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# Nocturia Think Tank: Focus on Nocturnal Polyuria: ICI-RS 2011

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The following is a report of the proceedings of the Nocturia Think Tank sessions of the annual International Consultation on Incontinence-Research Society, which took place June 13–15, 2011 in Bristol, UK. The report is organized into sections pertaining to the main topics of discussions having occurred at that meeting, centering on the relationship of nocturnal polyuria (NP) and nocturia but also synthesizing more current evidence advancing our knowledge of the diagnosis and management of nocturia. This article is not meant to be a comprehensive review on the subject of nocturia, a number of which are available in the recent literature. All authors were physically present during, or in a preliminary session just prior to, the meeting in Bristol. *Neurourol. Urodynam. 31:330–339, 2012.*


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## CLASSIFICATION OF NOCTURIA

Evaluation of nocturia begins with a history and physical examination which focuses on aspects such as sleep quality, urinary complaints, fluid intake, cardiac problems, type and timing of various medications, prior lower urinary tract surgery and other comorbidities that might account for excessive nocturnal urine output, detrusor overactivity or abnormal bladder sensory function. A key instrument in the evaluation and diagnosis of nocturia is the frequency volume chart (FVC), in which patients record the volume and timing of daytime and nighttime voids for 1–3 days. Based upon analysis of the 24-hr FVC, the patient may be categorized as having any of the following: (1) NP; (2) low bladder capacity (nocturnal and/or 24 hr); (3) mixed (a combination of NP and low global or nocturnal bladder capacity [NBC]); and (4) polyuria. Each category is associated with a differential of several medical conditions which may be investigated further and treated as part or all of the condition associated with nocturia (see Table I). Unfortunately, despite appropriate evaluation, in many patients clearly identifiable remediable conditions are not found, in which case nocturia may be idiopathic (“primary nocturia”), thereby requiring a therapeutic approach on an empiric basis. Multiple FVCs afford the physician an opportunity to review day-to-day differences in toileting habits and to discuss with the patient how the details of daily intake, activity, and bathroom availability relate to changes in FVC data. If average values of multiple FVCs are used consistently, the useful details of daily diary data differences may be obscured.

### Nocturnal Polyuria

Normally, urine is produced in an age-dependent circadian pattern. In young people (age <25 years) the mean nocturnal polyuria index (NPi, nocturnal urine volume [NUV]/24-hr urine volume) = 0.14 compared to that of older people (age >65 years) whose mean NPi = 0.34.[1] NUV is the sum of voided volumes during the hours of sleep which includes the volume of the first morning void assuming the latter takes place promptly upon arising. Accordingly, the International Continence Society has defined NP to exist when 24-hr urine production is within normal limits and NPi is greater than 0.33.[2] Several other definitions of NP have been used. They include NUV greater than 6.4 ml/kg, nocturnal urine output >0.9 ml/min (54 ml/hr) or higher[3] and >90 ml/hr.[4] Thus, for an “average” 70 kg person who sleeps about 8 hr, the upper limit of urine excreted during the hours of sleep is expected to be from 450 to 720 ml, depending upon the cut point used. Diagnosis of NP leads to a differential diagnosis including excessive evening fluid intake (behavioral factors), third

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**TABLE I. Diary-Based Categorization of Nocturia and Respective Underlying Medical Conditions**

| Nocturia category | Underlying medical conditions |
|---|---|
| Nocturnal polyuria | Congestive heart failure |
| | Diabetes mellitus |
| | Obstructive sleep apnea |
| | Peripheral edema |
| | Excessive nighttime fluid intake |
| | Idiopathic ("primary") |
| Diminished global or low nocturnal bladder capacity | Bladder outlet obstruction |
| | Nocturnal detrusor overactivity |
| | Neurogenic voiding dysfunction |
| | Cancer of bladder, prostate, or urethra |
| | Pelvic floor dysfunction |
| | Anxiety disorders |
| | Pharmacologic agents (e.g., cyclophosphamide, propranolol) |
| | Bladder, ureteral calculi |
| Polyuria | Uncontrolled diabetes mellitus |
| | Diabetes insipidus |
| | Primary polydipsia |

spacing (e.g., due to venous disease of the legs), cardiac dysfunction and obstructive sleep apnea.

### Decreased Bladder Capacity

The two types of nocturia due to diminished bladder capacity are (1) global (24 hr) decrease in bladder capacity as expressed by low maximum voided volume and (2) decreased nocturnal bladder capacity. In both conditions nocturnal urinary volume exceeds bladder capacity and the patient is awakened by the need to void because the bladder does not hold enough. Urological causes of low nocturnal and global bladder capacity include infravesical obstruction, idiopathic nocturnal detrusor overactivity, neurogenic voiding dysfunction, cystitis, bladder calculi, ureteral calculi and neoplasms of the bladder, prostate, or urethra. Urological evaluation for etiology of diminished bladder capacity includes cystoscopic and urodynamic techniques for diagnosing these disorders. Timing of medication intake should be carefully sought during the history-taking interview. Medications which pharmacologically decrease bladder capacity may cause nocturia if taken just prior to retiring. While there is clinical evidence that beta blocking drugs exacerbate involuntary bladder contractions in patients with neurological disease, these agents seem to have less effect on normal bladders.[5] On the other hand, beta blockers were not found to be associated with an increased prevalence of nocturia in the Boston Area Community Health Survey.[6] While urological causes for low bladder capacity may be found, it is often difficult to distinguish resulting global from nocturnal decreases in bladder capacity. To some extent, therefore, treatment of low bladder capacity may benefit patients during the day and not night, or vice-versa. Follow-up of such therapy is necessary in order to measure the benefit as specifically regards nocturia.

