

W4: Nocturnal LUTS in an older population

Workshop Chair: Karel Everaert, Belgium

13 September 2016 09:00 - 10:30

Start	End	Topic	Speakers
09:00	09:05	Introduction	Karel Everaert
09:05	09:25	Definitions and terminology	Alan Wein
09:25	09:45	Aging of the sleeping brain, consequences for LUTS	Donald Bliwise
09:45	10:05	Aging of the bladder, consequences for LUTS	Karel Everaert
10:05	10:25	Aging of the kidney, consequences for LUTS	An-Sofie Goessaert
10:25	10:30	Questions	All

Aims of course/workshop

The prevalence of lower urinary tract symptoms (LUTS) increases with age and the demography makes it an important socio-economic burden for society and individual. This workshop offers a comprehensive overview on the current knowledge on nocturnal LUTS in an aging population. Nocturnal LUTS are nocturia, nocturnal incontinence and bedwetting. Nocturnal LUTS occur due to a disruption of the circadian rhythms of brain, bladder and kidney resulting in changes in sleep, bladder function and urine production.

Learning Objectives

After this workshop participants should be able to:

1. Summarizing the changes in sleep patterns, bladder function and kidney function with increasing age provides insights into the pathophysiology of nocturnal LUTS
2. How to approach these symptoms in clinical practice or induce optimisation of treatment
3. Stimulate further research in this domain.

Target Audience

Urologists, Gynaecologists, Geriatricians and Nurses

Advanced/Basic

Advanced

Suggested Reading

See speaker information online

Karel Everaert

Aging of the bladder, consequences for LUTS

(Altered from Letter to the editor, accepted 2015, *Minerva urologica e nefrologica*)

Lower urinary tract symptoms (LUTS) show an increasing prevalence because of worldwide aging and population growth. In the light of the existing evidence and clinical experience, we propose a new concept to (a) classify symptoms and bother of lower urinary tract disorders and to (b) explain the underlying pathophysiology of LUTS in older patients.

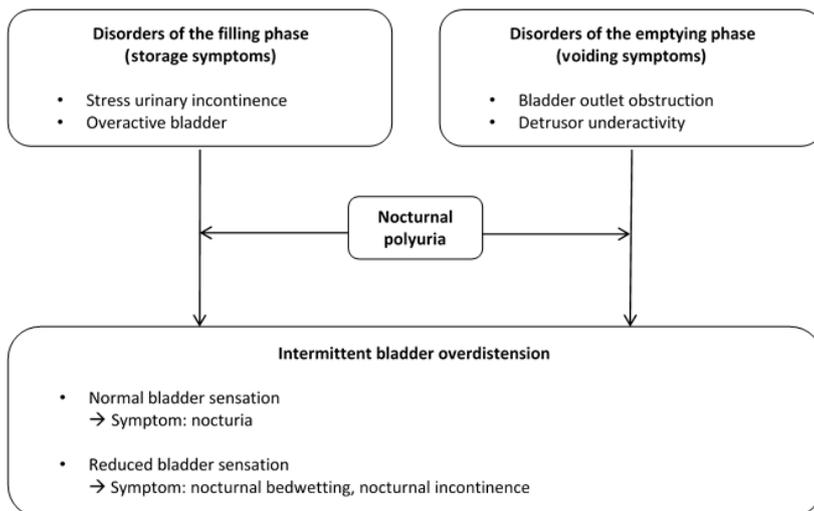
Daytime and nighttime LUTS

The presence of a single nocturia episode is often regarded as a storage symptom. Therefore, we assume that the prevalence of filling symptoms is overestimated, especially in older populations in whom nocturia is a very common complaint. For these reasons, we suggest separating daytime from nighttime symptoms and their bother in future research on LUTS. The first morning void should be included in the analysis of nighttime symptoms because, for example, morning overdistension of the bladder due to nocturnal polyuria can give rise to urinary incontinence while standing up in the morning, which is different from daytime LUTS.

Pathophysiology of LUTS

Symptoms as nocturia, frequency and urinary incontinence are typically attributed to underlying detrusor overactivity, but can also be the result of bladder outlet obstruction (BOO), detrusor underactivity (DU), nocturnal polyuria (NP) and loss of bladder sensation (LBS), which are all conditions that occur more frequently with increasing age. Our hypothesis is that abnormal filling or emptying of the bladder can be linked to intermittent overdistension of the bladder, especially in older patients with NP in whom this association seems strengthened (figure 1).

Figure 1: Novel concepts for future research on the underlying pathophysiology of lower urinary tract symptoms in older patients



Abnormal filling and intermittent overdistention: loss of bladder sensation and nocturnal polyuria

DU is not necessarily caused by a diminished detrusor contractility, but can also be the result of dysfunctional processing of afferent information from the filling bladder, with a diminished bladder sensation. Such a dysfunction of the afferent bladder innervation is typically seen in patients with diabetes mellitus. The additional impact of NP and a nocturnal voided volume over 625ml is a risk factor for incontinence material use, associated with a lower QOL. Consequently, NP seems to contribute to intermittent overdistension of the bladder, which leads to urinary incontinence rather than nocturia beyond 625 ml. These findings suggest that a reduced bladder sensation mainly leads to nocturnal bedwetting, while a preserved bladder sensation leads to nocturia in older patients with NP.

Abnormal emptying and intermittent overdistention: bladder outlet obstruction and detrusor underactivity

The combination of LBS and NP, together with BOO and DU might aggravate the intermittent (over)distension of the bladder in older patients.

Conclusion

1. Future research has to explore the link between intermittent (over)distention of the bladder and underlying disorders such as LBS, NP, DU and BOO by using extended bladder diaries including weight of incontinence and PVR after each micturition.
2. The suggestion to separate daytime from nighttime LUTS, together with their bother for the evaluation of LUTS in older patients needs further evaluation.

Alan Wein

Definitions and terminology

“If names are not correct, language will not be in accordance with the truth of things” (Confucius)

The International Continence Society published a document which standardized terminology for nocturia in 2002 (Neurourology and Urodynamics 2002; 21:167-178). This document is presently being revised by a committee headed by Hashim Hashim. As a member of this committee, I will report the most important changes in the course of this presentation at the ICS meeting, but this outline basically recapitulates the 2002 terminology with some notes regarding obvious issues.

Nocturia can be looked at as a sign (a term that applies to an objective observation apparent to the patient, physician and others; this can include observations from a frequency voiding chart, questionnaire, etc.), a condition (defined by the presence of urodynamic observations associated with characteristic signs and symptoms and/or non-urodynamic evidence of relevant pathologies), or a symptom (any subjective evidence of disease apparent to the patient) – it depends on how the word is utilized. Symptoms seem to be synonymous with “complaints”. Currently, nocturia is defined as a complaint that an individual has to wake at night one or more times to void. Each void under the current definition needs to be preceded and followed by sleep. This requirement in itself obviously creates problems. The definition is also problematic because it does not specify if the individual awakes because of a need to void; in other words, “convenience voids” (awakening for one reason unrelated to urination but urinating nevertheless) are currently counted in the nocturia total. The current definition does not specify “bother”. The term enuresis currently refers to any involuntary loss of urine, if it used to denote incontinence during sleep, it should always be qualified with the adjective nocturnal. Nocturnal enuresis then refers to the complaint of loss of urine during sleep.

Currently daytime frequency is defined as the number of voids recorded during waking hours and includes the last void before sleep and the first void after awakening in the morning. Twenty-four hour frequency refers to the total number of daytime voids

and episodes of nocturia during a specified 24-hour period. Twenty-four hour urine production refers to the volume of all urine for 24 hours. This begins after the first void produced after arising in the morning and ends by including the first void on arising the following morning.

Polyuria refers to a measured production of greater than 2.8 liters during a 24-hour period in adults. This is based on a 70kg person voiding greater than 40ml/kg. Nocturnal urine volume refers to the total amount of urine passed between the time the individual goes to bed with the intention of sleeping and the time of waking with the intention of rising. It excludes the last void before going to bed and includes the first void upon rising in the morning. The percentage of nocturnal urine volume during a 24-hour day differs with age. Currently the accepted normality definitions are 20% in young adults and 33% in those over the age of 65. Nocturnal polyuria refers to an increased proportion of the 24-hour output occurring at night. One problem, then, is defining “night”. Does this include the time from when the individual gets in bed with the intention of going to sleep to the time when the individual gets up in the morning without the intention of going back to sleep? The document gives the example of during the 8 hours while the patient is in bed. Nocturnal polyuria is offset by lower daytime production so the 24-hour production remains within normal limits. It should be noted that the definition of nocturnal polyuria is not shared consistently by all authorities. There are many iterations of this offered by many author; these include such diverse descriptions as greater than 6.4ml/kg, greater than 54ml/h, and equal-to or greater-than 90ml/h. As the volumes increase, the definitions become closer together. The diagnosis of nocturnal polyuria implies a differential diagnosis of causation which includes many entities, including medical conditions and an abnormality of nocturnal secretion of or action of arginine vasopressin. Maximum voided volume defines the largest volume of urine voided during a single micturition and is determined from a frequency volume chart (FVC) or bladder diary, an essential part of a nocturia evaluation. On the basis of a simple frequency volume chart, nocturia can be categorized as nocturnal polyuria; low nocturnal bladder capacity, despite a normal global bladder capacity; low global bladder capacity; and global polyuria.

