# Nocturia – the Cinderella of lower urinary tract symptoms

BY TIM LANE

Nocturia is defined as waking during the night (at least once) to urinate. The important part of the definition relates to the necessity of sleep to precede the episode (although whether sleep must follow the episode is less clear). The definition specifically excludes 'convenience' voids which is essentially where voiding takes place once awake and after having been awoken for other reasons (and there are so many of these!). There would appear to be an assumption that there should be a return to sleep after the void – but the intention to return to sleep (whether actually achieved or not) would appear to be the salient feature. There are a whole host of medical pathologies that are linked to its aetiology. It is a complex and highly multifactorial condition, which affects women and men with equal frequency (and this will surprise many). Nocturia represents a clinical entity in its own right and can have a significant impact on daytime function, quality of life and even mortality. Despite this, it has until recently remained a Cinderella subject – having been predominantly regarded as the preserve of the urologist and generally subsumed within the treatment of bladder outflow obstruction.

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What should we regard as normal when it comes to nocturia? The data we do have (usually accrued from questionnaire-based studies) is invariably unreliable – with recall bias having a major negative impact. Such bias is not a feature of frequency-volume charts (and the agreement between the two is often contradictory as a result). One study – the Krimpen Study – represented an attempt to use frequency-volume charts (FVC) to assess normal frequency and voided volumes in a community-based population with nearly 4000 men aged 50-75 years old (and living in a Dutch municipality) being evaluated with the aim of defining the natural history of male lower urinary tract dysfunction. In doing so the authors provided normal values for nocturnal urine production. Mean values approximated to 60mls/hour with higher values noted with increasing age. Diurnal frequency was generally higher in men with clinical evidence of benign prostatic hyperplasia (BPH). Nocturnal voiding frequency by contrast had a strong correlation with increasing age, clinically evident BPH (again), diuretic administration and nocturnal polyuria. Interestingly, increased nocturnal urine production is only a modest determinant of increased nocturnal frequency and reflects the multifactorial nature of the problem. A nocturnal hourly urine production of in excess of 90ml/hour is probably best regarded as abnormal.

There are many medical conditions that have been associated with nocturia. A careful interplay between bladder storage problems – which includes detrusor overactivity and bladder outflow obstruction – and polyuria (24-hour as well as specific nocturnal polyuria) no doubt exist to a greater or lesser extent across a whole spectrum of individuals. Understanding the relative contribution of each to the overall symptom complex is pivotal to achieving successful clinical interventions to ameliorate symptoms. One important study – the FINNO survey – undertook to identify those factors which influence nocturia in a large population-based study. The study identified a number of risk factors in both sexes. In men the principal determinants were urge-related voiding symptoms, BPH and sleep disruption (linked to snoring). Additionally, anti-depressant use and prostate cancer were identified as significant links to nocturia. In women, urgency, obesity and again snoring were predictive. Coronary artery disease and diabetes were also identified in the female cohort as risk factors. Bosch and Weiss have more recently carried out a review of a large number of population-based studies undertaken over a 20-year period. They found that the majority of studies suggested that the tendency for nocturia increased with age with two or more voids being reported in 20-30% in those between 50-70 years and 10-50% in those aged over 70 years. Whatever the description of nocturia provided it was therefore clear that nocturia increased with age. This increase however appears a result of an increase in age-related physiological changes (rather than age per se) and includes diminished bladder capacity, nocturnal polyuria and sleep disorders. Interestingly there seems to be little difference in the prevalence of nocturia between the sexes, although more young women and larger numbers of older men tend to report nocturia than their age-matched counterparts.

In recent years much has been gleaned about the risk factors for nocturia. They may represent lifestyle features or inherited characteristics, co-morbidities or environmental exposures. All are important because each allows for either a behaviour modification or treatment

intervention aimed at reducing or eliminating the impact of nocturia on the individual. They include lower urinary tract factors, cardiovascular disease (cardiac failure and hypertension), pulmonary disease, fluid volume disturbances, etc. Other factors include the socioeconomic, behavioural and lifestyle. An understanding of each allows for not only a better understanding but also a realisation that specific interventions may be forthcoming.