### Mixed Nocturia

Many patients with nocturia have a combination of NP and low nocturnal bladder capacity. Diminished NBC appears to play a greater role in the pathogenesis of nocturia in younger patients, whereas in older patients NP assumes relatively greater importance.[7] In view of emerging evidence of the multifactorial etiology of nocturia in individual patients,[8] the "mixed" category would seem to be particularly relevant, in that treatment yielding clinically satisfying outcomes will likely require institution of multiple incremental additive therapies.

### Polyuria

Polyuria is defined as a 24-hr urine output greater than 40 ml/kg, causing daytime urinary frequency and nocturia associated with a general increase in urine output, outstripping even normal bladder capacity. Inappropriate excretion of water in cases of polyuria leads to polydipsia in order to maintain homeostasis. Causes of global polyuria are uncontrolled diabetes mellitus, diabetes insipidus (DI), and primary polydipsia. DI is a disorder of water balance. Central DI is caused by deficient synthesis of antidiuretic hormone (ADH) secondary to loss of neurosecretory neurons in the hypothalamus or posterior hypophysis; nephrogenic DI is due to an inability of the kidneys to respond to ADH. When polyuria is demonstrated using the voiding diary, a water deprivation test may be performed to distinguish between DI and primary polydipsia which may be either dipsogenic or psychogenic.[9] Dipsogenic polydipsia is associated with a history of central neurological abnormality such as prior brain trauma, radiation, or surgery. Psychogenic polydipsia is a long-term behavioral or psychiatric disorder.

On balance it would seem that a diary-based classification scheme such as that presented above naturally should lead to rational, cause-specific therapy of nocturia. However, treatment of a condition which addresses each underlying pathophysiologic factor is not always practical. By way of analogy, even though erectile dysfunction, like nocturia, has multiple potential underlying causes such as hypogonadism, large vessel disease, small vessel disease, venous insufficiency and psychogenic factors, treatment usually follows an algorithm independent of etiology, and based more upon safest and least invasive treatment first followed by more invasive, higher risk treatment further on. Verification of a cause-specific treatment algorithm for nocturia mandates a considerable clinical research commitment in the future.

## NOCTURNAL POLYURIA IN OLDER MEN AS DEFINED BY THE KRIMPEN STUDY

According to the most recent ICS definition, NP is present when an increased proportion of the 24-hr output occurs at night.[10] The ICS standardization report on terminology further states that the normal range of nocturnal urine production (NUP) differs with age and normal ranges remain to be defined. Therefore, NP is present when greater than 20% (young adults) to 33% (over 65 years) is produced at night. However, these suggested definitions of NP, which refer to a day/night ratio in urine production were not based on normal distributions and were not properly validated.[11]

Clearly, FVCs are excellent tools to evaluate NUP in an epidemiological setting.[4] In the Krimpen study, urine production for each hour of the day was computed according to the method described by Van Mastrigt and Eijskoot[12]: urine production was assumed constant between two voidings and hourly urine production was estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition. NUP per hour was estimated as the mean between 1 am and 6 am, because 90% of the men were asleep in this period.

### Reference Values for Nocturnal Urine Production and Determinants of Nocturnal Urine Production in Older Men

At baseline, a 3-day frequency-volume chart was completed by 95% of the participants. Mean NUP was 60.6 (SD 32.6) ml/hr in men aged 50–78 years.[4] Linear regression analyses on NUP was performed to identify possible determinants. In multivariate analyses, the significant determinants of increased NUP are: age, smoking, and 24-hr polyuria.

The mean NUP in ml/hr for the age strata 50–54, 55–59, 60–64, 65–69, and 70–78 years were 53.4, 54.2, 58.3, 62.8, and 66.6 ml/hr, respectively. Mean NUP is significantly higher, that is, 100.9 ml/hr in men with 24-hr polyuria (>2,500 ml per 24 hr). Men who smoke have a slightly lower NUP (mean 47.5 ml/hr).

A cut-off value for increased NUP was defined using logistic regression analysis. The best model was the one with the highest percentage of explained variance, and was derived from ROC curves. Based on these analyses we suggest that a NUP exceeding 90 ml/hr is abnormal. However, about one-third of the men with "increased" NUP according to this cut-off value also have 24-hr polyuria.[4]

### Epidemiology of Nocturnal Polyuria in Older Men

To study the epidemiology of NP, urine production for each hour of the day was determined as described above. Two different definitions of NP were used:

(1) Nocturnal urine volume >33% of 24-hr total urine volume (abbreviated as "NUP33%/24 hr").
(2) Nocturnal urine production >90 ml/hr (abbreviated as "NUP90").

The percentage of men with NP was determined for the different age strata using these definitions.