Other definitions which are important for the vocabulary that surrounds nocturia include the following: (1) nocturia index (Ni) – this refers to the mean measured nocturnal urine volume divided by the maximal voided volume (aka functional bladder capacity). If this is greater than 1, then the nocturnal urine volume exceeds the bladder maximum storage capacity and by definition nocturia or enuresis results. One can easily calculate the predicted number of nightly voids (PNV) by subtracting 1 from the nocturia index (Ni-1). The NPi refers to the nocturnal polyuria index which is the mean measured nocturnal urine volume divided by the 24-hour urine volume. The mean NPi for individuals under the age of 25, is cited at 0.24 and for those over the age of 65, 0.34. The current definitions for nocturnal polyuria are not apt to be changed in the revised document, even though, as mentioned, many other iterations exist.

The existing definition of nocturia does not take into account those patients who may need to urinate several times before actually falling asleep. It does not include those who need to void multiple times during the night because of pain or hypersensitivity, often several times in a row with small amounts each time and those who simply may not be able to go to sleep. Under the current definition these voids do not qualify because each are not preceded and followed by sleep. The current definition obviously does not include people who suffer from insomnia. The word complaint implies that the nocturia is bothersome. Sometimes it is, sometimes it isn't. I suspect that the wording of the new definition will not include the word complaint. Thus, what at first seemed simple is not so simple. There are issues defining nocturia in terms of its relationship to sleep. Some feel that the definition should include only those who wake up more than once at night and separate convenience voids, although the distinction is not always crystal clear. Finally, from a simple frequency voiding chart, one can derive all of the parameters previously described and begin to formulate a differential diagnosis for the pathophysiology of nocturia in a particular individual.

The current nocturia committee is also reconsidering the terms “nocturnal enuresis” and “nocturnal incontinence”. Nocturnal enuresis is currently defined as the complaint of loss of urine occurring during sleep. It is incorrect to use the term nocturnal incontinence to describe what is actually nocturnal enuresis. The difference is the state of sleep.

Donald Bliwise

Aging of the sleeping brain: consequences for LUTS

Among insults to the aging brain, none is perhaps as cruel or insidious as the ability to sustain sleep. Declines with sleep quality throughout the middle age and older ages are nearly universal and have been found in nearly all mammalian species studied. Evidence for decreased integrity of sleep and wakefulness as a part of the aging process may even be found in more primitive species such as *Drosophila* and *C. elegans*. We and others have argued that sleep and its associated physiology may be among the most integrative markers of autonomic, endocrine, pulmonary and cardiovascular function ever recognized. Yet the effects of sleep and sleep loss on the central nervous system may even be more profound. Exciting new basic science suggests that loss of sleep can hasten abnormal protein aggregation and protein misfolding in brain regions that are indicative of the changes seen in Alzheimer's Disease and other forms of dementia, such as Lewy Body Dementia.

Enter into this matrix of complex organ system aging the simple act of nocturnal voiding, nocturia. A seemingly trivial event, nocturia is now becoming increasingly recognized as the most common cause of disturbed sleep in aged populations. Certainly there are other numerous age-dependent challenges to the integrity of the sleep cycle—these range from changes intrinsic to sleep itself (such as the decrease of deep, slow wave sleep and increase in stage 1 sleep), to specific disorders of sleep (such as

sleep apnea or restless legs syndrome), to medical (such as chronic pain) and psychiatric conditions (depression) to external environmental influences (reduced arousal threshold to light and sound or caregiver duties). As the normal circadian rhythm of the sleep wake cycle is dampened by the aging process, not only does nocturnal sleep deteriorate but the ability to remain vitally alert during the daytime hours also diminishes. Elderly humans (and indeed elderly animals of all types, be they diurnal or nocturnal) show an increased tendency to have brief bouts of daytime sleep, regardless of whether that daytime occurs during daylight hours (as humans) or during darkness (nocturnally active animals).

Recent research has suggested that one of the best single markers of nocturia's impact on sleep quality, length, depth, and integrity can be obtained not by a measure of number of voids (the most traditionally used measure of nocturia in epidemiologic studies) but rather by a rather simple metric referred to as the First Uninterrupted Sleep Period (FUSP), also known as the time to first void. This has been shown to be highly correlated with standard scales reflecting sleep quality. A relatively short FUSP indicates poorer sleep and even less deep sleep. And under intervention conditions, an increase in FUSP is associated with improved sleep and, has been demonstrated very recently, potentially better control over glucose. My presentation will review briefly the many recent and exciting findings in this area.

Bliwise DL. Cataloging nocturia (circa 2014). *Sleep* 2014; 37: 631-3.

Bliwise DL, Holm-Larsen T, Goble S, Nørgaard JP. Short time to first void is associated with lower whole-night sleep quality in nocturia patients. *J Clin Sleep Med* 2015; 11: 53-5.

An-Sofie Goessaert

Aging of the kidney, consequences for LUTS

An increased nocturnal urine production is limited to nighttime, hence the term nocturnal polyuria (NP). As long as the bladder capacity can cope with the increased urine production, NP will not lead to any symptom at night. When the bladder capacity is too small, NP can give rise to nocturia, but also enuresis nocturna or overflow incontinence due to overdistension of the bladder can occur. (1; 2) Patients do not often mention this kind of problem, unless casually during a doctor's visit prompted by another reason. These patients are often older and consider it a normal aging process or they are embarrassed in case of incontinence or they assume nothing can be done. (3) However, NP can be an indication of heart failure when third space fluid (leg edema) that has accumulated during daytime comes back in circulation at night when the patient is in a postural position triggering the RAAS system to maintain a normal blood pressure. (4; 5) Even if the underlying problem of NP is not that dramatic, as a doctor it is worthwhile to question the presence of nocturia and/or nocturnal incontinence to diagnose NP, since treatment can be easy and might resolve the "silent" impact of the sleep deterioration on daytime activities and general wellbeing.

A frequency-volume chart or bladder diary is indispensable in the analysis of nocturia, since it allows to identify the condition leading to nocturia. But once the diagnosis of NP is made, no validated investigation of the underlying pathophysiologic mechanism, water versus sodium diuresis, is at hand. While in patients without an evident non-urological cause of NP addressing the pathophysiologic mechanism behind it might be the only chance to find a proper treatment.

Evaluation of a renal function profile (RFP) in people >65 years old shows that patients with NP differ from controls without NP with different circadian rhythms in diuresis rate, creatinine clearance, free water clearance and sodium clearance. The difference in creatinine and sodium clearance, primarily occurring at the end of the night, might be related to associated comorbidities; while changes in free water clearance, more prominent in the beginning of the night, might be related to age. Furthermore, comparing results of nocturnal osmolality and sodium excretion between older people with no nocturia, 1 or 2 or more nocturia episodes per night shows no differences, opposed to results found in patients younger than 65 years old with increased sodium excretion only found in those getting up twice or more.

But who qualifies as older people? We analyzed the characteristics of adults with nocturia between 18 and 65 years old, with the upper age limit based on the age limit often used for definitions, such as the ICS definition of NP. (6) Until the age of 45, an increase in nocturnal frequency from 0 to 2 or more is not associated with an increase in nocturnal voided volume; it is associated with a decrease in functional bladder capacity. From 45 to 65 years old, an increase in nocturnal voiding frequency is associated with both reduced bladder capacity and increased nocturnal voided volume, with the latter associated with a decline in osmolality and a rise in sodium excretion. Based on these results, we might assume that the physiologic changes correlated to the aging process occur at a much younger age than 65.

