W10: Causes and Co-morbidities of Nocturia

Workshop Chair: An-Sofie Goessaert, Belgium
12 September 2017 09:00 - 10:30

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<th>Topic</th>
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<td>09:00</td>
<td>09:20</td>
<td>Phenotyping Nocturia – Judge a Book by its Cover?</td>
<td>An-Sofie Goessaert</td>
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<td>09:40</td>
<td>Sleep and Nocturia – Central Mechanisms into Business?</td>
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<td>Bladder and Kidney – Making the Bladder Gladder or Lowering the Water Levels?</td>
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<td>Questionnaire on Nocturia – to TANGO or Not to TANGO?</td>
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<td>Questions</td>
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**Speaker Powerpoint Slides**

Please note that where authorised by the speaker all PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website [www.ics.org/2017/programme](http://www.ics.org/2017/programme). Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

**Aims of Workshop**

Nocturia is a highly prevalent condition affecting both men and women of all ages. It is no longer a problem merely attributed to overactive bladder or benign prostate hyperplasia. There can be an impairment in one or more factors of the triad brain-kidney-bladder but also other factors such as obesity, hypertension, peripheral edema, sleep disturbance, depression, medication, etc can play a role.

The objective of this workshop is to provide an overview on causes and co-morbidities of nocturia and how to identify them.

**Learning Objectives**

This workshop should allow the attendant to know the answers to following questions:

1. What physical features can help you to identify possible causes or co-morbidities of nocturia?
2. How does sleep affect nocturia and how does nocturia affect sleep?
3. What not to miss in the work-up of nocturia?

**Learning Outcomes**

After this course the attendant should be aware of the most evident causes and co-morbidities of nocturia and he/she should be able to identify them in patients in clinical practice.

**Target Audience**

Urologists, Gynaecologists, Geriatricians and Nurses

**Advanced/Basic**

Basic

1. **Speaker 1: Phenotyping nocturia – judge a book by its cover?** - An-Sofie Goessaert, urology trainee, Ghent University Hospital Belgium

Nocturia is a complaint which seems to be invisible for anyone else but for the patient and for his or her bed partner, unless the patient is asked about it or mentions it him or herself. However, there are certain physical uitingen that can help you understand or suspect the underlying pathophysiology. It is obvious that you need a full medical history to get a direction on the pathophysiology, for example, the presence of kidney disease, diabetes, depression, etc., conditions that are also not necessarily clinically visible. But looking at your patient and examining your patient is as important for a good diagnostic workout.

What to do on a first consultation?

- Blood pressure > arterial hypertension?
- Weight assessment / waist circumference > obesity?
- Cardiovascular examination (shortness of breath, chronic coughing or wheezing, peripheral edema, confusion or impaired thinking, high heart rate) > cardiac failure?
- Digital rectal examination > benign prostate hypertrophy?

A few examples:

- Obesity:
Obesity is a multifactorial disease with adverse health consequences, such as cardiovascular disease, type 2 diabetes, hypertension, sleep apnea, and possibly depression, which may result independently in nocturia. Lifestyle-related factors may also be more common among the obese. It is possible that nocturia in some obese persons is related to excessive nighttime eating or drinking, especially consumption of alcohol. This can cause nocturnal polyuria, leading to an increased nighttime voiding frequency.¹

- **Arterial hypertension:**
The link between hypertension and NP can be explained by its stimulating effect on glomerular filtration, inhibiting effect on the ADH and its effect on the pressure-natriuresis relation in the kidney. This is a feedback system to control blood pressure, whereby increases in renal perfusion pressure lead to a decrease in sodium reabsorption and more sodium excretion.²⁻⁴

Healthy adults show a nighttime drop in blood pressure of at least 10%, however this is lacking in people with non-dipping hypertension, who show an enhanced sodium excretion.⁵ Such non-dipping hypertension has been linked to physical activity during nighttime, which supports the finding that non-dipping hypertension is more prevalent in patients who wake up to go to the toilet at night.²

- **Peripheral edema:**
Peripheral edema are common in patients with venous insufficiency, heart failure, hypertension and autonomic dysfunction. These patients typically accumulate fluid in their lower extremities while standing during daytime, but when they change to the supine position when going to sleep in the evening, this fluid is reabsorbed into the circulation. This present as a surplus of fluid to the circulatory system, which stimulates ANP and glomerular filtration and results in more nighttime urine production.⁵,⁶


2. **Speaker 2: Sleep and nocturia – central mechanisms into business?** – Karlien Dhondt, Ghent University Hospital Belgium

The aim of this talk is to demonstrate some interesting aspects on nocturia by focussing on sleep. More specifically, sleep fragmentation and dopaminergic neurotransmission. Before going into detail, we start with a few aspects about sleep physiology first.

