Nocturia

Tim Lane

Abstract

Nocturia is a poorly understood symptom complex. It is seldom the result of obstructive lower urinary tract symptoms alone. Its association with multiple medical comorbidities and nocturnal polyuria explains the generally poor response to interventions aimed at improving outflow obstruction or lessening the impact of bladder instability. Nocturia is increasingly recognized as a surrogate marker for poor health and one that carries with it an increased risk of mortality. The management of nocturia needs to address not only the underlying medical conditions, but also the impact of nocturnal polyuria – the latter through anti-diuretic pharmacology or by manipulating the timing of an individual's diuresis to avoid periods of sleep. Those interventions which increase the time before the first wake to void in an individual with several episodes of nocturia should be deemed of greater clinical significance than those that simply reduce the total number of voided episodes. In this respect an understanding of the restorative function of deep slow-wave sleep should not be underestimated. A failure to understand the fundamental causes of nocturia frequently results in an ineffective polypharmacy which further impacts on the quality of life in a predominantly senescent population.

Keywords Anti-diuretic pharmacotherapy; LUTS; nocturnal polyuria; sleep apnoea

Nocturia has been described as the '*Cinderella*' of lower urinary tract symptoms.[1] An often neglected and unappreciated symptom complex, its routine dismissal as a non-specific 'storage' symptom belies the significant impact on the overall health and well-being of an individual. In recent years, however, both its aetiology and management has been addressed in greater detail.[2] Most importantly of all is that it is predominantly a result of nocturnal polyuria. The International Continence Society defines *nocturia* as waking during the night (at least once) to urinate. The essential feature of the definition relates to the necessity of sleep to precede the episode and specifically excludes 'convenience' voids - voiding once awake having been awoken for other reasons. There is an implied 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.[3] Unlike many of the other symptoms associated with lower urinary tract dysfunction – nocturia has the potential to cause significant morbidity and mortality – especially in an elderly cohort of patients.

Epidemiology of nocturia

The prevalence of nocturia (a reflection of how widespread the condition is within the population) has, to a greater or lesser extent, been evaluated by a number of studies. Many have relied on questionnaires. While these studies provide a plethora of data relating to frequency, severity and bothersomeness of nocturia they are invariably affected by recall bias. As a result, there has been a move towards the use of frequency–volume diaries in more recent years (which are unaffected by recall bias). The best known of these recent studies is the Finnish National Nocturia and Overactive Bladder (FINNO) Study.[4] It used frequency–volume charts to assess both the frequency and the volumes of voided urine in a community of men and women aged 18–79 years old and residing in a Dutch municipality. The frequency-volume charts provided information both in respect of daytime voiding patterns, nocturia and urine volumes produced by night and by day. The authors of this study found that nocturnal voiding frequency had a strong relationship with age, clinical benign prostatic hyperplasia (BPH), the use of diuretics and nocturnal polyuria (where the total amount of urine production at night was greater than one-third of all urine produced in a 24-hour period). Between the ages of 50–59 years approximately 11% of men and 15% of women voided at least twice at night. In those between 60 and 69 years 37% of men and 22% of women voided twice at night and in the 70 to 79-year-old age group 44% of men and 34% of women had similar symptoms. The authors were able to place a value on the mean nocturnal urine production – that of 60 ml/h. As a result, they were also able to suggest that nocturnal urine production exceeding 90 ml/h was 'abnormal'. Overall nocturia was just as common in men as women (one out of eight men and women reporting two episodes of nocturia a night), but a more age-specific sub-group analysis suggested that nocturia was more common in young women than young men (greater than ten times as many) while in an older age group there was considerably more nocturia in men than women. Parity was achieved by the sixth or seventh decade. The prevalence of nocturia increased at a relatively steady rate with mean increases in odds ratio (OR) at 7.3% per year for men and 3.5% per year for women. So while there is a greater prevalence of nocturia among younger women, there is a higher rate of increase in nocturia among men such that there is an equalization of prevalence by middle age. While the prevalence of nocturia is by now perhaps better understood – its incidence (the rate of occurrence of new cases) is less clearly appreciated. There exists a paucity of such reports, which are in part a reflection of the difficulties in designing appropriate studies. Such studies would require repeated longitudinal assessments of a study group over time, are affected by the reversibility of the condition and sampling issues, etc. That said, there is some evidence to suggest that the incidence of nocturia ranges between 61 cases (per thousand patient years) in a younger cohort of patients (in their 50s) and 93 cases per thousand in an older cohort of patients (60 to 70-year-old cohort of patients).