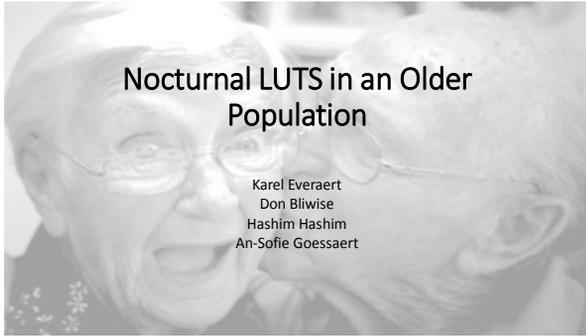
Reference List

1. Miller J, Hoffman E. The causes and consequences of overactive bladder. *Journal of Womens Health* 2006 Apr; 15(3):251-60.
2. Miller M. Nocturnal polyuria in older people: Pathophysiology and clinical implications. *Journal of the American Geriatrics Society* 2000 Oct; 48(10):1321-9.
3. Chen FY, Dai YT, Liu CK, Yu HJ, Liu CY, Chen TH. Perception of nocturia and medical consulting behavior among community-dwelling women. *Int Urogynecol J Pelvic Floor Dysfunct* 2007 Apr; 18(4):431-6.

4. Hirayama A, Torimoto K, Yamada A, Tanaka N, Fujimoto K, Yoshida K, et al. Relationship Between Nocturnal Urine Volume, Leg Edema, and Urinary Antidiuretic Hormone in Older Men. *Urology* 2011 Jun; 77(6):1426-31.
5. Torimoto K, Hirayama A, Samma S, Yoshida K, Fujimoto K, Hirao Y. The Relationship Between Nocturnal Polyuria and the Distribution of Body Fluid: Assessment by Bioelectric Impedance Analysis. *Journal of Urology* 2009 Jan; 181(1):219-24.
6. Cornu JN, Abrams P, Chapple CR, Dmochowski RR, Lemack GE, Michel MC, et al. A Contemporary Assessment of Nocturia: Definition, Epidemiology, Pathophysiology, and Management-a Systematic Review and Meta-analysis. *European Urology* 2012 Nov; 62(5):877-90.

Suggested reading

- Goessaert A.S., Krott L., Hoebeke P., Vande Walle J., Everaert K. Diagnosing the pathophysiologic mechanisms of nocturnal polyuria. *European Urology*, 2015. 67(2): 283-288.
- Goessaert A.S., Krott L., Vande Walle J., Everaert K. Exploring nocturia: gender, age, and causes. *Neurourol Urodyn*. 2015; 34(6): 561-565.



Nocturnal LUTS in an Older Population

Nocturnal LUTS are nocturia, nocturnal incontinence and bedwetting.

Nocturnal LUTS occur due to a disruption of the circadian rhythms of brain, bladder and kidney.

Resulting in changes in sleep, bladder function and urine production and in LUTS.

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- A shortened version of the handout will have been provided on entrance and that the full handouts for all workshops are available via the ICS website.
- Please switch off or make silent all mobile phones
- Please refrain from taking video and pictures of the speakers and their slides. PDF versions of the slides will be made available after the meeting via the ICS website.

13 September 2016
 ICS Meeting Workshop: Tokyo, Japan
 Nocturnal LUTS in an Older Population

Aging of the Sleeping Brain: Consequences for LUTS

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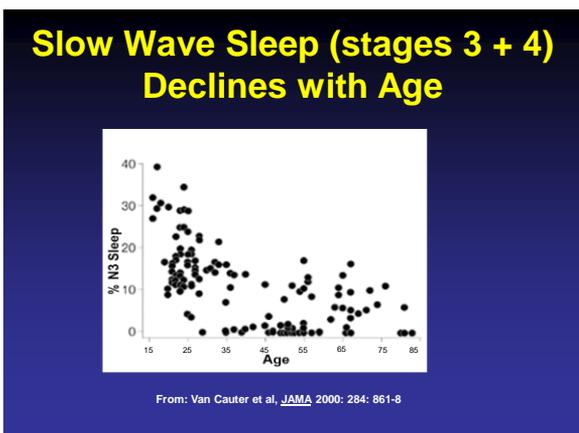
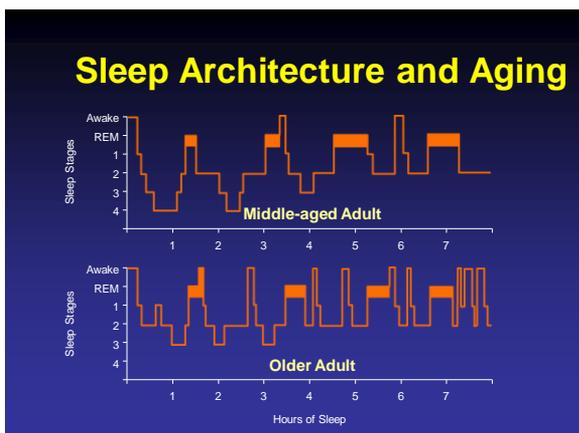
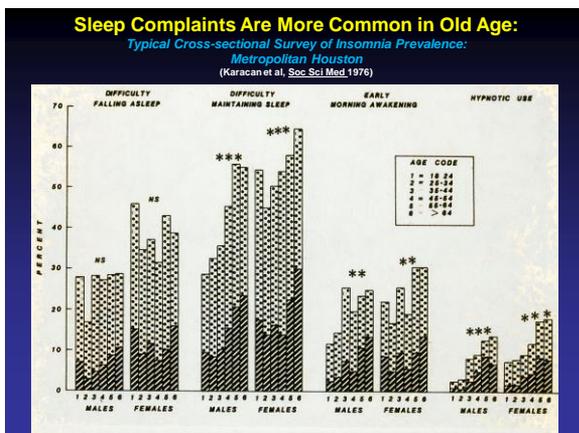
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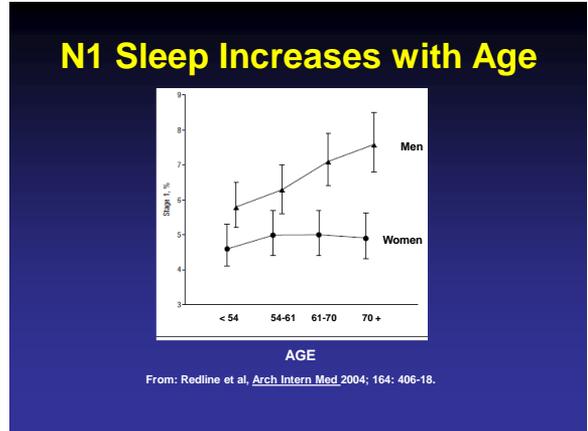
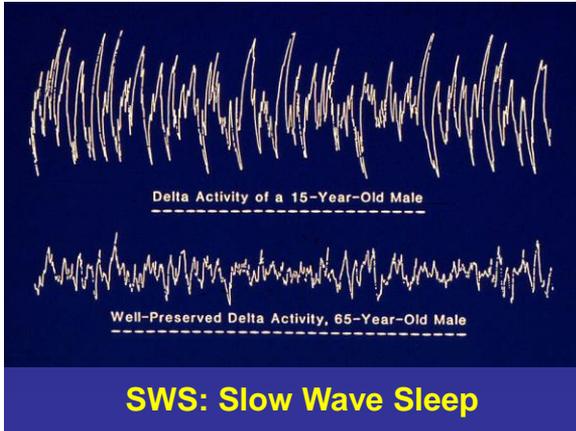
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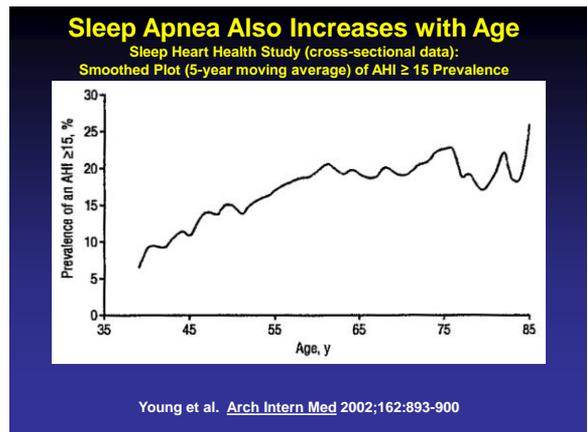
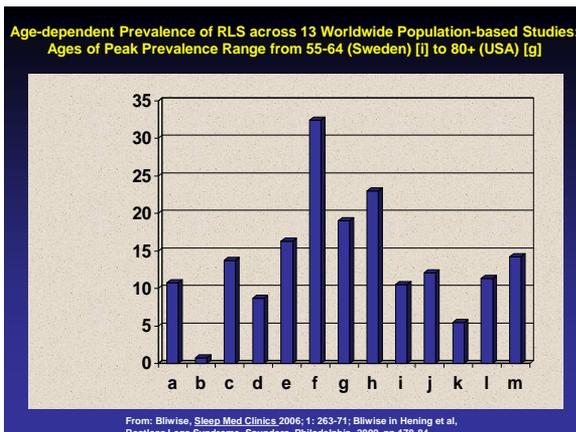
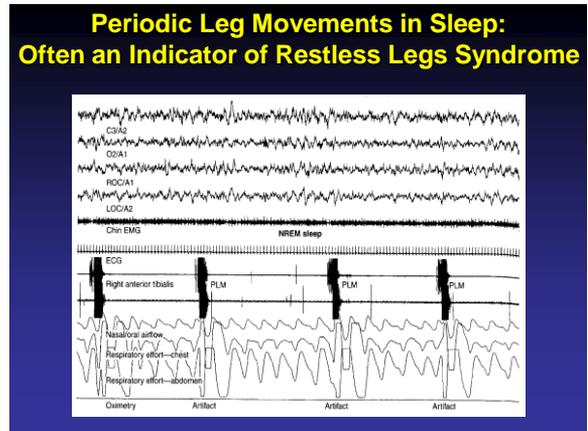
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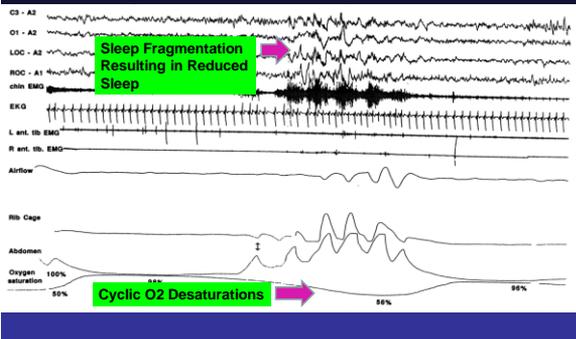




