-69,6)
65-69 yrs	56,7%	(51,0-62,3)	54,2%	(47,3-61,0)	66,2%	(58,4-74,0)	65,3%	(56,7-73,9)
70-78 yrs	56,9%	(49,5-64,3)	66,4%	(57,5-75,2)	64,1%	(52,0-76,1)	59,1%	(44,0-74,2)

b. Prevalence of nocturnal polyuria defined as NUP of > 90 mL/h

	Baseline		2.1-year follow up		4.2-year follow up		6.5-year follow up	
baseline age strata	Prevalence (n= 1521)	(95% C.I.)	Prevalence (n = 1,075)	(95% C.I.)	Prevalence (n = 798)	(95% C.I.)	Prevalence (n = 735)	(95% C.I.)
50-54 yrs	12,1%	(8,4-15,9)	14,3%	(9,4-19,1)	19,0%	(12,9-25,1)	19,0%	(13,1-24,9)
55-59 yrs	12,0%	(8,7-15,3)	11,6%	(7,8-15,3)	16,1%	(11,3-21,0)	17,2%	(12,1-22,3)
60-64 yrs	13,2%	(9,8-16,7)	20,1%	(15,3-24,8)	15,4%	(10,4-20,3)	25,7%	(19,3-32,1)
65-69 yrs	20,5%	(15,9-25,2)	19,7%	(14,2-25,2)	19,7%	(13,1-26,3)	20,8%	(13,5-28,2)
70-78 yrs	23,6%	(17,2-29,9)	23,0%	(15,1-30,9)	21,0%	(10,6-31,4)	25,6%	(12,0-39,2)

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

Yalkut, D., et al.: J. Lab. Clin. Med., 128: 322, 1996
Endeshaw, YW et al: J Am Geriatrics Soc. 52(6):957-60, 2004

Sleep Apnea

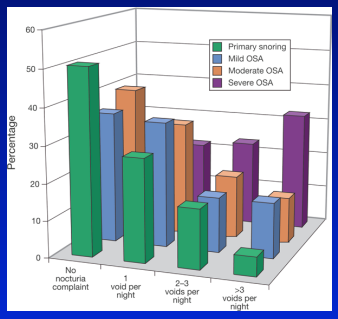
Increased airway resistance > hypoxia > pulmonary vasoconstriction > increased right atrial transmural pressure > increased ANP > increased renal sodium & water excretion

Sleep Apnea: Relation to Nocturia Severity

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

Hashim H, Coyne K, Chapple C, et al: Risk Factors and Associated Comorbid Conditions; Findings from an International Cross-sectional Study: EpiLUTS. EAU 2011

Nocturia as function of OSA severity



Kaynak H et al. J Sleep Res 2004;13:173–176

Drug effects causing nocturia

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

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

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

Increased urine output	*Insomnia and CNS effects*	*Direct LUT effects*
Diuretics	CNS stimulants (dextroamphetamine, methylphenidate)	Ketamine: Direct toxin
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	Psychotropics (MAOIs, SSRIs, atypical antidepressants)	
	Dopaminergic agonists (carbidopa)	
	Antiepileptics (phenytoin)	

FVC Determinants of Nocturia Severity in Men

	Nocturia patients (n=88)		Community dwelling older men (n=1082)	
Actual number of nightly voids versus	Correlation coefficient (Spearman's rho)	Significance (2-tailed)	Correlation coefficient (Spearman's rho)	Significance (2-tailed)
Nocturia index (Ni)	0.797	<0.001	0.658	<0.001
Nocturnal polyuria index (NPi)	0.545	<0.001	0.394	<0.001
Nocturnal urine volume (NUV)	0.463	<0.001	0.432	<0.001
Hours of sleep	0.306	0.011	0.272	<0.001
Nocturnal maximum voided volume (nMVV)	0.159	0.169	-0.146	<0.001
Mean nocturnal urine production (NUP)**	na	na	0.351	<0.001