Medical conditions associated with nocturia

For the practising urologist it is essential to realize that a patient presenting to the clinic with the principal complaint of nocturia should be evaluated outside the normally narrow confines of a lower urinary tract assessment – in large part because of the multifactorial nature of its aetiology. Nocturia (despite being the most prevalent of lower urinary tract symptoms) now holds the

Tim Lane ***FRCS(Urol) MD BSc(Hons)*** *is a Consultant Urologist (Laparoscopic and Robotic Surgery) at South Bedfordshire and Hertfordshire Urological Cancer Centre, The Lister Hospital, Stevenage, Hertfordshire, UK. Conflicts of interest: none declared.*

unique position in that it may arise purely as a result of pathologies unrelated to the urinary tract. As a result, it is useful to consider some of the possible causes under a number of distinct (but often interwoven) medical pathologies (Table 1).

Lower urinary tract conditions

Unsurprisingly a large number of pathologies related to the lower urinary tract impact on nocturia and are of course the richest source of potential interventions for the urologist charged with improving nocturia in a patient referred to the out-patient's department. In those men with impaired emptying of their bladder secondary to enlarged prostates there is an increase in LUTS – and this includes nocturia. This is related in part to incomplete bladder emptying and in part to detrusor overactivity. Impaired bladder emptying results in a bladder that empties poorly and that effectively has a lower functional capacity. A bladder that has emptied poorly before an individual retires to bed is much more likely to fill to a capacity that results in the patient being awoken from sleep to void. Treatments (as we will see) to improve bladder emptying have, however, only modest effects on nocturia and suggests that there are more profound influences on nocturia than bladder emptying alone. The indirect effect of impaired bladder emptying on bladder overactivity may well, however, be more significant. Over-active bladder symptoms are well documented as increasing with age and nocturia commonly occurs as a result of this. There are a wide variety of medical pathologies that can result in uninhibited detrusor contractions (dementia, Parkinson's disease, etc.) and impact upon nocturia as a result. Interestingly, urodynamic evidence points towards both impaired bladder contractility as well as detrusor overactivity with increasing age and might explain some of the anomalies in respect of treatment success (or otherwise) of therapies directed at pathologies in the LUT. Radiation cystitis, interstitial cystitis and urinary tract infection may all impact on nocturia by decreasing bladder capacity.

Cardiovascular problems

There is a large number of studies linking nocturia with cardiovascular disease, including from heart failure, coronary artery disease, venous stasis disorders and hypertension. In the majority of cases nocturnal polyuria is the principal mode by which these pathologies impact on nocturia. It is inevitable that a greater urine output at night (something that is normally kept to a minimum as a result of a physiological surge in AVP in the

Medical and urological conditions impacting on nocturia

Urological contribution	Shared care	Medical contribution
Diagnosis of LUTD		**Diagnosis of conditions causing NP**
• Urological/LUTS evaluation		• Evaluate patient's known conditions
• Nocturia symptom scores		• Screening for sleep disorders
• Bladder diary		• Screening for potential causes of polyuria*
Conservative management	**Conservative management**	**Management**
Behavioural therapy	• Antidiuretic	• Initiation of therapy for new diagnosis
• Fluid/sleep habits advice	• Diuretics	• Optimized therapy of known conditions
• Drugs for storage LUTS	• Drugs to aid sleep	
• (Drugs for voiding LUTS)		
• ISC/catherization		
Interventional therapy		**Potential causes of polyuria**
• Therapy of refractory storage LUTS		*Nephrological disease*
• Therapy of refractory voiding LUTS		• Tubular dysfunction
		• Global renal dysfunction
		Cardiovascular disease
		• Cardiac disease
		• Vascular disease
		Endocrine disease
		• Diabetes insipidus/mellitus
		• Hormones affecting diuresis/natriuresis
		Neurological disease
		• Pituitary and renal innervation
		• Autonomic dysfunction
		Respiratory disease
		• Obstructive sleep apnoea
		Biochemical
		• Altered blood oncotic pressure

From the EAU 2016 Guidelines in Urology with kind permission of Elsevier.