Periodic Leg Movements in Sleep (PLMS) Restless Legs Syndrome (RLS) in the Elderly



Polysomnographically Recorded Sleep Apnea: Two Key Components



Polysomnographic (PSG) Measures and Nocturia* Sleep Heart Health Study (n = 6342)

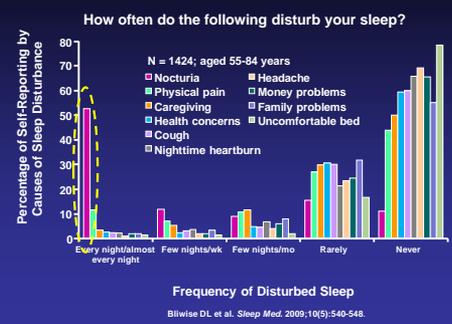
*NOTES: Nocturia defined as at least 1 awakening to use the bathroom ≥ 5 nts/month; Values represent median (IQR) or %
(Parthasarathy et al PLoS One 2012; 7:e30969)

PSG Measure	Nocturia	No Nocturia	Comparison (p)
Sleep Duration	365 (317, 404)	367 (322, 408)	.06
Sleep Efficiency	82.8 (75.4, 88.0)	85.1 (77.4, 90.1)	< .0001
Wake After Sleep Onset (WASO)	55.5 (34.0, 87.0)	43.5 (26.5, 76.5)	< .0001
N1%	4.6 (2.8, 7.2)	4.5 (2.8, 7.1)	.32
N2%	57.5 (49.3, 65.4)	57.2 (49.3, 64.9)	.30
N3%	16.7 (8.2, 25.7)	17.0 (8.2, 24.6)	.36
REM%	19.8 (15.4, 23.7)	20.5 (16.5, 24.3)	< .0001
AHI > 15 (%)	23.2	17.4	< .0001

Apart from Intrinsic Sleep Fragmentation, What Causes Poor Sleep in Old Age?

- **Nocturia**
- Pain
- Medications (e.g., beta-blockers, respiratory stimulants)
- Decreased physical activity (sedentary lifestyle)
- Increased susceptibility to arousal (decreased arousal threshold)
- Depression and anxiety, endogenous and environmental (bereavement)
- Decreased exposure to zeitgebers (light, social contacts, spouse)

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

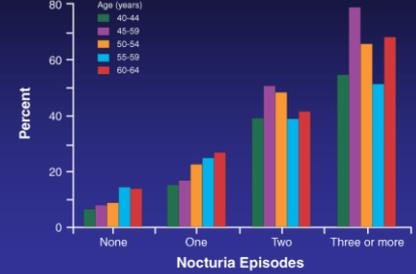


Nocturia and Poor Sleep Attributed Causes of Disturbed Sleep Maintenance 1485 Dutch Men and Women, Ages 50-93

Cause	Men %s	Women %s
Nocturia	72.1	63.5
Unknown	15.2	15.7
Anxiety	1.3	4.4
Worries	1.2	3.2
Other	10.2	13.2

From: Middlekoop et al. J Gerontol:Med Sci 1996; 51A, M108-15

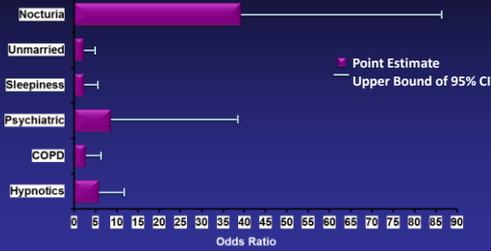
Nocturia and Poor Sleep Prevalence of Poor Sleep 3669 Swedish Women Ages 40-84



From: Asplund & Aberg. Maturitas 1996;24:73-81

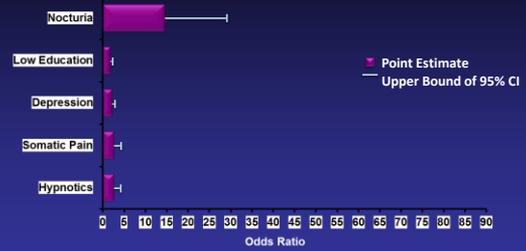
Multivariate Risk Factors for Insomnia in Elderly Taiwanese Men

Su et al. *Aust NZ J Psychiat* 2004; 38:706-13



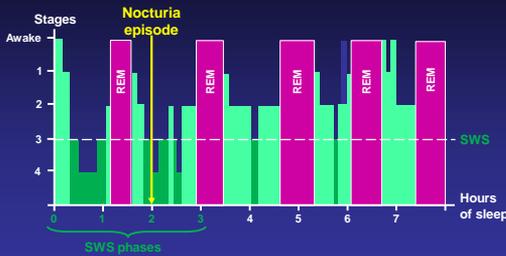
Multivariate Risk Factors for Insomnia in Elderly Taiwanese Women

Su et al. *Aust NZ J Psychiat* 2004; 38:706-13.



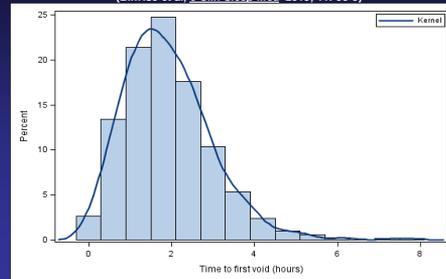
SWS May Be Interrupted by Nocturia

The first nocturia episode occurs within 2 to 3 hours on average



Frequency Distribution of Time to First Void (also called First Uninterrupted Sleep Period, FUSP) in Untreated Nocturia

(Bluijse et al. *J Clin Sleep Med* 2015; 11: 53-5)



Nocturia Disrupts SWS (Stg 3/4): Analysis by Number of Voids (Torimoto et al)

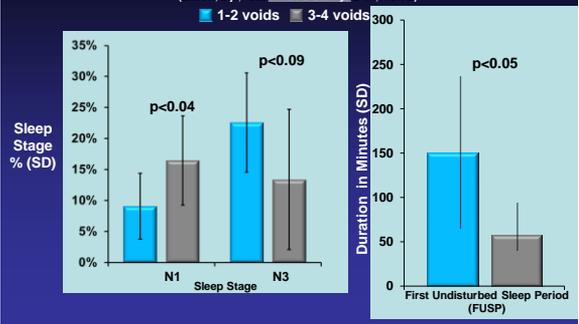
Sleep Measure	0-1 Voids Per Night	≥2 Voids Per Night	P
Total sleep, min (± SD)	331 (50)	313 (51)	NS
Stg 1/2 sleep, min (± SD)	176 (35)	168 (37)	NS
Stg 3/4 sleep, min (± SD)	62 (25)	40 (21)	0.014
REM sleep, min (± SD)	97 (25)	101 (32)	NS

Torimoto K et al. *NeuroUrol Urodyn* 2012;31:982-983.
Torimoto K et al. *J Urol* 2013;189:e537-e538.