When studying sleep, one has to bear in mind that sleep physiology is influenced by two important factors, which are known as the circadian rhythm, and the sleep homeostasis. In this context, there is a range of neurotransmitters that are or sleep or wake promoting. The circadian rhythm is the hour glass in which we can sleep, it is independent from the previous nights. On the contrary, the sleep homeostasis is based on how we slept the nights before and reflects sleep pressure that has been built up during the day.

Research of sleep and uro/nephrology in our Univeristy Center, started in pediatrics. We explored sleep by performing a full polysomnography in children with therapy resistant or dependent nocturnal enuresis (NE). The observations were tantalizing: we found increased cortical arousals (sleep fragmentation) associated with periodic limb movements (PLMS). This was later confirmed in a case control study. Later, the study was repeated in a homogenous group of children with monosymptomatic NE, and the same observations were found. However, compared to the pilot study in which more children with reduced bladder capacity were included, the PLMS-index was significant higher in the latter group (1).

A population based epidemiological study from Finland comprising a systematic evaluation of factors associated with nocturia in adults reported a correlate between RLS (strongly associated with PLMS in adults) and nocturia (2). One might suspect a persistent common pathophysiological mechanism with: sleep fragmentation, PLMS, NE or nocturia.

The observation of PLMS is of interest. PLMS are a well described feature in sleep medicine, they are seen on a PSG and are periodic short movements of the legs (flexion in the ankel, hip, knee). The pathophysiology of PLMS is caused by a disturbed dopaminergic neurotransmission. However, the cause of dopamine depletion can be variable. In case of dopaminergic

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depletion, the effect on motor, sensory nerves and autonomic balance are hypothesized to be less inhibited. Moreover, dopamine has also an important role in the mictury center in the brain.

The second part is the role of sleep fragmentation. The amount of cortical arousals reflects sleep fragmentation and this is known to cause sleep deprivation. The autonomic nerve system with a higher sympathetic output (increased blood pressure, increased heart rhythm)

A good model for explaining how these factors might interact is Parkinson disease.

The final conclusion is that dopaminergic dysfunction might be an important mediating factor in some phenotypes of nocturia and NE. This will be further explored in the future.

(2) K. Tikkinen et al. Am J Epidemiol 2009

3. **Speaker 3: Bladder and kidney – making the bladder gladder or lowering the water levels?** – Philip Van Kerrebroeck, Professor of Urology, Maastricht University Medical Center, the Netherlands

The International Continence Society (ICS) defines nocturia as ‘the complaint that the individual has to wake at night one or more times to void...each void is preceded and followed by sleep.’ Patients experiencing <2 voids/night in general do not experience significant bother. However bother, as well as morbidity and mortality, will be significant with >2 voids/night. Nocturia is an underreported, underdiagnosed, and undertreated condition, with many patients believing it to be a natural consequence of aging. Nocturia is associated with multiple medical conditions, and conveys an increased mortality risk.

The treatment of nocturia advanced because of the understanding that it is a distinct clinical entity with a number of pathophysiologic causes. Nocturia may be sub classified into three categories, based on the causative mechanisms:

1. Reduced Voided Volume, a reduced capacity for the bladder to store urine, whether globally or only during sleep
2. Global (or 24 hour) Polyuria, an overabundant production of urine during the diurnal plus nocturnal periods, quantified as a volume of greater than 40 ml/kg in 24 hours
3. Nocturnal Polyuria (NP) overabundant production of urine only at night, with 24 hour urine output remaining within the normal range. NP is defined as nocturnal urine production of > 20 % of 24 hour output in younger adults (21–35) and > 33 % of 24 hour urine output in older adults

Traditionally nocturia was believed to be primarily the result of either overactive bladder (OAB) or benign prostatic hyperplasia (BPH). This was seemingly confirmed in the 1990s when the increase in prostate outlet reducing procedures occurred with a concomitant decline in nocturia. However, NP is now recognized as a major etiology of nocturia. Data obtained from cohorts of the NOCTUPUS and US/CANADA trials, indicated that the majority of nocturia patients were found to have nocturnal polyuria. The NOCTUPUS trials were three randomized controlled trials studying the effect of desmopressin tablet formulation on subjects with nocturia. Upon enrollment, subjects completed 7-day frequency volume charts (FVC) recording the volume and time of their voids. Examining this data, it was found that the NP prevalence in records included in analysis (641/846) was 76 %. If the FVCs discarded from analysis due to incompleteness were assumed not have nighttime polyuria, the proportion with NP was 64 % (641/1003). Similarly, the United States/Canada trial was a phase III randomized double blind trial to evaluate efficacy of the treatment of nocturia with desmopressin Melt. This study indicated a NP prevalence in complete records (806/917) of 88 %. If the FVCs discarded from analysis assumed not have nocturnal polyuria, the proportion with NP was 57 % (806/1,412). Subgroup analysis showed increasing prevalence of NP with age, and a slightly higher occurrence in men compared to women. In the young (<65), NP affected 66 % (325/493) in the NOCTUPUS trial and 83 % (390/468) in the US/Canada trial, while the prevalence in patients >65 years old was 90 % (316/353) in the NOCTUPUS trial and 93 % (416/449) in the US/Canada Trial.

