

Clinical Focus Topic

NOCTURIA

BACKGROUND INFORMATION

As we all know, nocturia (*needing to wake through the night to void*) is a common complaint of men and women around the world. The incidence of nocturia is known to increase with age, with 50% of adults waking more than twice per night by age 80. As well as the obvious sleep deprivation, tiredness, and associated decreased quality of life, nocturia also dramatically increases the risk of falls in our elderly.

Personally, I find that I have many patients who state *"I can cope with going frequently during the day; I just want to be able to sleep through the night"*. So how do we treat this?? Well, the first step is to acknowledge that Nocturia isn't always simply due to high fluid intake, reduced bladder capacity or detrusor overactivity. In fact, Nocturia can often be a completely different mechanism to day frequency.

● ● ●

It is important to acknowledge that nocturia can often be
a completely different entity to day frequency

● ● ●

RESEARCH ABSTRACT

Title: Nocturia as a Manifestation of Systemic Disease
Authors: Gulur D, Meycha A and Drake M
Journal: British Journal of Urology, 2011. vol 107, no. 5, pp702-713

Nocturia is commonly referred to urologists, but the mechanisms underlying the problem, together with the appropriate clinical assessment and management, may lie outside the ordinary scope of the specialty. Some serious conditions may manifest nocturia as an early feature, often as a consequence of nocturnal polyuria (NP). Voiding frequency is influenced by rate of urine output, reservoir capacity of the bladder, lower urinary tract (LUT) sensation and psychological response.

Polyuria can result from polydipsia (increased thirst) or endocrine (hormonal) dysfunction. NP can result from endogenous fluid and solute shifts, cardiovascular and autonomic disease, obstructive sleep apnoea, and chronic kidney disease. Nocturia without polyuria occurs in the presence of LUT pathology, pelvic masses and sleep disturbance.

Drug intake can contribute to, or counteract, each of these problems. In assessing nocturia, clinicians need to consider an undiagnosed serious condition that may manifest nocturia as an early feature, or suboptimal management of a known condition. The frequency-volume chart is a key tool in categorizing the basis of

nocturia, identifying those patients with global polyuria or NP, for whom involvement of other specialties is often necessary for assessment and management.

Treatment should be directed at the cause of the problem, with a view to improving long-term health and health-related quality of life. Simple steps should be undertaken by all patients, including improvement of the sleep environment and behaviour modification. Evaluation of treatment response requires objective data to corroborate subjective impressions. Some mechanisms of nocturia do not reliably improve with treatment, leading to refractory symptoms.

The concept of “NOCTURIA” as a ‘SYMPTOM DIAGNOSIS’

In reality, most of our lower urinary tract “Diagnoses” are purely *symptom diagnoses*. ie they are not terms that give an indication of the pathophysiology underlying the symptom, they simply describe the symptoms themselves.

For example, even the ‘*diagnosis*’ of stress incontinence by ICS/IUGA as ‘the complaint of involuntary loss of urine on effort or physical exertion, or on sneezing or coughing’ (Haylen et al 2010) is only a term that classifies the patient’s incontinence based on symptoms. The definition gives no indication of the anatomical problem causing the incontinence. SUI can be due to fascial damage, pelvic floor muscle dysfunction, age related loss of urethral sphincter muscle fibres, sympathetic nerve damage preventing contraction of internal urethral sphincter during storage etc etc etc. It is for this reason, that in the area of SUI at least, it is now becoming common that stress incontinence be sub-classified into subtypes such as “Stress Incontinence with urethral hypermobility” versus “stress incontinence with intrinsic sphincter deficiency”.

As with Stress Incontinence, the diagnosis that someone has “Nocturia” is really only a reflection of the **symptom** of having to wake through the night to void. It does not give any information as to the true underlying cause of their nocturnal voiding. Not everyone’s nocturia is from the same cause. If we really want to effectively treat a person’s nocturia we must first be certain of why it is happening in their particular case.

The Nocturia Subtypes - Determining the Cause of Nocturia

It is now generally accepted that there are three very distinct sub-types of nocturia that each need to be treated very differently.

1. SUBTYPE ONE: Nocturia due to Generalised Polyuria
2. SUBTYPE TWO: Nocturia due to Nocturnal Polyuria
3. SUBTYPE THREE: Nocturia due to Reduced Bladder Capacity

In this newsletter I would like to focus on Subtype 2 (Nocturnal Polyuria), but let’s start with subtype 1.