### Age Group Specific Prevalence of Nocturnal Polyuria at Baseline and Follow-Up

The prevalence of NUP33%/24 hr and NUP90 in community-dwelling men between 50 and 78 years clearly increases with age.[4] The prevalence rate of men with NUP33%/24 hr, is high (>40%) for all age strata and rising from 41.8% (95% CI: 36.2–47.4) between 50 and 54 years, to 56.9% (95% CI: 49.5–64.3) between 70 and 78 years. For both definitions, a clear relation with advancing age was shown. The lowest prevalence was shown for the definition NUP90, rising from 12.1% (95% CI: 8.4–15.9) in men between 50 and 54 years, to 23.6% (95% CI: 17.2–29.9) in men between 70 and 78 years.[13]

The longitudinal evolution of the prevalence rates in the subsequent study rounds only showed slight variations over time for all definitions. The largest increase after 6.5 years of follow-up (from 47.5% to 62.5%) was shown for NUP33%/24 hr in men from the baseline age stratum of 60–64 years.[13]

## SLEEP APNEA AND NOCTURIA: UPDATE

Sleep disturbances such as insomnia, obstructive sleep apnea, restless legs syndrome and periodic leg movements, snoring and parasomnias, for example, sleep walking have been implicated in the etiology of nocturia. The precise relationship between sleep apnea and nocturia has not been thoroughly studied but it seems to be related to increased pressure in the right side of the heart. Obstructive sleep apnea is caused by a blockage of the airway, when the soft tissue in the rear of the throat collapses and closes during sleep. This sets-off a series of physiological processes: oxygen supply decreases, carbon dioxide levels increase and the blood becomes more acidic resulting in bradycardia and pulmonary vasoconstriction.[14] The patient then wakes up to breathe by which time the heart rate increases and the heart senses a false signal of fluid overload which results in the secretion of atrial natriuretic peptide (ANP) to get rid of sodium and water, resulting in nocturia.[15,16] The worse the sleep apnea, the worse the nocturia.[17] Treatment of sleep apnea with continuous positive airway pressure seems to reduce nocturia in these patients.[18]

In a cluster analysis of patients from the EpiLUTS study, sleep apnea was in the same cluster as nocturia in women but not in men.[19] However, as the number of nocturia episodes increased, so did the frequency of sleep apnea in both men and women (see Table II). Nocturia is an independent predictor for severe obstructive sleep apnea in patients with ischemic stroke[20] and seems to be a predictor of sleep apnea just like snoring.[8,21] Although the association between nocturia and sleep apnea is established from small clinical trials and epidemiological data we still do not know the exact relationship between the two and whether sleep apnea causes nocturia or vice versa. Sleep apnea also seems to be related to overactive bladder (OAB) syndrome,[22,23] benign prostatic enlargement,[24] and metabolic syndrome.[25]

We need research into this area of nocturia as well as looking at simple treatments such as weight loss for sleep apnea and its relationship to nocturia.

## SIMPLIFIED VERSUS EXTENDED ALGORITHM FOR EVALUATION AND TREATMENT OF NOCTURIA

Treatment algorithms for management of nocturia have proved difficult to develop, though several possible examples have been proposed and published. A simple algorithm suitable for primary care would be highly desirable, in view of the high prevalence of the condition. Such an algorithm needs to be simple and self-evident, communicating the importance of evaluating fluid intake and output, so the physician makes the distinction between lower urinary tract, renal and prerenal causes of nocturia. Thus the physician would be directed appropriately for initial investigation and management, including triggers to indicate whether a significant medical comorbidity may be present.[26] Such an algorithm should also

**TABLE II. Frequency of Sleep Apnea in Nocturia Subgroups**

| | Number of nocturia episodes | | | | |
|---|---|---|---|---|---|
| Sleep apnea or sleep disorder | 0 | 1 | 2 | ≥3 | *P*-value |
| Men | N = 4,318, 433 (10.0%) | N = 5,768, 742 (12.9%) | N = 2,196, 375 (17.1%) | N = 1,825, 372 (20.4%) | <0.0001 |
| Women | N = 3,834, 251 (6.6%) | N = 6,649, 574 (8.6%) | N = 2,954, 362 (12.2%) | N = 2,373, 455 (19.2%) | <0.0001 |

include steps for realistic appraisal of treatment response and appropriate follow up.

By its nature, nocturia is a multifactorial and complex interplay of body systems, and some of comorbidities may be medically significant.[8] Inevitably therefore, a simple algorithm will not necessarily yield a high proportion of patients achieving symptomatic response they would perceive to be adequate. Accordingly, a more complex algorithm, able to discern the numerous systems influencing nocturnal urine output, and their relative contribution, is going to be necessary for refractory bothersome nocturia in the secondary care setting. Such an algorithm needs to make allowance for broad assessment across multiple body systems, with the sensitivity to ascertain more specific testing according to phenotypic triggers, and then detailed evaluation and management which may fall into a specialist bracket. Much of the specialty work will fall outside the typical training experience of most urologists or urogynecologists, for whom endocrinology, autonomic physiology, and renal medicine are not core training topics. Accordingly, such an algorithm must reflect some key points:

the multidisciplinary nature of the team-working essential for comprehensive investigation and treatment success;
selective testing based on predictive criteria identified in history and examination;
identifying simple screening measures that can be done by secondary care physicians—so as to avoid interdisciplinary referral with no resulting benefit;
avoidance of treatment where satisfactory symptomatic response cannot be anticipated.