Avulova, van Doorn, Weiss et al AUA 2012 Abstract #1955

Low bladder compliance is a risk factor in nocturia severity

Cohort Based on Bladder Compliance (n)	Average ANV	SD	P-value	Confidence Interval
Bladder Compliance ≤20 cm/H2O (15)	3.6	1.24	0.0456	0.019-1.894
Bladder Compliance >20 cm/H2O (87)	2.6	1.75		
Bladder Compliance ≤40 cm/H2O (38)	3.5	1.64	0.0015	0.433-1.764
Bladder Compliance >40 cm/H2O (64)	2.4	1.64		
Bladder Compliance ≤60 cm/H2O (63)	3.3	1.76	0.0002	0.619-1.919
Bladder Compliance >60 cm/H2O (39)	2	1.32		

Tsui, Marshall, Weiss, Samson, Weinberger, Roudakova, Chouhan, Kavoussi, Blaivas. AUA 2013 abstract

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

Weiss JP, Stember DS and Blaivas JG: Nocturia in adults: Classification and etiology. Neurourol Urodyn 16:401, 1997

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

*Araki , Yokoyama T and Kumon H: Acta Med Okayama 58(1): 45-49, 2004

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

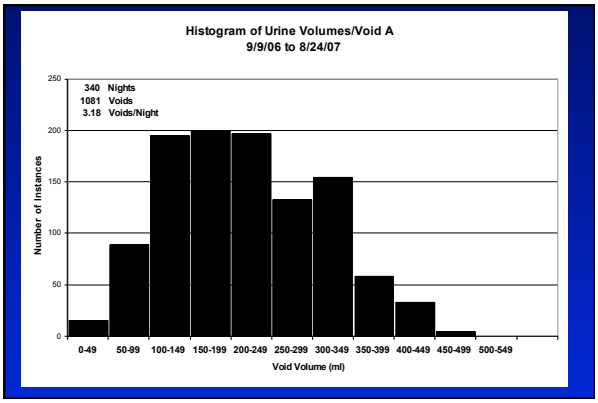
- 24 hour volume = 5000 ml
- NUV = 1500 ml
- MVV = 500 ml
- Ni = NUV/MVV = 3
- PNV = Ni-1= 3-1 = 2
- ANV = 2
- NBCi = ANV – PNV = 2-2 = 0 (nocturic voids at capacity)
- NPi = 1500/5000 = 30% (normal)

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)

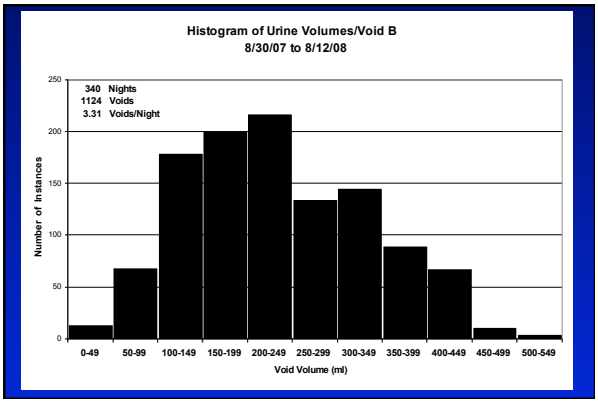
68 yo man with nocturia
data collected 9/9/06 - 10/28/08 (!!)

- 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.