1. Nocturia secondary to 24hour Polyuria >40mls urine prod per kg bodyweight

Polyuria refers to an overall excessive production of urine in 24hours, and is officially diagnosed if a person's urine production is more than 40mls per kg of bodyweight in 24hours.

ie 65kg person should produce no more than 2600mls of urine during a day and night

On average, a person will produce 30% of their urine 24hour output overnight. Obviously, having an overall increase in urine production (24hour polyuria) will result in a higher than normal night urine production. As a result, when assessing nocturia it is recommended to always start by ruling out generalized polyuria.

CALCULATING 24 HOUR URINE PRODUCTION:

TIME	Void Vol	
6.35am	250mls (1 st day)	Night Before Day Production
7.45am	220mls (2 nd day)	
10.30am	310mls (3 rd day)	
1.15pm	180mls (4 th day)	
3.00pm	260mls (5 th day)	
5.00pm	330ml (6 th day)	
7.30pm	140ml (7 th day)	
9.45pm	220ml (8 th day)	
12.10am	340mls (1 st night)	Night
3.30am	320ml (2 nd night)	
6.35am	310mls (1 st day)	Night 2 nd Day Production
7.50am	180mls	
10.00am	190mls	
12.45pm	210mls	
1.20pm	260mls	
3.40pm	390mls	
5.30pm	250mls	

Your patient completes a bladder diary for a day and a half. Important notes:

- She woke each day at **6.30am**.
- At night each day she went to sleep **10pm**.
- I have therefore highlighted her
 - **First am Voids** as **YELLOW**.
 - **Nocturia voids** **GREEN**.

When assessing for polyuria we need to calculate the urine produced through the day when awake and urine produced through the night when asleep.

NOTE The focus is on when the urine is produced not when it is voided.

- Calculation of Day urine production starts after the first AM void (because the first AM void is actually part of the urine produced over the prev night)
- Night urine production includes the nocturia voids AND the first AM void because all of that urine was produced overnight.

DAY URINE PRODUCTION = 220 + 310 + 180 + 260 + 330 + 140 + 220 = **1660mls**

NIGHT URINE PRODUCTION = 340 + 320 + 31 = **970mls**

24HOUR URINE PRODUCTION = **2630mls**

The above example has a 'reasonable' urine production level. Whilst it is possibly a little high for someone weighing 60kg (total should be 60 x 40 = 2400mls) it is not extremely excessive. All we would need to do for this person would be to simply reduce their fluid intake by 1-2 cups per day, particularly before bed.

However!!!!!! If this person was producing 4.2L of urine, their polyuria would require further investigation.

A Note on Diabetes Insipidus

Often people think that polyuria is simply due to the 'person drinks too much'. Whilst this may be true (some people are just in the habit of drinking too much), there can also be much more serious causes of high thirst and high urine production. One such example is diabetes insipidus. Contrary to popular belief, diabetes insipidus is a completely different condition to Diabetes Mellitus, and has nothing to do with blood sugar levels.

I have included a brief summary on Diabetes Insipidus that I have taken from the US National Library of Medicine webpage:

Reference for Information Below: <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001415/>

DIABETES INSIPIDUS

"Diabetes insipidus is a condition that occurs when the kidneys are unable to conserve water during their functioning of filtering blood. The amount of water conserved by the kidneys (and therefore prevented from leaving the body as urine) is primarily controlled by antidiuretic hormone (ADH). ADH is commonly known as vasopressin, and is a hormone produced in the hypothalamus, then stored / released by the pituitary gland.

There are two types of Diabetes Insipidus (DI):

- *Central* *DI caused by a lack of ADH production in the hypothalamus (ie brain problem)*
- *Nephrogenic:* *DI caused by a failure of the kidneys to respond to ADH (kidney problem)*

Central diabetes insipidus can be caused by damage to the hypothalamus or pituitary gland as a result of head injury, infection, loss of blood supply to the gland, surgery or tumors. There is also a form of central diabetes insipidus that runs in families.