Whilst many algorithms have been proposed, none has been drawn up with an interdisciplinary dialogue sufficient to meet these needs. This would be an ambitious and challenging process, as it would require a substantial array of specialists; urology, urogynecology, renal medicine, internal medicine, neurology, geriatrics, cardiovascular medicine, sleep medicine, respiratory medicine, etc. Nonetheless, the benefits to patients and the medical profession that would result if such a consensus could be achieved render the development of a combination of simple primary care and extended secondary care algorithms a clinical priority and a research priority.

## RECOMMENDATION FOR BEST CURRENT NOCTURIA-SPECIFIC SLEEP QUALITY QUESTIONNAIRES

Nocturia is bothersome for a remarkable proportion of the general population and is associated with impaired quality of life (QoL).[27] The assessment of the impact of these adverse effects has evolved from generic to specific with the evolution of instruments specifically designed and validated for this purpose. Generally, condition-specific measures are more responsive to small changes. On the other hand, global measures provided by a generic QoL instrument can be more robust and give an indication of the impact on everyday activities and overall well-being compared with narrower information from a condition-specific instrument (see Table III).[28]

The Nocturia-specific Quality of Life Questionnaire (N-QOL) is a condition-specific questionnaire developed for men with nocturia.[29] The N-QOL is a 13-item instrument, available in 17 languages, and takes approximately 5 min to complete.[30] After initial evaluation in small focus groups and psychometric validation, reproducibility and validity of the total score and subscale scores have been demonstrated. Subscales that have been identified within this score include sleep/energy and bother/concern, both of which have high loading factors for nocturia impact. N-QOL scores were shown to correlate with sleep quality (measured by the Pittsburgh Sleep Quality Index (PSQI))[31] and energy/vitality and social functioning (measured by the SF-36 Health Survey (SF-36)). The N-QOL has been shown to demonstrate differences in scores between individuals experiencing one, two, and three voids/night indicating discriminant validity. In a Taiwanese study,[32] the validity of N-QOL was also shown among women. However, responsiveness to change and clinical significance of change of scores remains to be assessed in an intervention study. The N-QOL represents the first questionnaire to have been specifically developed to assess nocturia impact on QoL. Another instrument specifically validated for assessment of the impact of nocturia is the Nocturia, Nocturnal Enuresis and Sleep-Interruption Questionnaire (NNES-Q).[33] It has been validated in a mailed questionnaire study among elderly. NNES-Q includes 12 questions on nocturia, nocturnal enuresis, sleep-interruptions, treatment and physical function. NNES-Q remains to be validated in a younger population and in clinical practice.

Attempts have been made to correlate scales assessing lower urinary tract symptoms with impact of nocturia. Coyne et al.[34] found that the Urinary Sensation Scale (USS) discriminated nocturia in women but not in men. Van Dijk et al. assessed 1,000 Dutch men and women using the Bristol Female Lower Urinary Tract Symptoms Questionnaire (BF-LUTS), the Sleep Wake Experience List (SWEL[35]), and the RAND-36 scales.[36] They noted nocturia effects mediated by sleep problems having statistically significant effects on BF-LUTS subscales, SWEL, and RAND-36 scores.[37,38] Similarly, the BPH Impact Index,[39] ICS QoL,[40] BPH survey,[41] Veterans Affairs Questionnaire,[42] and the Olmstead County Questionnaire[43] have been used to capture the impact of nocturia in men. The Incontinence Impact Questionnaire (IIQ[44]) and King's Health

**TABLE III. Questionnaires Employed in Study of Nocturia**

| Questionnaire (see text) | Use in genders | Comments |
|---|---|---|
| ICIQ-N-QoL | Both | Nocturia-specific |
| NNES-Q | Both | Nocturia-specific; validated in elderly only |
| DAN-PSS | Both | Assesses not only nocturia severity but also bother; validated in men; nocturia questions seem not gender-specific |
| AUA-SI/IPSS | Both | Assesses nocturia severity |
| BF-LUTS | Both | Assesses nocturia severity; validated in women; nocturia question seems not gender-specific |
| ICS QoL | Men | 6 questions as part of the ICS "BPH" questionnaire |
| BPH Impact Index/Symptom Problem Index | Men | Does not assess nocturia but questions on health feeling with and social implications of LUTS |
| EuroQoL-5D, SF-36, RAND-36, 15D | Both | Generic health-related quality of life instruments |

Questionnaire[45] have been used in women for assessment of this symptom.[46] Among both genders, occurrence and bother of nocturia was assessed by the Danish Prostatic Symptom Score (DAN-PSS) in a Finnish population-based study.[8] Most respondents reported bother from nocturia with two voids/night and moderate bother only with three or more nocturia episodes.

Relation of nocturia with health related QoL has also been assessed by the generic 15D instrument (including 15 dimensions of QoL).[8,47] In a Finnish population-based study,[27] reporting two voids/night was related with clinically importantly impaired QoL whereas a single episode was not. This finding is consistent with a US female urology clinic study and a community-based Taiwanese study[48] which proposed that clinically significant nocturia is $\geq$2 voids per night. In the US study,[49] the American Urologic Association Symptom Index (AUA-SI[50]) and the Symptom Problem Index (SPI) was used, whereas the N-QOL[29] was used in the Taiwanese study.