Perhaps unsurprisingly, a large number of lower urinary tract factors have been linked to nocturia and are strong predictors for nocturia. Whilst the International Continence Society (ICS) definition allows nocturia to exist as an entity in itself (and unrelated to the lower urinary tract) it is equally clear that many with existing lower urinary tract symptoms (LUTS) will affect bladder function both by day and by night. Global polyuria, nocturnal polyuria and reduced functional capacity were all found to contribute to nocturia. Oestrogen deficiency in post-menopausal women results in an array of structural and functional changes, which cause irritative symptoms and subsequently nocturia. Diminished bladder capacity (for example, as a result of an overactive bladder) essentially results in bladders emptying at a volume less than the functional bladder capacity; all of which may contribute to nocturia. Bladder capacity can similarly be reduced by radiation cystitis, interstitial cystitis and malignancy. Cardiovascular diseases can also impact upon nocturia and include congestive cardiac failure, ischaemic heart disease and venous related pathologies. Not all the associations are necessarily easy to explain; others are. Heart failure (especially right-sided) results in an increase in atrial natriuretic peptide (ANP), which has a direct natriuretic effect (as well as through suppression of renin and aldosterone secretion). In those with oedema forming states (including those with venous system dysfunction) there may be considerable third-spacing of fluid in the lower extremities which become mobilised to within the vascular system when the patient becomes supine. It has been postulated that hypertension may have some impact on the resetting of the pressure natriuresis centres in the kidney and so exert an effect on nocturia accordingly. Chronic obstructive airways disease also has an impact on nocturia. Possible mechanisms of interaction again relate to pulmonary hypoxia and ANP secretion. Asthma and emphysema have also been implicated. The relationship between smoking and nocturia remains uncertain. Some studies report a protective effect of smoking (a nicotine-induced arginine vasopressin stimulated reduction in nocturnal urine production has been postulated) but others have suggested an association with increased episodes of nocturia. Associations with regular exercise are also somewhat indeterminate but at least one study suggests a protective effect of exercise. Evening fluid consumption almost certainly contributes to nocturnal polyuria. Arginine vasopressin (AVP) plays an adjunctive role. The nocturnal secretion of AVP is certainly blunted with age such that the diurnal variation changes to a more uniform pattern of secretion (and consequently a greater night time secretion pattern). All in all there is an exaggerated natriuresis to fluid challenges (especially late in the evening).

Nocturia has a tremendous impact on an individual's quality of life. At the most basic level nocturia is associated with an increase in daytime fatigue but at other levels is associated with depression and a deleterious effect on general mood, etc. For those individuals who require care from a relative there is also a cost, with higher levels of depression and chronic illness amongst their carers. This, for many, is indication enough for intervention. A counterpoint argument could nevertheless question why should we be so concerned about nocturia? It may be bothersome but it is hardly life-threatening? The surprising answer to that however is just that – it can be life-threatening. Indeed, the impact of nocturia has long been underestimated. Significantly it has been linked not only with poor daytime functioning and decreased quality of life indices, but also with mortality. The increased risk of mortality associated with nocturia should not – on further reflection – be as surprising as it might at first appear given that nocturia is associated with a number of potentially serious medical problems, which include cardiovascular disease, hypertension, diabetes and renal disease. Nevertheless, there are studies, which continue to show a link even after controlling for these. It would appear that nocturia may be (in some way) a marker of overall poor health, its influence perhaps mediated by sleep. One of the clearest (and most easily understood) consequences of nocturia is the impact on quality of life (and mediated through reduced levels of daytime functioning). There seems to be little doubt amongst researchers that poor sleep is the critical link. Short periods of sleep have also been linked with both abnormalities of endocrine dysfunction as well as glucose metabolism. For periods of sleep less than six hours there is an association with impaired glucose tolerance and type II diabetes mellitus (even after a number of confounding factors have been accounted for). Obesity and hypertension have similarly been linked. Gangwisch proposes that sleep deprivation reduces the secretion of leptin, increases that of ghrelin, raises overall levels of appetite, blunts insulin sensitivity and raises blood pressure. Experimental models of sleep deprivation have induced an underlying inflammatory process reflected by raised levels of interleukins and circulating leukocytes, as well as rises in C-reactive protein. All these are known to have an impact on cardiovascular disease. Others have suggested a link between sleep and the immune system and suggested (phylogenetically at least) that mammalian sleep patterns fuelled the immune system and reduced infection status. Some researchers have demonstrated that susceptibility to an administered rhinovirus was greater in those with reduced sleep duration and reduced sleep efficiency. A direct link between sleep deprivation and nocturia has also been linked with the risk of falls in the elderly. An increased risk of hip fractures in men with nocturia has been shown to be independent of age and if one considers an established 5-6% in hospital mortality rate then it is clear that there are potentially serious sequelae. Likewise it is very probable that the adverse effects of nocturia on sleep may impact on a whole range of other accidents whether traffic or workplace-based. Sleep apnoea is a particularly interesting situation where (rather than a sleep problem arising as a result of nocturia) a primary sleep disorder directly impacts on nocturia. In obstructive sleep apnoea, interruptions in breathing may cause a drop in blood oxygen levels. ANP is released as a result of airway-obstruction related hypoxia which in turn causes pulmonary arterial constriction and an increase in right atrial pressure (which consequently