Nephrogenic DI involves a defect in the parts of the kidneys that reabsorb water back into the bloodstream. It may occur as an inherited disorder, or by certain drugs (such as lithium, amphotericin B, and demeclocycline), high levels of calcium in the body (hypercalcemia) and kidney disease (such as polycystic kidney disease)

Symptoms

- *Excessive thirst - may be intense or uncontrollable, may involve a craving for ice water*
- *Excessive urine production*

Treatment

Central diabetes insipidus may be controlled with vasopressin (desmopressin, DDAVP), taken as either a nasal spray or tablets.

If nephrogenic DI is caused by medication (for example lithium), stopping the medication may help restore normal kidney function. However, after many years of lithium use the nephrogenic DI may be permanent.

Ultimately, hereditary nephrogenic DI and lithium-induced nephrogenic DI are managed by drinking enough fluids to match urine output.

A PAST PATIENT OF MINE....

I can distinctly remember a patient I had about 6-7 years ago. She presented with a very flat, unemotional affect. On taking her history she explained that she had very severe bipolar that was controlled by Lithium, but that there were two main side effects. First was that the high dose of lithium meant that she didn't really outwardly demonstrate any emotion, and second was that she was continuously thirsty. She explained that there was no way for her to drink less fluid whilst on lithium (she drank 5.5L per day and had urine output of about the same), and going off lithium was not an option because of her bipolar.

What was interesting was how realistic she was. I can still remember her saying to me..... "I know that you are not going to be able to reduce how often I need to pass urine, I would just like to be able to not wet myself".

This patient did have a nocturia of 4 voids per night (about every 1.5hours), but we didn't even try to change it. She had a nephrogenic diabetes insipidus as a side effect from her lithium and her bladder capacity was fine. Every volume was about 400mls. What we did try to change was the degree of urgency she felt at 400mls, and her ability to control her urine when she was woken at night and was trying to get to the toilet. We did standard pelvic floor strengthening, urge suppression strategies etc etc.

However..... there are causes for Nocturia that aren't related to an excessively high 24hour urine production....

2 Nocturia due to Nocturnal Polyuria - >33% of 24hr Urine Production at Night

Nocturnal polyuria is not related to the kidneys producing too much urine overall, rather, the problem is simply with 'when' in the day the kidneys are producing it. Whilst some people may have a normal 24hour urine production overall, they may produce a disproportionately large percentage of urine during sleeping hours. This is referred to as **NOCTURNAL POLYURIA** and is estimated to be the cause of **70% of patients with nocturia**.

CLINICAL NOTE

The first step in assessing nocturia is screening for systemic polyuria.

However...

After ruling out generalised polyuria (by calculating total urine production in 24hours), the next step should always be to calculate whether the ratio of day: night urine production is abnormal.

To determine whether a person has specific nocturnal polyuria we simply work out the nocturnal urine production as a percentage of the total 24hour urine production. The value should always be less than 33%.

Note - The body is naturally meant to increase arginine vasopressin (ADH) production overnight so as to reduce urine production. Young adults tend to have a very efficient ADH release meaning they often produce 20% or less of their 24hour urine production overnight. With age however, it is known that this circadian ADH production often reduces resulting in higher and higher volumes being produced. With that said, the nocturnal urine production should still never exceed 33% even in older adults.

TIME	Void Vol
6.35am	250mls (1 st day) ✘
7.45am	220mls (2 nd day)
10.30am	310mls (3 rd day)
1.15pm	180mls (4 th day)
3.00pm	260mls (5 th day)
5.00pm	330ml (6 th day)
7.30pm	140ml (7 th day)
9.45pm	220ml (8 th day)
12.10am	340mls (1 st night)
3.30am	320ml (2 nd night)
6.35am	310mls (1 st day)
7.50am	180mls
10.00am	190mls
12.45pm	210mls
1.20pm	260mls
3.40pm	390mls

✘
 Day Production
 Night
 ✘
 2nd Day Production

DAY URINE PRODUCTION = 220 + 310 + 180 + 260 + 330 + 140 + 220 = **1660mls**
NIGHT URINE PRODUCTION = 340 + 320 + 31 = **970mls**
24HOUR URINE PRODUCTION = **2630mls**

Remember:

NIGHT URINE PRODUCTION includes the nocturia volumes and the first AM volume as the urine was produced overnight.