Kobelt et al., in a Swedish population, assessed the relationship between two generic QoL instruments (the EQ-5D (EuroQol[51]) and the SF-36[52]—specifically the vitality and energy domains) and the Short quantitative Work Productivity and Activity Impairment (WPAI[53]) in a group of nocturic patients compared with controls. Nocturia resulted in significantly lower vitality and utility as aspects of quality-of-life.[54] Furthermore, increasing nocturia was related with impaired work productivity.

We recommend use of the N-QOL for baseline and follow-up assessments of nocturia therapy until other clinically validated options become available. However, generic QoL instruments and other possible effects of nocturia, such as diminished work productivity, could also be included in outcome assessment.

## SUMMARY OF MEDICATIONS CAUSING INCREASED URINE OUTPUT (AS A SIDE EFFECT) AND THEIR MECHANISMS

Knowledge of patient medication intake including over-the-counter medications and vitamins is of significant value in the evaluation of patients with nocturia. Diuresis is an expected outcome in patients on diuretic therapy and may contribute to global or NP; however, there is a long list of medications that contribute to the condition due to the secondary renal effect of the medication on water or salt balance. Medications can cause polyuria by increasing water intake (polydipsia), by interfering in renal ability to concentrate urine (DI), by causing venous stasis, or via unknown mechanisms (see Table IV).

It is important to review water homeostasis to understand some of the mechanistic pathways through which certain medications contribute to polyuria. Excessive filtration of a poorly reabsorbed solute such as glucose, mannitol, or urea can depress reabsorption of NaCl and water in the proximal tubule and lead to enhanced excretion in the urine. Poorly controlled diabetes mellitus with glycosuria is the commonest cause of solute diuresis, leading to volume depletion and serum hypertonicity. Common iatrogenic solute diuresis occurs from mannitol administration, radiocontrast media, and high-protein feedings (enterally or parenterally), leading to increased urea production and excretion.[55]

Formation of large volumes of dilute urine is usually due to polydipsic states or DI. Primary polydipsia can result from habit, psychiatric disorders, neurologic lesions, or medications. During deliberate polydipsia, extracellular fluid volume is normal or expanded and plasma vasopressin (AVP) levels are reduced because serum osmolality tends to be near the lower limits of normal. Drugs that produce dry mouth (phenothiazine and anticholinergics) or any peripheral disorder causing pathologic elevation of renin and/or angiotensin can cause primary polydipsia. An important cause of NP is pedal edema, which results in NP via mobilization of fluid when the patient retires to the reclining position during sleep. NP is associated with venous insufficiency, congestive heart failure, and medications. Examples of the latter include non-steroidal anti-inflammatory drugs (via suppression of AVP-inhibiting prostaglandin E2) and thiazolidinedione antidiabetic agents.

**TABLE IV. Summary of Medications Causing Increased Urine Output**

| Medication | Mechanism of increased urine output |
|---|---|
| Ethanol, morphine, glucocorticoids, fluphenazine, haloperidol, promethazine, oxilorphan, butorphanol | Inhibition of endogenous vasopressin secretion |
| Lithium, demeclocycline, cisplatinum, methoxyflurane, amphotericin B, foscarnet, ifosfamide, clozapine | Reduced renal aquaporin-2 levels |
| Conivaptan, tolvaptan | V2-receptor antagonist |
| Calcium channel blockers | Direct blocking of proximal tubular sodium reabsorption or increased atrial natriuretic peptide levels |
| Carbonic anhydrase inhibitors | Reduced sodium and bicarbonate reabsorption in proximal tubule |
| Excessive vitamins A and D; thiazides | Hypercalcemia proximate consequence, secondary renal concentrating defect |

Arginine vasopressin (AVP) is one of the most important hormones in water homeostasis. It binds to the type 2 vasopressin receptor (V2R) on the basolateral membrane of principal cells in the collecting ducts and connecting tubules, activates adenylyl cyclase (AC), increases intracellular cyclic adenosine monophosphatase (cAMP), and stimulates protein kinase A (PKA) activity. The resulting increase in cellular cAMP and PKA activity triggers an increased rate of insertion of water channel-containing vesicles (aquaporin 2) into the apical membrane that increases permeability of the apical membrane.[56] For maximum concentration of urine, large amounts of urea must be deposited in the interstitium of the inner medulla. $V_2$-receptor activation also increases urea permeability by 400% in the terminal portions of the inner medullary collecting duct. $V_2$ receptors increase urea permeability by activating an AVP-regulated urea transporter most likely by PKA-induced phosphorylation.[57] In addition to the above, $V_2$-receptor activation also increases $Na^+$ transport in the thick ascending limb and collecting duct of the nephron.