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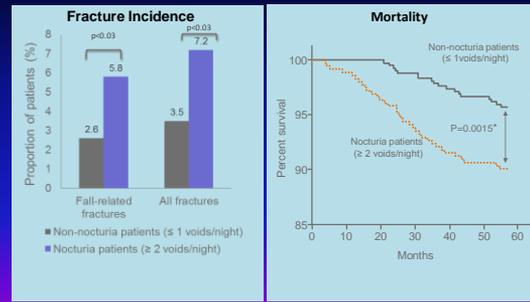
Polysomnographic Comparison of Nocturia Patients with 1-2 Voids vs 3-4 Voids on Sleep Lab Night: All Patients without Sleep Apnea (AHI < 5.0)

(Bluijse, Dijk, Juul. *NeuroUrol Urodyn* 2015; 34: 392)



Why Treat Nocturia?

Nocturia Predicts Fall-related Fractures and Mortality in the Elderly



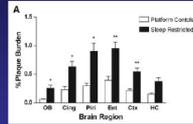
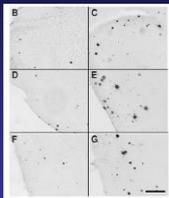
Kaplan-Meier estimates show significantly lower mortality in patients without nocturia than patients with nocturia (log rank test p=0.0015); CI, confidence interval. (Nakagawa H et al. J Urol 2010;184:1413-1418)

21 Days of Chronic Sleep Restriction in Mice Results in Beta-amyloid (Aβ) Plaque Deposition

(Kang et al, *Science* 2009; 326: 1005-7)

Controls Sleep Restricted

Olfactory Bulb
Piriform Cortex
Entorhinal Cortex



Improvement in Nocturia is Associated with Improvements in Sleep Quality

One hour increase in FUSP was associated with a significant improvement in 7 out of 8 components of the Pittsburgh Sleep Quality Index (PSQI)

PSQI Scale Component	n	Parameter estimate	SE	p-value
Global	607	-0.488	0.054	<0.0001
Sleep Quality	633	-0.106	0.012	<0.0001
Sleep Latency	609	-0.079	0.015	<0.0001
Sleep Duration	632	-0.068	0.013	<0.0001
Sleep Efficiency	632	-0.102	0.018	<0.0001
Sleep Disturbances	634	-0.044	0.012	=0.0002
Sleep Medication	634	-0.016	0.016	=0.30
Daytime Dysfunction	634	-0.075	0.014	<0.0001

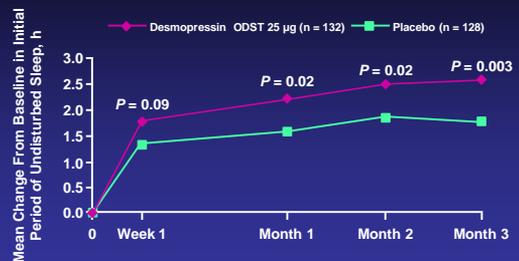
Bliwise et al, *Sleep Medicine* 2014; 15: 1276-8

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

Open label, single-group design of a muscarinic antagonist (Takao et al, *Urology* 2011; 78: 648-652)

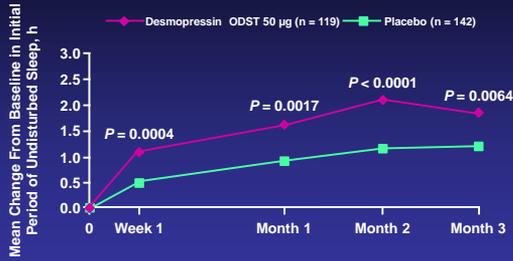
	BASELINE	8 WEEKS	P
SLEEP LATENCY (mins)	13.8 (13.9)	13.1 (10.8)	.683
TOTAL SLEEP TIME (mins)	352.2 (46.4)	368.8 (44.4)	.030
SLEEP EFFICIENCY (%)	73.0 (7.2)	75.7 (6.2)	.007
WAKE AFTER SLEEP ONSET (mins)	98.0 (40.0)	89.6 (35.5)	.096
NUMBER OF AWAKENINGS	30.8 (7.7)	29.6 (7.7)	.272

Increase in FUSP With Desmopressin Melt (25 µg) in Women Over 3 Months' Nightly Administration



Sand PK et al, *J Urol* 2013; 190:958-964.

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

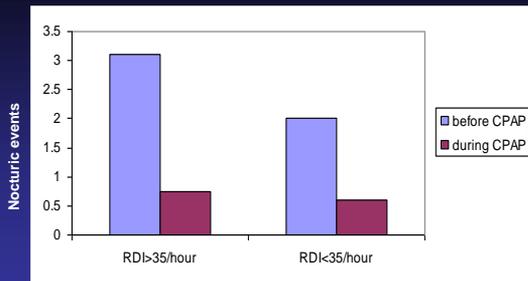


Weiss JP et al. *Urol*. 2013; 190:965-9729.

Treating Sleep Apnea with Nasal CPAP

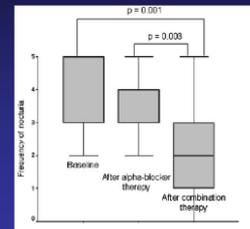


Nocturia Episodes Reduced by CPAP



From: Margel et al, *Urology* 2006; 67:974-7.

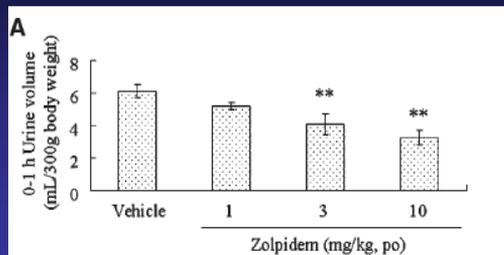
GABAergic Medication May Enhance Efficacy of Nocturia Rx Additive Effects of Zolpidem + α Blocker



Song & Ku, *Int Urol Nephrol* 2007; 39: 1147-52

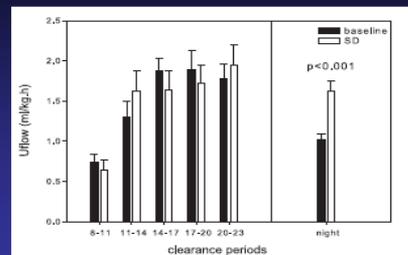
Water-loaded, wild-type rats show dose-dependent, zolpidem-induced decreases in urine volume the 1st hour after oral administration

(Yokoyama et al, *NeuroUrol Urodynam* 2010; 29: 587-91)



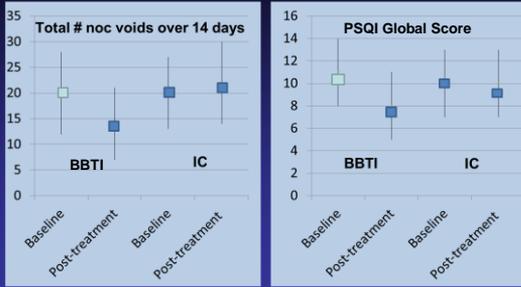
Sleep Deprivation in Humans Increases Urine Production

24 hrs sleep deprivation vs normal sleep with H₂O and Na intake controlled (Kemperis et al, *Am J Physiol Renal Physiol* 2010; 299: F404-11)



Can Treating Insomnia Behaviorally Benefit Nocturia in the Elderly?