Nocturnal Polyuria Index:

Calculation of the percentage of urine production that occurred overnight.

Noct urine production / Total 24hour urine production x 100

970mls / 2630mls = 36%

CAUSES OF NOCTURNAL POLYURIA

1. High Evening Fluid Intake

The most obvious cause of nocturnal polyuria is an excessively high fluid intake in the 2-3 hours before bed. In this situation the easy solution is to start limiting fluid intake after a certain time. However, there are other causes as well.

2. Evening Diuretic Medications

Some medications (eg some antihypertensives) are designed to increase urine output. Many older adults take these medications before going to bed, dramatically increasing their urine production rate over night. Encouraging patients to discuss with their GP about whether they can change the timing of the medications can be a simple way to reduce *nocturia* if nocturnal polyuria is the problem.

3. Lower Limb Fluid Pooling

Poor venous return can result in venous congestion and lower limb fluid pooling during the day. On reclining in bed at night the backflow of fluid to the kidneys can result in a sudden increase in urine production. Simple management can to simply raise feet for an hour or two before bed (eg whilst watching TV) and regularly perform ankle exercises. In more extreme circumstance, prescribing properly fitted compression stockings (eg JOBST 20-30mmHg) for patients to wear during the day to prevent the LL pooling can dramatically reduce nocturnal urine production.

4. Sleep Apnea

This is probably the most under-recognised cause of nocturia. The Atria of the heart have the ability to release a hormone called "Atrial Natriuretic Peptide". This hormone is released if the heart picks up an abnormally high blood pressure. Basically, ANP reduces blood pressure by acting on the kidneys to increase diuresis . Increasing diuresis means that more fluid from the blood is drawn across the membranes in the nephron and turned into urine, which reduces blood volume and ultimately reduces blood pressure.

So what happens in Sleep Apnea?

During episodes of obstructive sleep apnea the person attempts to inspire on a closed glottis.

- Attempted inspiration with a closed glottis → increased intrathoracic Pressure
- Increased pressure is sensed by baroreceptors in the atria and incorrectly interpreted as pressure from increase in blood pressure or possible pulmonary oedema.
- The atria respond by releasing ANP so as to increase water excretion and reduce blood pressure / pulmonary oedema.
- This ultimately results in an increased urine production purely at night during sleep , but not during the day in waking hours when the apnea episodes aren't occurring.

I have included some research abstracts for you on the following page.....

Title **Obstructive Sleep Apnea, Nocturia and Polyuria in Older Adults**
Authors Umlauf M, Chasens E, Greevy R, Arnold J, Burgio K and Phillion D
Journal Sleep, 2004 vol 27, no. 1, pp139-144

Thirty community-dwelling elders with a mean age=65.5, SD=8.4years and symptoms of nocturia and sleep disordered breathing, volunteered to participate.

Measurements:

1. Urine and blood specimens were analyzed for ANP and AVP content.
2. Apnea: defined as a decrease in airflow of \geq 90% for a minimum of 10 seconds.
3. Hypopnea: defined as 30% decrease in airflow and at least 3% decrease in SaO₂ for a minimum of 10 sec.
4. AHI: apnea-hypopnea index = the sum of apneas + hypopneas divided by hours of sleep.

Results:

The study found that 20/30 subjects who reported both nocturia and sleep disordered breathing had clinically diagnosable Obstructive Sleep Apnea on testing.

The study also found that whilst there was no correlation with Arginine Vasopressin, there was a strong correlation between a high apnea-hypopnea index, night-time urine production and Atrial Natriuretic Peptide excretion

Conclusion: In subjects with elevated AHI (>15), night time urine production and ANP excretion are elevated.

Title **Continuous Positive Airway Pressure Reduces nocturia in patients with obstructive sleep apnea**
Authors Margel D, Shochat T, Getzler O, Livne P and Pillar G
Journal Urology, 2006 vol 67, no. 5, 974-977

To examine whether treatment with continuous positive airway pressure (CPAP) reduces nocturia in patients with obstructive sleep apnea (OSA).