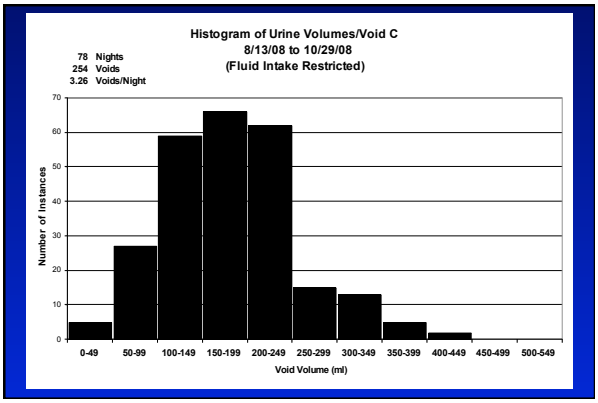
68 yo man with nocturia
data collected 9/9/06 - 10/28/08

- 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

	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: Discussion

Nocturnal polyuria, merely a cause of nocturia?

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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).(6) 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.

<u>Nocturnal polyuria and neurogenic bladder disease</u>

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.

1. Sumit Kumar, Tomas Berl. Diseases of Water Metabolism. In: Robert W.Schrier, editor. Atlas of Diseases of the Kidney. 1 ed. Wiley-Blackwell ; 1999.
2. Szollar S, North J, Chung J. Antidiuretic-Hormone Levels and Polyuria in Spinal-Cord Injury - A Preliminary-Report. Paraplegia 1995 Feb;33(2):94-7.
3. Zahariou A, Karagiannis G, Papaioannou P, Stathi K, Michail X. The use of desmopressin in the management of nocturnal enuresis in patients with spinal cord injury. Eura Medicophys 2007 Sep;43(3):333-8.
4. Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. Bju International 2011 Mar;107(5):702-13.
5. Ganong WF. Review of Medical Physiology. 22th ed. McGraw-Hill Companier; 2005.
6. van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JLHR. Prevalence, Incidence, and Resolution of Nocturnal Polyuria in a Longitudinal Community-based Study in Older Men: The Krimpen Study. European Urology 2013 Mar;63(3):542-7.

7. Carter PG, Cannon A, McConnell AA, Abrams P. Role of atrial natriuretic peptide in nocturnal polyuria in elderly males. European Urology 1999 Sep;36(3):213-20.
8. Tani M, Hirayama A, Fujimoto K, Torimoto K, Akiyama T, Hirao Y. Increase in 24-hour urine production/weight causes nocturnal polyuria due to impaired function of antidiuretic hormone in elderly men. International Journal of Urology 2008 Feb;15(2):151-4.
9. Abrams P, Cardozo L, Khoury S, Wein A. Incontinence. 4th International Consultation on Incontinence 2009.
10. Shamliyan T, Wyman J, Bliss DZ, Kane RL, Wilt TJ. Prevention of urinary and fecal incontinence in adults. Evidence report/technology assessment. 2007 Dec(161):1-379.
11. Jeong SJ, Cho SY, Oh SJ.: Spinal cord/brain injury and the neurogenic bladder. Urol Clin North Am. 2010, 37:537-46.
12. Wein AJ, Kavoussi LR, Novick AC, et al.: Campbell-Walsh urology ninth edition: Lower urinary tract dysfunction in neurologic injury and disease. Edited by Wein AJ. Philadelphia: Saunders Elsevier; 2007: 2011-2031
13. Gormley EA.: Urologic complications of the neurogenic bladder. Urol Clin North Am. 2010, 37:601-7.
14. Assadi F, Czech K, Palmisano JL. Autonomic dysreflexia manifested by severe hypertension. Med sci monit 2004; 10(12):77-79

Similarities between nocturnal enuresis in children and nocturia in adults - *What can we learn?*

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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.