Brief Behavioral Treatment for Insomnia (BBTI) vs Information Control (IC)
(Tyagi et al, *J Am Geriatr Soc* 2014; 62: 54-60)

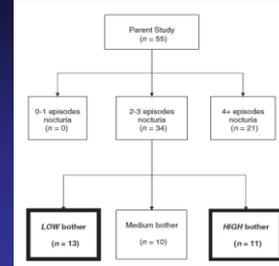


Thank you for your attention
dbliwis@emory.edu

Nocturia ≠ Bother

Selected AUA-7 items in relation to sleep diaries

(Vaughan et al, *Int J Clin Pract* 2012; 66: 369-73)



Nocturia Frequency Does Not Always Equate With Bother to Patients

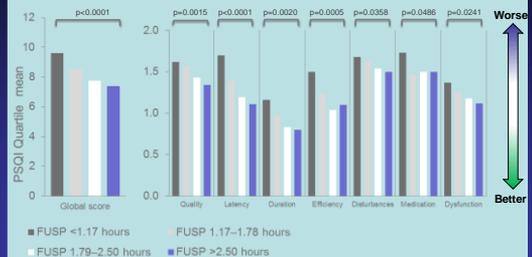
- Patients with nocturia who report high levels of bother are significantly more likely to have difficulty initiating sleep, difficulty returning to sleep, and greater morning fatigue

Sleep Characteristic	High Bother ^a	Low Bother ^a	P
Sleep duration, min	n = 8 380.0 ± 90.1	n = 12 425.0 ± 80.7	0.3
Time to initiate sleep, min	n = 11 47.7 ± 34.4	n = 13 23.5 ± 13.6	0.05
Time to return to sleep, min	n = 10 28.9 ± 16.1	n = 12 15.4 ± 9.6	0.03
Morning fatigue ^b	n = 11 3.3 ± 0.7	n = 13 2.5 ± 1.0	0.04

^aMean ± standard deviation.
^bSubjective morning fatigue and sleep ratings; higher scores = worse fatigue or sleep characteristics; scores range from 1 to 7.
Vaughan CP et al. *Int J Clin Pract*. 2012;66(4):369-373.

Short FUSP Associated with Worse Whole-night Sleep in Nocturia Patients

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



NOTE: p values indicate differences in the Pittsburgh Sleep Quality Index (PSQI) scores between patients with shortest and longest first uninterrupted sleep period (FUSP) (from Bliwise DL et al. *J Clin Sleep Med* 2015;11:53-55)

Nocturia Disrupts SWS (Stg 3/4): Analysis by Timing of First Void

Sleep Measure	First Void <i>During</i> First 2 Sleep Cycles	First Void <i>After</i> First 2 Sleep Cycles	P
Total sleep, min (± SD)	306 (54)	330 (47)	NS
Stg 1/2 sleep, min (± SD)	170 (41)	171 (33)	NS
Stg 3/4 sleep, min (± SD)	37 (24)	56 (22)	0.023
REM sleep, min (± SD)	95 (35)	103 (25)	NS

Toimisto K et al. *Neurosci Lett*. 2012;31:982-983.
Toimisto K et al. *J Urol*. 2013;189:e557-e558.

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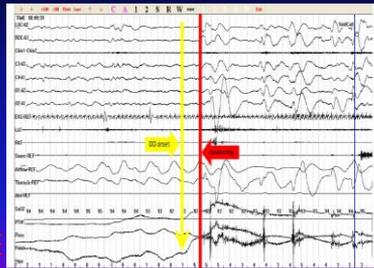
Chicken and Egg

- Do patients awaken because of the need to void? **OR...**
- Do patients awaken from other causes and then appreciate bladder sensations that prompt the bathroom trip?

Detrusor Overactivity (DO) during Sleep in Patients with Overactive Bladder (OAB) (confirmed via daytime cystometrogram)

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

DO defined as pressure of ≥ 2 cm H₂O for ≥ 1 sec



Pves: bladder pressure
Pabd: abdominal pressure
Pdet: detrusor pressure (Pves - Pabd)

(Krystal et al. *J Urol* 2010; 184: 623-8)

Bidirectionality in a Longitudinal Study of Nocturia and Poor Sleep

5-year follow up of the BACH Cohort

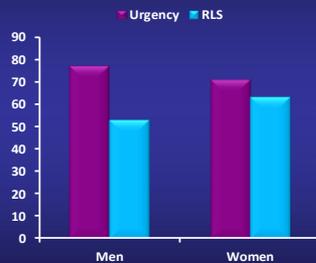
(Araujo et al. *J Urol* 2014; 191: 100-6)



Controlling for baseline sleep (or nocturia) and controlling for age, sex, race, SES, diabetes, heart disease, alcohol, physical Activity, smoking, anti-depressants, sedative/hypnotics, stimulants

Attributable Fraction (%) of Nocturia Cases Eliminated If Exposure was Eliminated (Finland Study): Restless Legs

Awakening Because of Urge vs. Voiding When Awake



Urgency: Danish Symptom Score

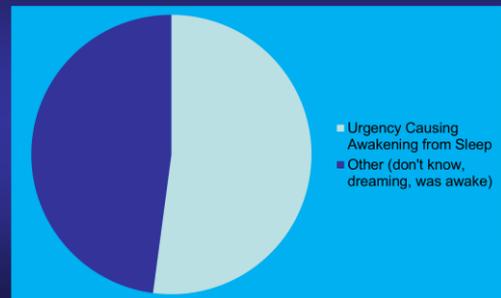
RLS (Restless Legs Syndrome): Nordic Sleep Questionnaire

Tikkinen et al. *Am J Epidemiol*. 2009;170: 361-368.

Nocturia in the Sleep Lab

Only half of the awakenings attributed to urinary urgency

(Pressman et al. *Arch Int Med* 1996; 156: 545-60)





Aging of the bladder, consequences for LUTS

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Ghent University Hospital
Belgium

Everaert Karel

Affiliations to disclose*:

Ferring, Medtronic, Allergan, Astellas : research grants, consultant, lecturer

* All financial ties (over the last year) that you may have with any business organization with respect to the subjects mentioned during your presentation.

Funding for speaker to attend:

- Self-funded
 Institution (non-industry) funded
 Sponsored by: *Astellas, Allergan*

Content

Introduction
 Physiopathology of aging of the bladder
 Prevalence of LUTS in older people
 Circadian rhythm bladder in older people
 Multifactorial LUTS in older people
 Discussion/conclusion

Introduction

Lower urinary tract symptoms (LUTS) show an increasing prevalence because of worldwide aging and population growth.

Most causes of LUTS seem to increase with age and multifactorial pathology is rather a fact than not.

Summation of events during life result in multiple deficits (bladder contractility, obstruction, sphincter lesion, urine production, sensation,...) and probably the number of deficits or the number of remaining systems determine if symptoms will appear

Gavrilov L et al 1991



Physiopathology of aging of the bladder

Physiopathology of aging of the bladder

Aging of the bladder itself : barely evidence, no truly longitudinal studies available

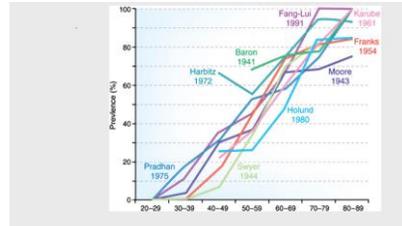
Mostly conclusions on cross sectional human or experimental animal studies

As today we can study LUTS in older people based on filling and emptying phase of the bladder and its outlet. This concept can be used to understand the consequences of aging related to the bladder and its outlet.



Prevalence of LUTS in older people

Prevalence of LUTS in older people: BPH



Prevalence of histological benign prostatic hyperplasia (BPH) by age group in nine autopsy series from around the world.¹

Roehrborn C, 2016

Prevalence of LUTS in older people: BPH

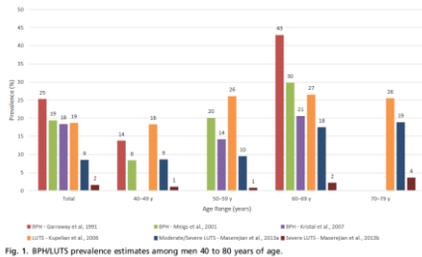


Fig. 1. BPH/LUTS prevalence estimates among men 40 to 80 years of age.

Egan K 2016

Prevalence of LUTS in older people: OAB

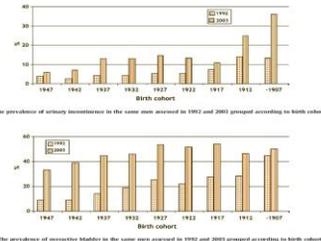
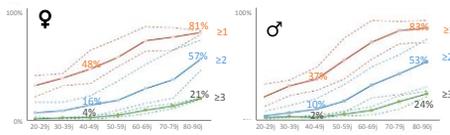


Fig. 1 - The prevalence of urinary incontinence in the same men as in Fig. 1 and 2003 grouped according to birth cohort.

Fig. 2 - The prevalence of overactive bladder in the same men as in Fig. 1 and 2003 grouped according to birth cohort.

Malmsten U et al 2010

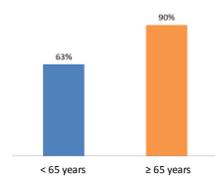
Prevalence of Nocturia in older people



Comu et al. European Urology 2012; 62:877-890

Prevalence of Nocturnal polyuria in older people

Nocturnal polyuria in patients with nocturia ≥ 2 increases with age (n=845)



Abrams P et al. NeuroUrol Urodyn 2004;23:466

Day (D-LUTS) and nighttime (N-LUTS) LUTS

The presence of a single nocturia episode is often regarded as a storage symptom. Therefore, we assume that the prevalence of filling symptoms is overestimated, especially in older populations in whom nocturia is a very common complaint. In older age 90% of the patients with nocturia have nocturnal polyuria.