4. **Speaker 4: Questionnaire on nocturia – to TANGO or not to TANGO?** – Wendy Bower, Department of Medicine and Community Care, Melbourne Health and Department of Medicine, Dentistry and Health Science the University of Melbourne.
The causal pathway of nocturia is multi-factorial and differs between patients. There are significant interactions between voiding at night and markers of poor health. A comprehensive multidisciplinary assessment metric that identifies co-existing causes of nocturia beyond the urinary tract was warranted.

This presentation describes the development and use of TANGO a screening tool to target the aetiology of nocturia and guide outcomes. A Cochrane-style review identified variables carrying a significant risk in relation to nocturia severity. Discriminating items in robust tools measuring co-morbidities were collected; pertinent clinical measures were added. After removal of item duplication, the self-completed 57 item questionnaire (TANGO) was piloted (n=22), modified, then completed by 300 patients ≥40 years of age with nocturia who were presenting to the sleep disorder, diabetes, rehabilitation, continence or falls and balance clinics, or in-patients of aged care or rehabilitation wards.

Endorsement of items was analysed; those with a high floor effect (i.e. >70% of responses “never” or its equivalent), an inter-relationship >0.8 (i.e. redundant) or >50% missing data were removed. Measures included in their entirety were subject to exploratory factor analysis to identify items with multiple loadings. Psychometric properties were used to reduce the initial TANGO metric to a short form.

Non-urinary tract factors identified on the causal pathway of nocturia clustered into the domains of mental health, cardiovascular, metabolic, sleep and inflammatory conditions and medication. List 1 shows the metrics from which TANGO items were drawn. A medical history checklist was added to the questionnaire along with a clinician-completed section of physical measures (height; weight; neck, waist and hip circumferences; heart rate; blood pressure; TUG Test).

List1: Metrics from which TANGO items were sourced:
- Overactive Bladder Symptom Score
- International Prostate Symptom Score
- Epworth Sleepiness Scale
- Pittsburg Sleep Quality Index
- Insomnia Severity Index
- STOPBang Obstructive Sleep Apnea Questionnaire
- AUSDRISK Diabetes Risk Assessment Tool
- Hospital Anxiety and Depression Scale
- EQ-5D-3L Health Status Questionnaire
- SF-36 Health Status Questionnaire
- Brief Pain Inventory (Short Form)
- Psoriatic Arthritis Screening and Evaluation Questionnaire
- General Practitioner Cognitive Screening Test

The TANGO Short Form was developed from items significantly associated with high frequency nocturia. Patient self-completion required between 30 seconds and 2 minutes. Test-retest reliability of this new metric demonstrated substantial to excellent agreement (Kappa 0.6 to 0.79 and 0.8 to 1.00 respectively). This tool has the potential to improve evaluation across disciplines and medical specialties and to smooth inequalities associated with current care of patients with nocturia.
Causes & Co-morbidities of nocturia

12 September – ICS 2017

An-Sofie Goessaert

Country: Belgium
Profession: Urology trainee, postdoc researcher
Experience & Qualifications: MD, PhD. PhD on nocturia in adults, with special emphasis on pathogenesis of nocturnal polyuria and potential therapeutic strategies. Member of the International Nocturnal Polyuria Research Group.

Karlien Dhondt

Country: Belgium
Profession: Child & adolescent psychiatrist, somnologist
Experience & Qualifications: MD, PhD, Child & adolescent psychiatrist, somnologist. Main experience in the link between sleep disorders and nocturnal enuresis.

Philip Van Kerrebroeck

Country: The Netherlands
Profession: Professor of Urology at the University of Maastricht, and works as a urologist at the Maastricht University Medical Centre, the Netherlands.
Experience & Qualifications: MD, PhD, professor. Professor Van Kerrebroeck was for 8 years Chairman of the Standardisation Committee of the International Continence Society and was first author of the Standardisation report on Nocturia and is past Chairman of the ICI-ICS Nocturia Think Tank.

Wendy Bower

Country: Australia
Profession: continence physiotherapist, currently PI investigator of the TANGO study
Experience & Qualifications: MD, PhD, continence physiotherapist. Main experience in incontinence issues in children. She is the Principle Investigator of the TANGO study, an initiative targeting underlying aetiology to guide treatment in people with nocturia.