		NE in children	Nocturia in adults
Definition:		involuntary urinary incontinence at night while being asleep	the need to wake up once or more at night to void with each void preceded and followed by sleep
Prevalence:		- 10% in 7-year-olds - 0,5% in adults	- 50% in >50-year-olds - 4-7% in healthy schoolchildren
Genetics:	- *Familial occurrence* - *Genetic factors*	- 66% has a first degree relative affected - chromosomes 12q, 13q and 22q are involved, phenol- and genotype are not closely linked	- Familial occurrence proven in twin studies - Prevalence differs according to ethnicity, but no related genotypes have been unraveled
Underlying condition:	- *Bladder dysfunction / reduced bladder capacity* - *Nocturnal polyuria*	- OAB due to delayed maturation of the CNS; lazy bladder syndrome; dysfunctional elimination syndrome - nocturnal urine output exceeding 130% of the expected bladder capacity for age; due to water- or solute-handling disturbances	- OAB, obstruction (BPH, strictures), cancer of the bladder or prostate, bladder hypersensitivity, calculi, vesicoureteral reflux, bladder diverticula and infection - 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
Comorbidities / Consequences:	- *Quality of sleep* - *Physical health / mental health* - *Quality of life*	- superficial, fragmented sleep with inappropriate arousal; PLMD, RLS, sleep apnea - constipation, dysfunctional elimination syndrome; psychological problems: Low self-esteem, behavioral problems, concentration disorders and aggressive behavior, ADHD - affected due to above mentioned comorbidities and consequences; also family is affected	- fragmented sleep; insomnia, sleep apnea - hypertension, obesity, diabetes, cardiovascular events, falls and fractures; daytime fatigue, personal distress, decreased cognitive function and even depression - affected due to above mentioned comorbidities and consequences; also family is affected
Treatment:	- *Antimuscarinics* - *antidiuretic treatment* - *other*	- second-line treatment, combination therapy - first-line treatment when due to nocturnal polyuria; effective in one-third, low prevalence of side effects - urotherapy, enuresis alarm, neurostimulation	- reduction of nocturia episodes with max. 50%, only when underlying OAB - first-line treatment when due to nocturnal polyuria, effective in 33-67%, side effects in 7% - lifestyle changes, surgery

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)

Long-term follow-up of enuretic patients

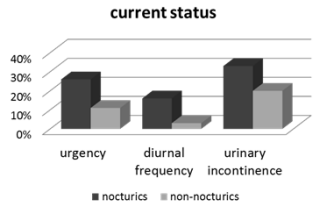
Results:

Questionnaires from 516 patients (41%): mean age 17 (SD 3,2), 331 male (64%) and 184 female (36%) participants; 35% reports nocturia

Variable	Nocturics N=182	Non-nocturics N=334	P-value
Age (mean,SD)	18 ± 3,7	17 ± 2,9	0,001*
Sex: male (N, %)	101 (56%)	230 (69%)	0,002*
female (N, %)	81 (44%)	103 (31%)	

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

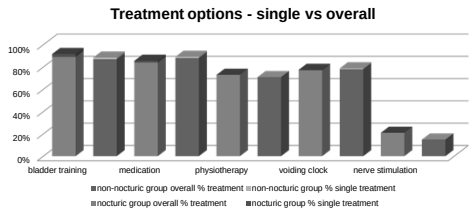
Long-term follow-up of enuretic patients



Urinary incontinence	Nocturics	Non-nocturics	P-value
Leaks before getting to the toilet	27 (15%)	29 (9%)	0,029*
Leaks when asleep	21 (12%)	15 (4%)	0,002*

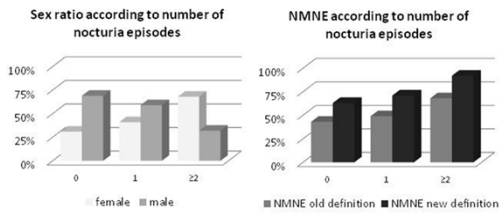
Long-term follow-up of enuretic patients

Variable	Nocturics	Non-nocturics	P-value
NMNE (new definition)	135 (74%)	211 (63%)	0,022*
Primary nocturnal enuresis	145 (80%)	263 (79%)	0,894



Long-term follow-up of enuretic patients

One, two and three nocturia episodes were reported by 157 (86%), 22 (12%) and 3 (2%) subjects, respectively



Long-term follow-up of enuretic patients

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

Notes