For these reasons, we suggest separating daytime from night time symptoms and their bother in future research on LUTS.

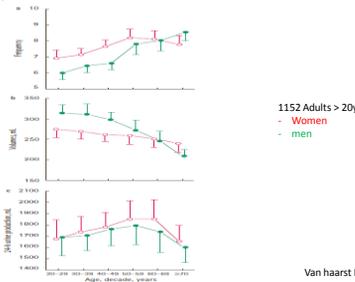
The first morning void should be included in the analysis of night time symptoms because the nocturnal polyuria / diuresis can give rise to LUTS while standing / waking up in the morning. These first morning void related LUTS have clearly a different cause than daytime LUTS.

No evidence for this statement but we suggest to try your history taking this way, and you will be amazed how much more complete your history will be without loss of time.



Circadian rhythm of bladder function in older people

Circadian rhythm of bladder function in older people



Van haastert E et al 2004

Circadian rhythm of bladder function in older people

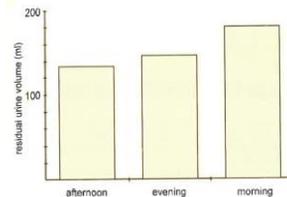
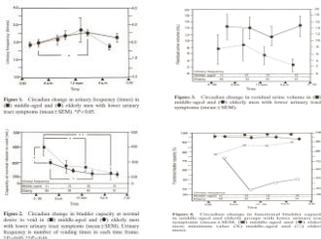


Fig. 3 Mean residual urine volumes in the afternoon, evening and early morning, averaged over all 14 patients and the 2 visits. Early morning residual urine is significantly larger than either of the other two

Griffiths D et al 1996

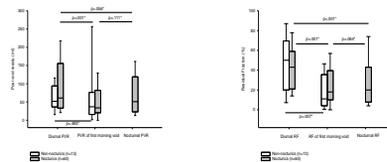
Circadian rhythm of bladder function in older people compared to middle aged men



Wakako Satoh et al 1999

Circadian rhythm of bladder function in older people

Real life study in 73 residents without and with nocturia (≥2 voids/night)
 Intact cognition, moderate daily life activities impairment, median 84 years [82-89]



PVR= post void residual, V= voided volume, RF = residual fraction = PVR / (PVR+V) x 100%
 *p-values are from Mann-Whitney U-test for skewed data

Decalf et al 2015-2016

Multifactorial Nocturia

	Number nocturia episodes			P-value
	0 (n=38)	1 (n=21)	≥2 (n=29)	
Mean functional bladder capacity (ml)	280 [133–663]	186* [61–438]	170** [74–483]	0.001****
Nocturnal urine production (ml)	385 [180–817]	392 [150–917]	759**** [237–1,567]	0.001****

Nocturia is multifactorial (bladder and kidney) in young and middle aged adults
The more frequent the nocturia the more combinations of NP and RBC are seen (p=0.020)

Goessaert et al. Neurourol and Urodyn 2014 Jun 18

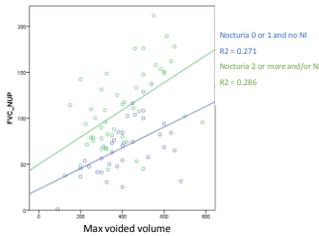
Multifactorial N-LUTS

“Denk droog or Think dry” is a project aiming to optimize the diagnosis of incontinence in older people. All included patients were evaluated with a battery of tests in a tertiary referral center. Interim analysis after including 92 patients:

	N= 92
Age (years)	73 (69-79)
M/F (%F)	13/79 (86)
BMI (kg/m ²)	27 (24-31)

47 out of 92 incontinent patients had N-LUTS (nocturia (2 or more) and/or nocturnal incontinence)

Multifactorial N-LUTS

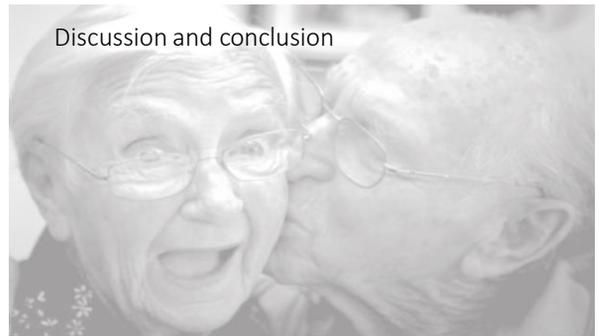


Multifactorial N-LUTS

No nocturnal incontinence and nocturia ≤1 versus nocturnal incontinence and/or nocturia ≥2				
	AUC	Cut-off	Sensitivity (%)	Specificity (%)
Nocturnal LUTS index				
NUP (leakage) / MUV	0.868	1.85	79	81
Nocturnal polyuria index (%)				
NUP/24 UP (leakage)	0.800	37	79	69

Multifactorial N-LUTS

	NPI>33 (n=67)	NPI<33 (n=21)	P-value	N-Luts>1.85 (n=44)	N-Luts<1.85 (n=39)	P-value
Age	74 (69-79)	72 (69-75)	0.130	74 (69-80)	73 (69-77)	0.185
Male/female (%female)	11/59 (84)	2/20 (91)	0.723	8/36 (82)	3/36 (92)	0.204
Frequency volume chart						
Nocturia ≥1	57 (85)	17 (81)	0.676	43 (98)	31 (80)	0.011
Nocturia ≥2	36 (54)	6 (29)	0.209	36 (82)	6 (15)	<0.001
Nocturnal incontinence	31 (46)	5 (24)	0.07	24 (55)	12 (31)	0.045
Nocturnal incontinence or nocturia ≥2	40 (60)	7 (33)	0.036	37 (84)	10 (26)	<0.001
Maximum voided volume <250ml	11 (16)	2 (10)	0.439	10 (23)	3 (8)	0.075



Discussion and conclusion

Discussion and conclusion

N-LUTS and split bother

Clinical practice: just try your history taking this way, you will be amazed how much more complete it will be without loss of time.

Include first morning void as symptom is related to nocturnal diuresis

Need for clinical validation

Discussion and conclusion

N-LUTS in older people :

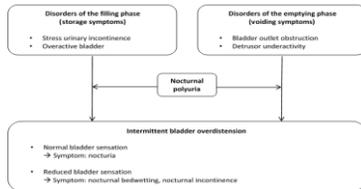
Highly prevalent
Rather multifactorial LUTS
Think bladder and kidney, it is rarely not the combination

Residual urine and residual fraction are worse during the day, no need for nocturnal observations

We suggest the N-LUTS-index with a cutoff of 1.85: a high sensitivity and specificity and the index correlates with symptoms

Discussion and conclusion

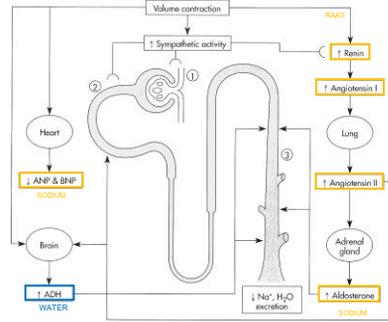
Figure 3: Novel concepts for future research on the underlying pathophysiology of lower urinary tract symptoms in older patients.