Workshop 10 – Causes & Co-morbidities of Nocturia

Start End Topic Speakers
09:00 09:20 Phenotyping Nocturia – Judge a Book by its Cover? An-Sofie Goessaert
09:20 09:40 Sleep and Nocturia – Central Mechanisms into Business? Karlien Dhondt
09:40 10:00 Bladder and Kidney – Making the Bladder Gladder or Lowering the Water Levels? Philip Van Kerrebroeck
10:00 10:20 Questionnaire on Nocturia – to TANGO or Not to TANGO? Wendy Bower
10:20 10:30 Questions All
Please complete the in-app evaluation in the workshop before leaving.

Step 1, open app and select programme by day

Step 2, locate workshop – Causes & Co-morbidities of Nocturia

Step 3, scroll to find evaluation button

Step 4, complete survey

• A shortened version of the handout has been provided on entrance to the hall

• A full handout for all workshops is available via the ICS website.

• Please silence all mobile phones

• Please refrain from taking video and pictures of the speakers and their slides. PDF versions of the slides (where approved) will be made available after the meeting via the ICS website.

**NEW FOR 2017**

Phenotyping nocturia

Judge a book by its cover?

An-Sofie Goessaert

Urology Dept., Ghent University Hospital, Belgium

Affiliations to disclose:

Nothing to declare

Funding for speaker to attend:

- Self-funded
- Institution (non-industry) funded
- Sponsored by:
To know

The obvious

• Age
• Gender
• Ethnicity

The background

• Risk of nocturia increases with age
• Men & women are equally affected
• Higher prevalence rates in blacks and Hispanics compared to Caucasians

To ask

The obvious

• Alcohol / drinking habits
• Medication
• Sleep

The background

• Suppression of ADH
• Increase of 24h urine production
• Increase of ANP (sleep apnea)
To see
The obvious
• Mobility
• Peripheral edema
• Obesity
The background
• Neurological damage
• Nocturnal fluid redistribution
• Cardiovascular disease, diabetes mellitus, hypertension, sleep apnea,…

To examine
The obvious
• Enlarged prostate
• Hyperglycemia
• Hypertension
The background
• Decreased bladder capacity
• Glucosuria
• Nocturnal natriuresis

To know
Age
Gender
ethnicity
Drinking habits
Medication
Medical history
Quality of sleep
Quality of life
Daily activities
Mobility
Peripheral edema
Obesity/cachexia
Skin colour
(see picture (very different))
Prostate
Urinary flow
Heart rate
Blood pressure
Blood sugar
Creatinine
Breathing
Reduced bladder capacity
24h polyuria
Nocturnal polyuria
OAB, BPH, bladder stone, bladder cancer
Diabetes, polydipsia
Impairment ADH, RAAS, ANP

To continue… frequency volume chart!
An-Sofie Goessaert – Urology Dept., Ghent University Hospital, Belgium

Questions?
an-sofie.goessaert@ugent.be
Urology Department, Ghent University Hospital, Belgium
NDPIA, INPRG

References
Sleep and Nocturia – are central mechanisms into business?

ICS Firenze
12th of September 2017
Karlien Dhondt, MD, PhD
Center for Neurophysiological Monitoring
Ghent University Hospital, Belgium

OUTLINE
• The impact of nocturia on sleep AND wakefulness
• The association of nocturia and sleep disorders
• Potential underlying central mechanisms in nocturia

• Reasons for nocturnal awakenings (US, by age group)

• Nocturia is an independent predictor of insomnia and of deterioration of sleep quality
• Difficulties falling back to sleep
• Fewer hours of sleep
• Nocturia is known to impair mental functioning, quality of life and productivity
• Patients with two or more voids a night have a higher risk of mortality

• First uninterrupted sleep period (FUSP) (Bliwise et al. Sleep Med 2015, J Clin Sleep Med 2015)

When comparing the average PSQI scores among those in the lowest compared to the highest quartile of time to first void, there was a statistically significant difference among all PSQI subscales.

Anconi-Israel et al. Sleep Med Rev, 2015
OUTLINE

• The impact of nocturia on sleep AND wakefulness
• The association of nocturia and sleep disorders
  • PLMS in sleep
  • OSAS
• Potential underlying central mechanisms in nocturia

I. Obstructive sleep apnea and nocturia

- Decreased nocturnal plasma renin an aldosterone secretion
- Increase in atrial natriuretic peptide (severe cases)
  • Nocturnal natriuresis
  • Increased diuresis
- Treatment with C-pap
  • Reverses effects of decreased plasma renin/aldosterone secretion
  • Normaking sodium output
  • Normalizing nocturnal diuresis
- Increase in sleep fragmentation
  • Increase in autonomic arousal
  • Sympathetic coarcture

II. Nocturnal enuresis in childhood and sleep: the presence of Periodic limb movements in sleep (PLMS)

Epidemiological study

- Strong association with RLS symptoms and PLMS findings on PSG

Restless leg syndrome (RLS) and PLMS?