releases ANP) resulting in increased sodium and water excretion as well as the inhibition of other regulatory mechanisms.

Therapies aimed at improving both nocturia and its sequelae have been extensively addressed in the literature, but there is little real help for the vexed physician and still much controversy about their utility. In many cases they simply serve to add to a growing list of medications in an elderly population. Many conventional treatments seek to address associated LUTS (for example), which are thought to impact on nocturia (perhaps via a reduction in the functional bladder capacity). The use of antimuscarinics to reduce nocturia in patients with overactive bladders probably serves only to obtund those episodes of nocturia associated with urgency rather than impacting on nocturia itself (for which it probably has little utility). Likewise the efficacy of interventions for bladder outflow obstruction (which include an assessment of their effects on nocturic frequency) have also been studied. Whilst some modest effects have been reported for alpha-blockade these are probably not significant. Similarly, combination treatment with both alpha-blockade and five-alpha reductase inhibitors fared no better. Interestingly, surgical interventions for bladder outflow obstruction (in the form of a transurethral resection of prostate (TURP) at least) would appear to be more effective in reducing nocturic episodes – between 0.8 and 1.6 per night. A variety of theories have been proposed and include deafferentation of the afferent neurons responsible for initiating involuntary detrusor contractions. Antidiuretic therapy (specifically treatment with desmopressin) is effective and reflects an underlying nocturnal polyuria in many patients with nocturia. Inappropriate water intake can lead to hyponatraemia and is the main safety consideration (and not recommended for treatment in the over 65-year-old group of patients). Because of this many who might otherwise have benefited from therapy are effectively excluded from treatment.

## Summary

Nocturia is multifactorial in aetiology and is best regarded as a clinical entity in its own right. It represents an interplay between nocturnal polyuria, functional bladder capacity and global polyuria. Numerous co-morbidities impact on nocturia and range from cardiovascular and pulmonary pathologies to behavioural and lifestyle factors. Many of the pharmacological interventions generally associated with the lower urinary tract are ineffective and reflects their minor role in the aetiology of nocturia. Whilst desmopressin treatment is effective in those with established nocturnal polyuria – it is not recommended in the over 65 year cohort (effectively excluding many who would have otherwise have benefited from treatment). A multidisciplinary approach to these patients is recommended.

**Recommended reading**

Weiss MD, FACS JP, Blaivas MD, et al. *Nocturia: Causes, Consequences and Clinical Approaches.* Springer. ISBN: 978-1-4614-1156-7.

**Declaration of competing interests:**
None declared.

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