Aging of the kidney - consequences for LUTS

Aging of the kidney – consequences for LUTS

Aging of the kidney - consequences for LUTS



Aging of the kidney - consequences for LUTS

Nocturnal polyuria in adults can be based on:

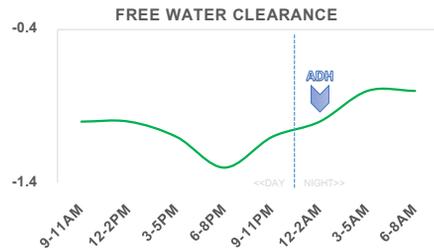
↓ Water diuresis – ADH deficiency

>> free water clearance

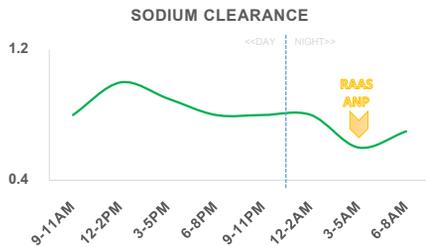
↓ Sodium diuresis – RAAS / ANP deficiency

>> sodium clearance

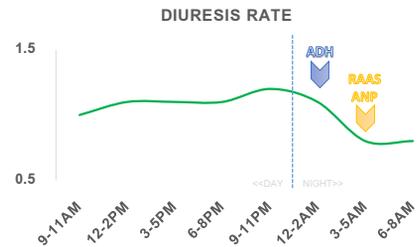
Aging of the kidney - consequences for LUTS



Aging of the kidney - consequences for LUTS



Aging of the kidney - consequences for LUTS



ADH in older people:

- ↓ Blunting of nocturnal phase of ADH secretion
- ↓ Potential gender-related difference: 2x higher plasma ADH concentration in older men compared to women (controversial)

ADH in older people:

- ↓ Increased osmoreceptor sensitivity > greater response of ADH response to stimuli
- ↓ Impaired baroreceptor function > less to no stimulation of ADH release by blood pressure reduction or upright position

Water diuresis in older people:

- ↓ Decline in renal concentrating capacity
- ↓ Not due to inadequate response of ADH to stimulus of water deprivation but to impaired renal tubular response to ADH

RAAS in older people:

- ↓ Lower levels of plasma renin activity and aldosterone in supine position
- ↓ Decreased conversion of inactive to active renin > decreased aldosterone production
- ↓ Age does not affect the ability of the adrenal gland to synthesize and secrete aldosterone nor renal tubular responsiveness to aldosterone

ANP in older people:

- ↓ Increases with aging
 - ↓ Stimuli which can increase intracardiac pressure result in a greater increase of plasma ANP
 - ↓ Renal response to ANP may also be greater
- > *Direct natriuretic effect*

ANP in older people:

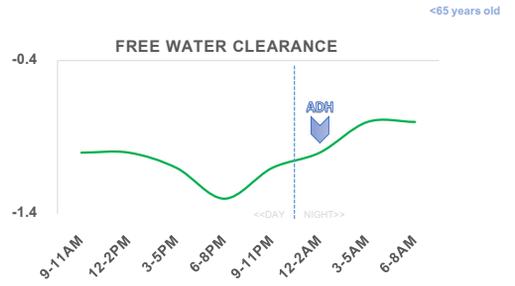
- ↓ High levels of ANP suppress renin secretion and activity and angiotensin II
 - ↓ High levels of ANP suppress aldosterone secretion directly
- > *Indirect natriuretic effect*

Aging of the kidney - consequences for LUTS

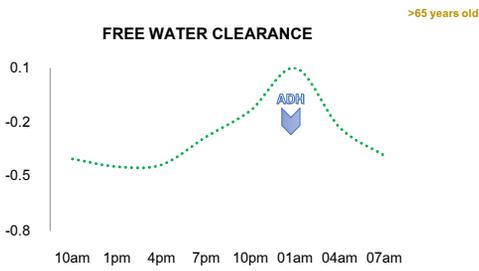
Sodium diuresis in older people:

- ↓ Impaired ability of the kidney to retain sodium
- ↓ exaggerated sodium excretion after acute water load with expansion of intravascular volume, in patients with hypertension

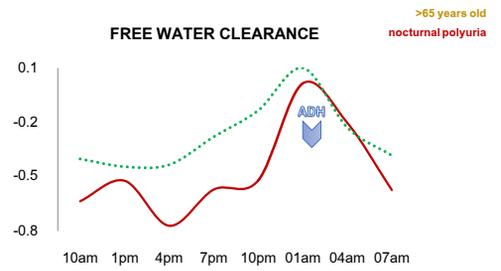
Aging of the kidney - consequences for LUTS



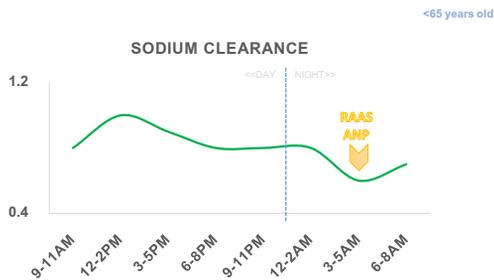
Aging of the kidney - consequences for LUTS



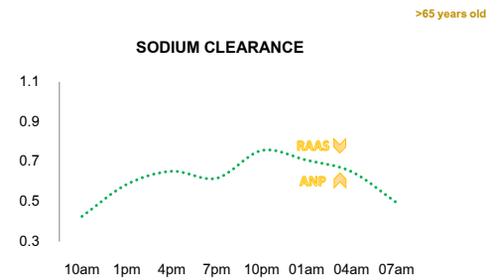
Aging of the kidney - consequences for LUTS



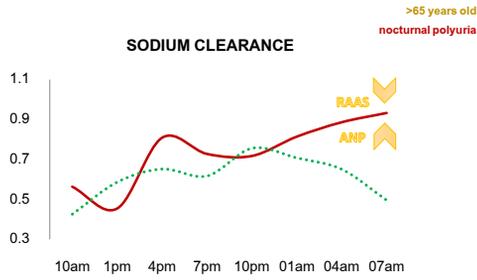
Aging of the kidney - consequences for LUTS



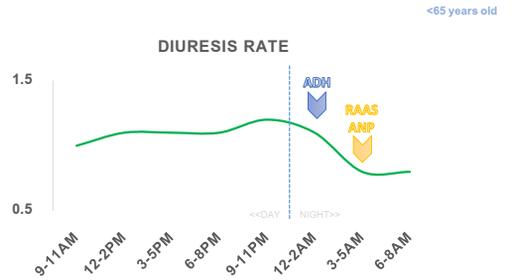
Aging of the kidney - consequences for LUTS



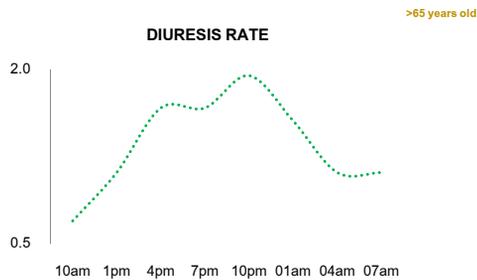
Aging of the kidney - consequences for LUTS



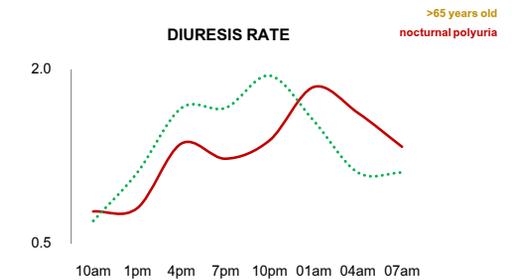
Aging of the kidney - consequences for LUTS



Aging of the kidney - consequences for LUTS



Aging of the kidney - consequences for LUTS



Aging of the kidney - consequences for LUTS

Nocturnal polyuria in older people: if resulting in nocturnal LUTS (nocturia/enuresis)

- ┆ Careful history, physical examination and routine laboratory tests
- ┆ Frequency volume chart
- ┆ Renal function profile (for example day/night collection)

Aging of the kidney - consequences for LUTS

Nocturnal polyuria in older people:

Edema	Impaired renal concentrating capacity	Osmotic diuresis	Excessive fluid consumption	Urinary frequency
Heart failure	Diabetes insipidus	Diabetes mellitus	Polydipsia	Urinary tract infection
Liver failure	Hypercalcemia			Chronic interstitial cystitis
Venous insufficiency	Hypokalemia			
Renal disease	Renal insufficiency			
hypoalbuminemia				

Nocturnal polyuria in older people: if resulting in nocturnal LUTS (nocturia/enuresis)

Treatment	Dose
DDAVP (desmopressin)	0,1-0,4mg (oral), 60µg (melt)
Tricyclic antidepressant (imipramine)	1mg/kg BW at 8PM
Furosemide	40mg 6h orally before bedtime
Behavioral interventions	- Decreased evening fluid intake - Avoidance of alcohol and caffeine - Prompted voiding schedule

Aging of the kidney can lead to nocturnal polyuria, which in turn can lead to (bothersome) nocturnal LUTS, such as nocturia and/or nocturnal incontinence

Diagnostic approach consists of medical history, clinical examination, frequency-volume chart and if needed, renal function profile

Treatment depends on the predominant pathophysiologic mechanism (ADH or RAAS)

Nocturnal polyuria in older people: pathophysiology and clinical implications. Miller M. JAGS. 2000; 48:1321-1329.

Diagnosing pathophysiologic mechanisms of nocturnal polyuria. Goessaert et al. Eur Urol. 2015; 67(2): 283-288.

THANK YOU FOR YOUR ATTENTION