- movement disorder: PLMS-index (per hour of sleep)>5
  - Causes sleep fragmentation
  - Cortical arousal / Autonomic arousal

- dopaminergic neurotransmission hypothesis:
  - At least, PLMS are partially under dopaminergic control
  - Pharmacological trials with DA agonists reduce PLMS
  - Neuro-imaging studies
  - Decrease regulation of TH level binding to potassium/multide nucleus
  - SPECT D2 receptor binding impaired throughout the striatal brain region

- But:
  - no differences in dopamine/metabolites concentration in CSF
  - no differences in dopamine transporter (DPICT)

OUTLINE

• The impact of nocturia on sleep AND wakefulness
• The association of nocturia and sleep disorders
• Potential underlying central mechanisms in nocturia
Dopaminergic neurotransmission

- Two types of receptors: D1 like (D1, D5), D2 like (D2, D3, D4)
  - D1 receptors are more abundant than D2 receptors in neocortical areas, particularly in prefrontal regions
  - Cortical D1 receptor system plays a key role in executive functioning, working memory, attention, and inhibition, which depends on frontal lobe integrity

- Projections:
  - From the spinal cord perspective (A)
  - Central brain regions (B)

A/ SPINAL CORD PERSPECTIVE

- PLMS
  - The role of dopaminergic neurotransmission
    - From the spinal cord perspective (D2 receptor)
    - Motor inhibition
    - Sensory inhibition
    - Inhibits sympathetic activity

B/ CENTRAL DOPAMINERGIC SYSTEM

- D1, D2 receptor
  - D1 inhibits micturition reflex
  - D2 relaxes urethral sphincter

- Animal pharmacological studies (cats)
  - Increasing DA during bladder filling phase
  - DA control bladder function
  - D1 antagonist: bladder hyperactivity
  - D2 antagonist: no effect on urethral sphincter

Causes of dopaminergic hypofunction?

- Genetics
  - HTRD9 polymorphism
  - Iron storage
- Circadian disorder (hypothalamus)
- Sleep deprivation (animal studies): decrease of tyrosine hydroxylase
- Aging; loss of dopaminergic neurotransmission
  - Human molecular imaging studies have consistently found an age-related decrease of D2 receptor markers in the magnitude of 5–10% per decade, starting in early adulthood
  - Loss of D1 receptor densities in the striatum of around 8% per decade

Dopamine receptor subtypes and their roles in regulation of BP

The solid lines indicate the interaction based on direct evidence, whereas the broken lines shows an interaction based on indirect evidence.
• Nocturia and age
• PLMS and age

Allen et al. JAMA 2005
Age distribution and prevalence

• PLMS

Age distribution of the survey population compared with international norms.

Prevalence of RLS suffers by age and sex.

Age distribution of the group of RLS sufferers compared with the remainder of the survey population.

BTBD9 polymorphism

Spinal cord: decreased sensory/motor inhibition; PLMS
Spinal cord: increased sympathetic outflow

Central: decreased inhibition micturition reflex; bladder hyperactivity

Dopamine depletion

Sleep fragmentation/sleep deprivation

Conclusions

*SLEEP FRAGMENTATION/SLEEP DEPRIVATION
*INCREASED AUTONOMIC AROUSAL
*DOPAMINERGIC NEUROTRANSMISSION
*CIRCADIAN RHYTHM

NOCTURIA

28/09/2017

K. Dhondt
Nocturia is a multifactorial medical condition

Nocturnal polyuria
- Insufficient nocturnal sleep
- Sleep disorders
- Reduced bladder capacity
- Inadequate fluid intake

Global polyuria
- Diabetes mellitus/insipidus
- Primary polydipsia
- Medication, excessive fluid intake

Sleep disorders
- Primary or secondary sleep disorders
- Neurologic conditions, psychiatric disorders, chronic pain, medication, alcohol

Reduced bladder capacity
- Benign prostatic hyperplasia (BPH), neurogenic bladder, idiopathic nocturnal detrusor overactivity, other urological conditions/disorders/malignancies, anxiety disorders, medication (e.g. beta blockers)

Nocturia is primarily caused by nocturnal polyuria

Nocturia in women often attributed to overactive bladder (OAB)

What causes nocturia in women?