DI can be caused by either insufficient AVP (central DI) or the lack of AVP effect (nephrogenic DI). Inhibitors of vasopressin secretion (central DI) include *ethanol*, *phenytoin*, low doses of morphine, glucocorticoids, *fluphenazine*, *haloperidol*, *promethazine*, oxilorphan, and *butorphanol*. Lithium is the most common cause of drug-induced nephrogenic DI. As many as 10–20% of patients on chronic lithium therapy develop some degree of NDI. Lithium is known to reduce $V_2$-receptor-mediated stimulation of AC and produces a dramatic (95%) reduction in renal aquaporin (AQP2) levels in animals. Other causes of NDI include antibiotics like demeclocycline, cisplatin, methoxyflurane, amphotericin B, *foscarnet*, ifosfamide, *clozapine*. The antibiotic *demeclocycline* attenuates the *antidiuretic*

effects of vasopressin, probably owing to decreased accumulation and action of cAMP.[58]

Lack of AVP-stimulated activation of the V2 receptors in the connecting tubules is the basis of AVP receptor antagonists' induction of polyuria. Conivaptan and tolvaptan (V2-receptor antagonists) are developed to treat hyponatremia in euvolemic/hypervolumic patients.[58]

Many calcium-channel blockers produce polyuria via a direct blocking of the reabsorption of sodium in the proximal renal tubule[59] or alteration in ANP plasma levels.[60]

Carbonic anhydrase inhibitors (methazolamide and acetazolamide) act upon carbonic anhydrase, located at the luminal border of cells of the proximal tubule.[61] When the enzyme is inhibited there is an increase in urine volume, and a change to an alkaline pH, with subsequent decrease in the excretion of both titratable acid and ammonia.[62]

Drugs causing hypercalcemia can produce polyuria. Chronic hypercalcemia leads to a defect in concentrating ability that may induce polyuria and polydipsia in up to 20% of patients. The mechanism is incompletely understood, but downregulation of AQP2 water channels, and calcium deposition in the medulla with secondary tubulointerstitial injury and impaired generation of the interstitial osmotic gradient may play important roles. Hypervitaminosis A, hypervitaminosis D, and thiazide diuretics can result in hypercalcemia.

## PHARMACOTHERAPY OF NOCTURNAL POLYURIA WITH ANTIDIURETICS

Before using pharmacotherapy to treat NP, relevant comorbidities (DI, heart failure, and renal insufficiency) should be addressed.

Further, non-invasive treatments should be considered (evening fluid, caffeine and alcohol reduction as well as stockings, warm sleep environment and socks).

If this approach is insufficient, antidiuretic treatment with desmopressin is indicated.[63] Desmopressin, internationally registered as a treatment for NP, is a synthetic analogue of AVP, the endogenous ADH. Desmopressin is a selective vasopressin-2 receptor agonist which has its effect predominantly on antidiuresis. It has neither vasoconstrictive nor oxytocic effects, unlike its native congener.

The antidiuretic treatment of NP has been reviewed in 2010.[64] It was concluded that desmopressin has a significant beneficial clinical and statistical effect on nocturnal voiding frequency, sleep, bother, QoL, and productivity.

Recently the results of a randomized, single blinded, placebo controlled trial with 136 men with benign prostatic hyperplasia (BPH) older than 65 years of age was published.[65] All men suffered from nocturia, NP and had an International Prostate Symptom Score of 14 or higher. It was concluded that low dose oral desmopressin (0.1 mg) is an effective and well-tolerated treatment for NP among such patients. A clinical response (decrease of 2 or more voids per night) was achieved in 35 patients (61.4%) receiving desmopressin and in 8 placebo-treated patients (13.8%) ($P < 0.001$). It was found that long-term desmopressin therapy gradually decreases serum sodium and might induce hyponatremia even in patients with normal baseline serum sodium.[65] Kang et al.[66] analyzed the short term effect of desmopressin. They compared an adult group (20 patients <64 years of age) with an elderly cohort (14 patients >65 years of age) having NP. Desmopressin appeared to be well tolerated and effective after a treatment period of 2 weeks in both groups. Only two patients (from the elderly cohort) developed hyponatremia, which resolved after discontinuation of therapy.

Lee et al.[67] performed a dose-titration study followed by a treatment period of 4 weeks with the individual optimum oral dose. They enrolled 103 patients with mixed nocturia. Ninety-four patients completed the dose-titration study and 90 patients (95.7%) completed the treatment-period (one withdrawal because of neck-stiffness and three withdrawals because of loss to follow-up). The optimum doses were as follows: 44% (n = 41) of patients received 0.1 mg oral desmopressin, 33% (n = 31) received 0.2 mg of desmopressin, and 23% (n = 22) received 0.4 mg of desmopressin. In 72% of the patients (n = 68) (95% CI: 0.63–0.81) ($P < 0.001$), the mean number of nocturnal voids decreased significantly from 3.20 to 1.34 after the 4-week treatment with desmopressin. The number of patients that reported a good night sleep increased significantly from 19.8% to 78.7% after 4 weeks of desmopressin treatment ($P < 0.001$).

Overall it can be concluded that desmopressin is an effective treatment option for NP and nocturia.[68,69]

## DESMOPRESSIN: GENDER DIFFERENCES

Whilst there is considerable evidence to suggest that increasing age and female gender are risk factors for developing hyponatremia whilst taking desmopressin therapy[70] until recently there have been few data assessing gender differences in relation to antidiuretic response.