Methods

This prospective clinical study recruited patients referred to the Rambam Sleep Laboratory with suspected OSA. Only those with confirmed OSA after testing remained in the study and were treated with CPAP

Nocturia was assessed at four time points:

- Baseline (1 week at home before testing at laboratory)
- Diagnostic night in the laboratory;
- After 1 to 3 months of stable CPAP treatment at home

RESULTS:

- 97 patients completed the study
 - o Mean age of 55 +/- 12 years,
 - o BMI 33 +/- 7 kg/m²
 - o Respiratory disturbance index was 34 +/- 24/hr
- 73/97 patients reported improvements in nocturia with CPAP
- Nocturia episodes were
 - o At home before CPAP: 2.5 +/- 2.4 times/night;
 - o With CPAP 0.7 +/- 0.6 time/night (P < 0.001).

CONCLUSIONS:

CPAP appears to be an effective treatment for nocturia associated with OSA.

A REVIEW – available free on pubmed

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1893114/?tool=pubmed>

Title Continuous Positive Airway Pressure Treatment for sleep apnea in older adults

Authors Weaver and Chasens

Journal Sleep Medicine Review, 2007 vol 1, no. 2, 99-111

Daytime sleepiness and sleep disordered breathing are increased in older compared to middle-aged adults. The cognitive and cardiovascular sequelae associated with obstructive sleep apnea (OSA) have significant implications for the older adult who may already be suffering from chronic illness. Most of the evidence supporting the utilization of continuous positive airway pressure (CPAP) for the treatment of OSA has been generated from studies employing samples consisting predominately of middle-aged adults. To examine the efficacy of CPAP for the treatment of obstructive sleep apnea in older adults with an emphasis on adherence and related treatment outcomes, this paper reviews findings from clinical trials including older individuals as well as those specifically targeting this population.

These studies have demonstrated that **following CPAP therapy, older adults have** increased alertness, improved neurobehavioral outcomes in cognitive processing, memory, and executive function, **decreased sleep disruption from nocturia** and a positive effect on factors affecting cardiac function, including vascular resistance, platelet coagulability and other aspects of cardiovascular health.



Following CPAP therapy, older adults had
decreased sleep dysfunction from nocturia



Physiological differences in respiratory structure and function between younger and older adults of similar disease severity are believed to result in older individuals requiring titration at lower CPAP levels. Once initiated, CPAP treatment is tolerated by older adults, including those with Alzheimer's disease. Patterns of adherence in older individuals are consistent with that of middle-aged adults.

TARYN'S FINAL SUMMARY re Nocturia - Clinical Implications

There are so many different lower urinary tract symptoms that we regularly attempt to treat. Often, many of the symptoms appear at first glance to all related. Personally, I tend to find this is the trap many people fall into when trying to improve a person's symptoms of day and night urinary frequency.

It is tempting to think that when a person presents with a day frequency of 14 / day and a night frequency of 4 / night that the cause behind the symptoms is probably linked.....an in reality, often it is.

If a person has reduced bladder capacity, increased bladder sensation, or a high post-void residual then this is likely to impact on both their day and night frequency. In attempting to improve these factors it can be easy to forget that there can be additional factors coming into play with their nocturnal frequency. I believe the most overlooked of these is the relationship with sleep apnea.

Whilst I don't tend to do much paediatrics I do remember reading some studies that showed even in children, removal of adenoids or tonsils that were impacting on breathing during sleep had a dramatic effect on nocturia and nocturnal enuresis. The difficult part is probably explaining to parents why they should consider a specialist consult for removal of their tonsils to stop them wetting the bed!!

Anyway..... the point of all of this was the more accurate diagnosis of nocturia.

My suggestion for Patients with Nocturia:

STEP ONE: Get them to do an accurate bladder diary

STEP TWO: Check the 24hour urine production

If the person has an abnormally high urine production or reports abnormally high thirst that is not explained by medications make sure they have had a medical review first for conditions such as diabetes insipidus.

If they are on drugs giving a nephrogenic diabetes insipidus be realistic to how much you are going to improve both their day frequency and nocturia.

STEP THREE: If their 24hour urine production looks normal calculate what percentage is being produced overnight (night production) / (24hour production) x 100

If their NPI is >33% consider a sleep apnea assessment, strategies to reduce lower limb pooling, discussion with GP regarding any pre-bed medications, reducing fluid intake before bed

STEP FOUR if you have ruled out polyuria and nocturnal polyuria causes, it is likely they have reduced bladder capacity / increased bladder sensation so go to your usual OAB treatments.