Overactive bladder diagnosis does not exclude nocturnal polyuria
- In EPIC, \(12.8\%\) of women responders had OAB and amongst women with OAB, \(74\%\) had nocturia
- Overall, about \(62\%\) of patients with OAB + nocturia have nocturnal polyuria (NP)
- Rate of NP in women with OAB + nocturia increases with age
- Prevalence aged 65–74=0.86 [95% CI: 0.62–1.00]

62% of patients diagnosed with OAB and nocturia have nocturnal polyuria
Nocturnal polyuria is inadequately treated in OAB patients on solifenacin monotherapy

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

Increase in FUSP with desmopressin Melt (25 µg) in women over 3 months’ nightly administration

What causes nocturia in men?
Many factors lead to nocturia, although it is often (mis)attributed to prostate problems in men

Thinking beyond the prostate
• Nocturia in men traditionally regarded as due to detrusor overactivity or bladder outlet obstruction (BOO) – caused by BPO
• However, 83% of male patients with nocturia have nocturnal polyuria (NP)

Causes of male nocturia (total n=41)

<table>
<thead>
<tr>
<th>Causes of male nocturia (total n=41)</th>
<th>Patients (%)</th>
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</thead>
<tbody>
<tr>
<td>Single isolated causes</td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>8 (19.5%)</td>
</tr>
<tr>
<td>Small nocturnal bladder capacity</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>BOO</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Sleep apnoea syndrome</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diverse combinations</td>
<td></td>
</tr>
<tr>
<td>NP + small nocturnal bladder capacity</td>
<td>6 (14.6%)</td>
</tr>
<tr>
<td>NP + BOO</td>
<td>8 (19.5%)</td>
</tr>
<tr>
<td>Small nocturnal bladder capacity + BOO</td>
<td>4 (9.7%)</td>
</tr>
<tr>
<td>Triple combinations</td>
<td></td>
</tr>
<tr>
<td>NP + small nocturnal bladder capacity + BOO</td>
<td>6 (14.6%)</td>
</tr>
<tr>
<td>NP + small nocturnal bladder capacity + sleep apnoea syndrome</td>
<td>2 (4.8%)</td>
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Are classical BPO treatments good enough?
• Various methods of treating BPO – based on assumption that all symptoms caused by prostate problems
  – α-adrenoceptor antagonists
  – 5a-reductase inhibitors
  – TURP
  – Phytotherapy
  – Combination therapy
• These can be effective for some LUTS, but nocturia – rated the most bothersome of LUTS – may not be significantly improved

TURP has limited effect on nocturia
• 118/138 (85.5%) patients with BPO had nocturia before TURP
• After treatment, 91 of these (77.1%) still reported nocturia
• Improvement in nocturia score (1.0) significantly inferior to improvements for all other IPSS symptoms

<table>
<thead>
<tr>
<th>Patients scoring ≥2 score before TURP</th>
<th>Patients scoring ≥2 score after TURP</th>
<th>Rate of response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary frequency</td>
<td>102</td>
<td>77%</td>
</tr>
<tr>
<td>Voiding frequency</td>
<td>116</td>
<td>63%</td>
</tr>
<tr>
<td>Interurgency</td>
<td>101</td>
<td>33%</td>
</tr>
<tr>
<td>Urgency</td>
<td>103</td>
<td>70%</td>
</tr>
<tr>
<td>Weak stream</td>
<td>122</td>
<td>35%</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>84</td>
<td>18%</td>
</tr>
<tr>
<td>dribbles</td>
<td>111</td>
<td>10%</td>
</tr>
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TURP not the answer – are other mechanisms involved?
Tamsulosin OCAS not significantly better than placebo in reducing nocturnal voids

- 8-week study, n=117
- Some improvements in overall IPSS scores BUT
  - Mean reduction in number of nocturnal voids not significantly greater with tamsulosin OCAS than placebo (p=0.10)
  - Increase in duration of undisturbed sleep not significantly greater with tamsulosin OCAS than placebo (p=0.20)

Up to 95% of BPE patients have NP and nocturia resistant to α₁-blocker therapy

- 55/58 patients (95%) with LUTS suggestive of BPE found to have NP
- Of these, 20 received α₁-blocker therapy for 6 weeks
  - NP unchanged in 75%
  - No significant difference in mean nocturnal urine production before and during therapy

NP often underlies failure of α₁-blocker treatment for nocturia

- Of 41 patients with nocturia which was not responsive to α₁-blocker treatment, 85.4% found to have nocturnal polyuria
- Treatment specifically for nocturnal polyuria may improve nocturia

For once ...

... men aren't so different from women

They may benefit similarly from desmopressin treatment for nocturia!