Previous studies have demonstrated the diurnal variation in ADH secretion in 69 healthy volunteers and have shown a twofold higher concentration in male subjects when compared to female subjects[71] although since urine osmolality were similar in both groups[72] this suggests that women have a higher renal sensitivity when compared to men. Furthermore there is some evidence to suggest that estrogens lower the plasma osmotic threshold for antidiuretic hormone[73] and consequently increase renal sensitivity.

The concept of a possible gender difference is supported by genetic research which has shown significantly more V2 receptor (V2R) mRNA in female rats when compared to male rats and a greater sensitivity to V2R agonist administration.[74] Further work has demonstrated that mutations in the AVPR2 gene, located on the X chromosome may cause polyuric, polydipsic, and antidiuretic disorders. Clinically these appear to be less severe in the female phenotype when compared to the male phenotype probably due to female carriers "escaping" X inactivation, thereby causing phenotypic variability.[75] In addition the AVPR2 gene has a high probability of escaping X inactivation[76] and hence may be responsible for gender differences in renal V2R expression.

The gender differences in renal sensitivity and response have also been demonstrated in clinical studies investigating the use of desmopressin in the management of nocturia. Two double blind placebo controlled studies, the Noctupus studies, have been reported in 144 women[77] and 151 men.[78] Although neither of these studies were specifically designed to investigate for gender differences in response to therapy further analysis of the results suggests that women experienced greater efficacy when compared to men. The primary endpoint of both studies was the number of subjects with a $\geq$50% reduction in nocturnal voids. This was achieved in 46% of women as compared to 34% of men. In addition, women were found to have a 78% increase in mean time to first nocturnal void as compared to a 59% increase in men.

Whilst evidence from the Noctupus studies would certainly suggest a gender difference in the efficacy of desmopressin more direct evidence is provided by a recently completed North American trial of desmopressin orally disintegrating

tablets (Minirin Melt).[79] In the first double blind phase of the study subjects were randomized to placebo or oral desmopressin (10, 25, 50, or 100 μg), for 1 month, and were then invited to continue in a 12-month open label extension study. Overall 799 subjects were recruited with 710 (89%) completing the double blind phase and 665 continued into the open label extension study. The co-primary endpoints were the mean change in nocturnal voids from baseline and the proportion of subjects with >33% reduction in mean nocturnal voids. A dose response effect was seen during the study with a significant difference in efficacy between the 50 and 100 μg doses when compared to placebo. The 25 μg dose was shown to have a clinical effect, although not significantly greater than placebo, whilst the 10 μg dose was sub-therapeutic. However a subsequent post hoc analysis has shown a significantly greater decrease in NUV in women at the lower doses of 10 and 25 μg when compared to men. Equally the $ED_{50}$ was found to be lower in women when compared to men (16.1 μg vs. 43.2 μg) suggesting significantly higher sensitivity to desmopressin in women. This finding is also supported by a five-fold higher risk of hyponatremia, defined as a sodium level below 130 mmol/L, in women over 50 years old at the 50 μg dose when compared to men. Consequently, whilst 50–100 μg is an efficacious dose in men these findings would suggest that 25 μg is equally efficacious in women and in addition there were no observed instances of hyponatremia at this low dose level.[80]

In conclusion, the emerging evidence would appear to suggest that women have an increased sensitivity to desmopressin and may therefore achieve a similar clinical effect with a lower therapeutic dose. In clinical practice this should allow physicians treating women with nocturia to minimize the risk of hyponatremia whist still achieving a meaningful clinical effect.

## ANTIMUSCARINICS AS THERAPY FOR NOCTURICS

Despite commonly reported statistically significant results, nocturia has not shown a clinical significant response to traditional therapies for OAB, including antimuscarinics.[81] Simple logic would predict this, using as a model the "typical" patient with OAB who has 12 voids a day with 1–4 episodes of arising from sleep to void and 50% of the voids occurring with urgency. An effective antimuscarinic will reduce the episodes of urgency by 50% with a drug/placebo ratio of approximately 2:1. For reduction in nocturia, this would amount to, assuming that the only effect of the antimuscarinic would be on the urgency-associated episodes, a reduction in nocturia from 4 to 3, 3 to 2.25, and 2 to 1.5. Clearly the benefit would be most appreciated by those more severely afflicted with nocturia, if the theory is correct. The following citations prove the point. These are not meant to select any particular drug(s) for criticism, merely to support the initial statement.