Increase in FUSP with desmopressin Melt (50 µg) in men over 3 months' nightly administration

- Combination therapy may also be used for patients with nocturnal polyuria

  - Combination therapy should also take NP into account to alleviate nocturia
  - Patients may have:
    - BPO + NP
    - OAB + NP
    - BPO + OAB + NP
  - Therefore:
    - Antimuscarinic + α₁-blocker + desmopressin
      - Clinical studies to evaluate benefits of combination therapy are warranted

Combination therapy may also be used for patients with nocturnal polyuria

- Combination therapy should also take NP into account to alleviate nocturia
- Patients may have:
  - BPO + NP
  - OAB + NP
  - BPO + OAB + NP
- Therefore:
  - Antimuscarinic + α₁-blocker + desmopressin
    - May be required for successful nocturia treatment

NP: nocturnal polyuria; BPO: benign prostatic obstruction; OAB: overactive bladder
Nocturia needs to be treated according to its causes

- If a patient has nocturia and diagnosis of OAB or BPO, they may ALSO have NP
- If NP present, consider combination therapy:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Desmopressin</th>
<th>Anticholinergic</th>
<th>α₁-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAB</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>BPO</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>NP + OAB</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NP + BPO</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>OAB + BPO</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>NP + OAB + BPO</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Conclusions

Think on the bladder and the kidneys!

- >80% of patients with nocturia have nocturnal polyuria (NP)
- NP comorbid with BPO and/or OAB must be addressed
- desmopressin successfully treats nocturia caused by NP
- combination therapy (desmopressin + anticholinergics + α₁-blockers) is feasible to improve nocturia in patients with BPO and/or OAB with NP

www.europeanurology.com/nocturia
Development of TANGO, a screening tool to identify co-existing causes of Nocturia

A/Prof Wendy Bower FACP
Department of Medicine and Community Care, Melbourne Health
Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne

Affiliations to disclose†:
Ferring Pharmaceuticals

Funding for speaker to attend:
☐ Self-funded
☐ Institution (non-industry) funded
☒ Sponsored by: Ferring

Targeting Aetiology of Nocturia
Guides Outcomes

AIM: To develop a brief patient-completed screening tool to capture all-causes of nocturia

To be used in conjunction with
- Bladder diary
- Sleep measures
- Renal function tests
- Urine flow dynamics
- Patient-Reported Outcomes

TANGO Study Overview

Stage 1
- Literature Review: associations with nocturia ≥1/night

Stage 2
- Development of TANGO Long Form (LF)

Stage 3
- Development of the TANGO Short Form (SF)

Stage 4
- Psychometric Testing of the TANGO SF

Stage 5
- Implementation; Sustainability & Promotion

.. nocturia is outside the category of a storage lower urinary tract symptom (LUTS)

Gulur 2011; Drake 2015

Frequency, Urgency and Nocturia

“...no single variable affected 50% or more of men with nocturia

...in women multiple correlates predictive of night voiding”

Tikkinen 2010
Nocturia: Causal inter-relationships

Stage 2: Development of TANGO LF
- Variables having a significant risk association with nocturia of ≥ 1/night identified
- TANGO Long Form developed
  - 6 domains
  - 57 items, 10 clinical measures
  - self-completed questionnaire
- Sample size: N=250 patients
- ≥ 40 years age, nocturia ≥ 1/night,
- Recruited from Sleep / Continence / Falls and Balance / Rehabilitation services at RMH

Stage 3: Development of TANGO SF
- TANGO Long Form
  - Removal of demographic items designed only for descriptive analysis.
  - Removal of items with a high floor effect (>70% “never” or equivalent).
  - Removal of items of low clinical relevance/non-significant association.
  - Removal of redundant items showing high correlation with other items (>0.6).
- TANGO Short Form

TANGO: Methods
- Short form:
  - Retained items with:
    - Direct causal link to nocturia
    - High endorsement
    - Significant association with nocturia ≥ 2
    - Significant association with high bother
  - Items worded according to cut-off from analysis
  - Pilot of Short Form on 10 adults → modification of wording when problematic

The TANGO Short Form Screening Questionnaire
Stage 4: Psychometric Testing

Objective: To establish test-retest reliability of the TANGO SF

Setting & Participants: 40 rehabilitation inpatients

Inclusion Criteria:
- ≥ 40 years of age
- LOS ≥5 days from initial contact by RA

Exclusion Criteria:
- Conditions associated with atypical nocturia; urinary catheterisation; cognitive impairment or limited English that precluded questionnaire completion

Results: Substantial to perfect agreement (Kappa 0.61-1.0) demonstrated on 17 of the 22 TANGO SF items

TANGO RESULTS

- 23 item screening tool for aetiology of nocturia
- Identifies clinically relevant causes of nocturia
- Minimum time burden
  - Patient completed
- Easy to interpret visually
  - Interpretation guideline under development
- May direct treatment to underlying causes
  - Multi-modal therapy
  - Facilitate right treatment for right patient
GENDER-SPECIFIC VERSIONS