Brubaker and Fitzgerald[82] pooled data from four trials (3 months each) which included men and women with nocturia treated with solifenacin 5 and 10 mg, and placebo. Results were categorized as "all" and those with and without NP. The only statistically significant difference from placebo was in the no NP group. Reduction in nocturic episodes in the placebo group was 1.70–1.27; for both S5 and S10, 1.66–1.05. Rackley et al.[83] reported on a population of OAB patients with an average of 2.5 episodes or more of nocturia, treated with a nighttime dose of tolterodine LA 4 mg. Results were characterized into total nocturia episodes, those not due to OAB (no urgency), those due to OAB and to "severe OAB" (severe urgency). The median percentage reductions in nocturia were not statistically significant versus placebo for the total and non-OAB nocturia events but were for OAB and severe OAB events. Respectively, the later reductions were 30 versus 22% (baseline 2.5 for drug, 2.4 for placebo) and 59 versus 43% (baseline 1.03 and 0.96). Although a "signal" exists, the clinical significance is, at best, arguable. Zinner et al.[84] compared the results with trospium 20 mg bid to placebo in a 12-week trial. The decreases in nocturia amounted to 2.10–1.63 for drug, 2.00–1.71 for placebo, statistically significant for the drug. Rudy et al.[85] used the same design with almost identical results: 2.10–1.63 for drug, 2.00–1.71 for placebo. Studies looking at the effects of fesoterodine on nocturia failed to show statistically or clinically significant changes.[86–89] In a head to head comparison of tolterodine and fesoterodine, Kaplan et al.[90] reported a 33.3% reduction in nocturnal micturitions at 12 weeks for fesoterodine (baseline 2.2), 33.3% for tolterodine (baseline 2.3), and 27.3% for placebo (baseline 2.1). The fesoterodine reduction was statistically significant versus placebo ($P < 0.05$), but the calculated reduction is hardly clinically relevant.

Although those patients with severe OAB may benefit from antimuscarinic therapy, this is the only group that would be expected to have any positive result with respect to nocturia, but this effect is minimal. At best in such patients, this could be additive in a multimodal approach to the management of nocturia.

## EVIDENCE FOR TREATMENT OF NOCTURIA VIA COMPRESSION DEVICES, TIMED DIURETICS, AND BEHAVIORAL TREATMENT

NP can be directly addressed using compression stockings to reduce peripheral edema, timed diuretics to induce urine output prior to sleep, and by changing patterns of fluid intake through behavioral treatments such as fluid management. Because these treatments are non-specific, there is wide general recommendation for their use, but little direct evidence for the effectiveness of these treatments.[91]

### General Advice

Nighttime fluid intake and coffee intake, practices providers commonly target in patients with nocturia, were not associated with nocturia in a study of elderly patients.[92] Fluid manipulation will more likely affect symptoms than will caffeine changes.[93] Intervention trials manipulating 24-hr total fluid intake (though neither fluid type nor timing) with fluid intake reduction (by 25%) showed a small, statistically significant reduction (0.1 episode less on average) in nocturia.[94] Individuals had difficulty maintaining prescribed alterations of either 50% greater or less fluid intake, and will not likely be a meaningful intervention.

### Compression Devices

Peripheral third-spacing of fluids is common in middle-aged and elderly patients; with elevation of the legs, these fluids are mobilized and can result in significant nocturia. The volume of accumulated extracellular fluid, specifically in the lower extremities, correlates with NUV.[95] However, studies of compression devices with nocturia as a measurable outcome have not been performed. In an open "label" study, there was a large treatment effect from combined therapy which included the use of lower extremity stockings in 45% of 55 men who had >2 episodes of nocturia associated with peripheral edema, recruited from a primary care clinic.[96] There was no

control group in this study and compliance with wearing the stockings was not assessed.

### Timed Diuretics

Diuretics given at bedtime would dramatically exacerbate the problem of nocturia; diuretics given late in the afternoon so that their effect is complete by bedtime can improve nocturia. Reynard et al.[97] asked middle-aged men with LUTS to keep a FVC, and in those with NP, 40 mg of furosemide 6 hr before usual bed time resulted in a significant reduction (net reduction of 0.5 fewer episodes in treatment versus control) in night-time frequency and percentage voided NUV. Staggered furosemide and desmopressin might provide a rational treatment for nocturia in the elderly[98] although diuretic-induced sodium loss may predispose such patients to hyponatremia with the combination.

Behavioral treatment: Fluid management is widely used to manage OAB, especially where a frequency/volume diary has recorded high fluid intake and urine output in individuals. In a large multicenter study of women with OAB, Zimmern and coworkers found that general fluid instructions contributed to reduction of UUI symptoms in women taking anticholinergic medications, with a decrease in the number of voids per 24 hr. Specific nighttime volumes were not reported.[99] Two trials have shown that combined behavioral therapy, including fluid timing instructions, pelvic floor muscle exercises and urge-suppression strategies, reduces nocturia to a greater extent than oxybutynin. The first study was a post hoc analysis of a treatment trial in women with urge urinary incontinence (behavior vs. bladder relaxant vs. placebo). Here, combined behavioral therapy resulted in greater mean changes in nocturia ($-0.5$) when compared to either individually titrated oxybutynin IR ($-0.3$) or to placebo (0.0).[100] Similar results were later demonstrated in men whose 24-hr urinary frequency did not resolve with an alpha-blocker therapy run-in. For nocturia reductions, behavioral therapy and pelvic floor muscle exercises added to alpha-blocker therapy resulted in greater changes in nocturia when compared to individually titrated oxybutynin XL (mean reduction $= -0.70$ vs. $-0.32$ episodes/night; $P = 0.05$).[101] The clinical benefit of this statistically borderline improvement in nocturia, as is the case with many of its treatments, is likely to be unappreciated by most patients.

## CONCLUSIONS

Advances in diagnosis and management of nocturia were discussed amongst a large cross section of international experts during the 2011 Bristol ICI-RS meeting. At the present time it appears that NP is the greater of the multiple treatable substrates comprising the genesis of this extremely common, bothersome and potentially morbid condition.

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