- Low testosterone levels in men and oestrogen in women is associated with ↑ water and salt diuresis
  - Sex hormones stimulate ANP → to reduce sodium load → ↑ GFR → ↑ urine production
- Testosterone deficiency is associated with:
  - Hot flushes and sweating
  - Insomnia or other sleep disturbances
  - Lower sleep efficiency: ↑ nocturnal awakenings, ↓ time in slow-wave sleep? Modulated via adiposity (Barrett-Connor 2008).
- Low testosterone levels frequently coexist with obstructive sleep apnoea (men)
  - Higher apnea-hypopnea index
  - More sleep time with O₂ saturation levels < 90%.
- Progesterone and estrogen deficiency
  - Difficulty staying asleep
  - Night sweats

GENDER-SPECIFIC VERSIONS

- TANGO-M extra variables
  - I wake from sleep because of night sweats / feeling hot
  - I wake from sleep because of feeling cold
  - I have not had my testosterone levels checked
- TANGO-F extra variables
  - I have difficulty staying asleep at night because of feeling hot / sweating
  - My last menstrual period was more than 1 year ago
  - I do not take oestrogen (tablets or patches)
TANGO Sensitivity

TANGO Domains

- CV-Metabolic
- Sleep
- Nocturia
- Wellbeing
- LUTS

TANGO Sensitivity

- Nocturia
- CV-Met
- Sleep
- LUTS
- Wellbeing

TANGO extension

- Develop Patient Reported Outcomes from
  - Sleep
  - LUTS
  - QoL
  - Consumer perspective
- Methodology: n=204 data sets that included
  - Pittsburgh Sleep Quality Index (PSQI),
  - ICIQ-Overactive Bladder
  - ICIQ-Female Lower Urinary Tract Symptoms Long Form
  - ICIQ-Male Lower Urinary Tract Symptoms Long Form
  - Nocturia Quality of Life
- Associations between episode frequency, bother and variables

Descriptive findings (N=1 vs N≥2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Light (n, %)</th>
<th>Night (n, %)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency [n, % daily]</td>
<td>21 (34%)</td>
<td>103 (73%)</td>
<td>5.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgency Incontinence [n, % daily]</td>
<td>12 (20%)</td>
<td>67 (44%)</td>
<td>3.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bother due to nocturia [n, % moderate bother]</td>
<td>17 (27%)</td>
<td>105 (74%)</td>
<td>7.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FUST in hrs (median, IQR)</td>
<td>4.1 (3.5-5.4)</td>
<td>2.5 (2.0-3.0)</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep Efficiency (median, IQR)</td>
<td>88 (76-97)</td>
<td>81 (64-94)</td>
<td>0.97</td>
<td>0.010</td>
</tr>
<tr>
<td>Overall sleep quality [n, % fairly to very bad]</td>
<td>15 (24%)</td>
<td>61 (43%)</td>
<td>2.37</td>
<td>0.012</td>
</tr>
<tr>
<td>Discomfort breathing whilst sleeping [n, % ≥ weekly]</td>
<td>2 (3%)</td>
<td>24 (17%)</td>
<td>5.94</td>
<td>0.018</td>
</tr>
<tr>
<td>Sleep Latency (≥30 mins)</td>
<td>18 (29%)</td>
<td>62 (44%)</td>
<td>1.91</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Establish “predictors” of nocturia:
- High frequency and nocturia-related bother

What matters to patients?
- on-line data collection of ranked bother of Nocturia

TANGO UNo

You Know. We Want to Understand.

UnO – We want to Know (n=500)

Link through our new TANGO Research Group Facebook page

https://www.surveymonkey.com/r/TANGO-OS
## Bother Reasons Ranked

<table>
<thead>
<tr>
<th>Reason</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trouble getting back to sleep</td>
<td>32</td>
<td>27.8</td>
</tr>
<tr>
<td>Disturbed/disrupted/broken sleep</td>
<td>31</td>
<td>27.0</td>
</tr>
<tr>
<td>Having to get out of bed</td>
<td>19</td>
<td>16.5</td>
</tr>
<tr>
<td>Fatigue/tiredness next day</td>
<td>12</td>
<td>10.4</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>6.0</td>
</tr>
<tr>
<td>Bother to others</td>
<td>6</td>
<td>5.2</td>
</tr>
<tr>
<td>No or very little bother</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Getting to the toilet on time</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Grumpy/bad mood next morning</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Bladder Discomfort</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Concern re: falling in dark</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Worry that condition will worsen</td>
<td>1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

## Current work

- Translation of TANGO
- Establishing concurrent validity
- Developing an in-patient version: TANGO-NOW

For more information:
wendy.bower@mh.org.au