Table 1

evening) will result in a greater need to void. The mechanism, however, by which these pathologies impact on nocturnal polyuria is not always quite so clear. In cases of heart failure (incompletely treated) the impact on nocturnal polyuria is better understood and is mediated by atrial natriuretic peptide (ANP). It has an important role in sodium excretion via its suppression of renin and aldosterone excretion and via a direct natriuretic effect. ANP (released from the cardiac atrium) increases GFR and filtration fraction which increases diuresis and natriuresis.

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 mobilized to within the vascular system when the patient becomes supine. One mechanism by which hypertension might impact on nocturnal polyuria might be by resetting the pressure natriuresis centre in relation to the kidney.

Pulmonary pathology

Patients with COPD, asthma and emphysema have a common pattern of increased airway resistance. This increased airway resistance raises ANP which in turn increases renal sodium and water excretion which ultimately impacts on nocturia via nocturnal polyuria. Haemodynamic changes, pulmonary hypertension and hypoxia have all been mooted as possible causes for ANP release.

Sleep disturbance

There is a very large number of sleep-related factors which may lead to nocturia and include insomnia, snoring, restless leg syndrome and a variety of sleep disorders related to conditions such as depression and anxiety or alternatively related to neurological disorders such as Alzheimer's disease, Parkinson's or dementia. 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. Deep slow-wave sleep patterns occur in the first few hours of sleep and are widely believed to provide the most restorative aspect of sleep. It is through a reduction in this aspect of sleep that most daytime fatigue and somnolence is contributed to. As such waking at night is not only important in respect of the number of episodes but also the timing of those awakenings.

The impact of nocturia

The impact of nocturia has been underestimated for many years. While it has been clear that they cause bothersome symptoms (alongside other storage symptoms such as urgency and daytime frequency) to a greater degree than obstructive symptoms, it is perhaps less widely appreciated that the impact can be more global. Nocturia impacts further through loss of sleep which results in daytime fatigue, lower quality-of-life indices and a perception of poorer overall health. The quality-of-life impact is generally greater in those waking to void on at least two occasions (and something supported by both the FINNO study, a US-based study in women and a community based study in Taiwan).[2,4] Poor sleep and fatigue are the clear links with these quality-of-life indices. There is evidence to suggest that there are mechanisms of action which link reduced periods of sleep with deleterious effects on the metabolic and endocrine systems. Short periods of sleep have been linked with both abnormalities of endocrine dysfunction as well as glucose metabolism. For periods of sleep less than 6 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). A lack of sleep reduces leptin and increases ghrelin levels, it increases appetite and blunts insulin sensitivity – all of which could mediate the deleterious effects of sleep deprivation. Sleep deprivation has been demonstrated to increase interleukin circulation as well as peripheral circulating white cells. Likewise, CRP levels have also been shown to rise. All this is significant insofar that cardiovascular disease and obesity have been characterized at some level as an inflammatory process. Work continues to identify the specific associations of sleep disturbance – such as sleep continuity and sleep efficiency – with quality of life issues. Some researchers have demonstrated that susceptibility to an administered rhinovirus was greater in those with reduced sleep duration and reduced sleep efficiency. There are some very particular concerns in an elderly population. Some are obvious. Falls and fractures contribute to both an increase in morbidity as well as mortality. One study in a Japanese community-based study of an elderly population demonstrated that in those who were awoken to void on at least two occasions a night, there was a double the risk of falls and fractures. 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. The impact on caregivers is less well defined but there is some evidence that the impact is of a similar level. Efforts to treat nocturia in an elderly population are frequently misguided. Despite the increased understanding of the multi-factorial nature of nocturia there is still a tendency for nocturia to be attributed to either BPH or overactive bladder. As a result, many elderly patients not only face inappropriate therapy with alpha-blockade, anticholinergics and subsequent polypharmacy but they also miss out on opportunities to address significant medical co-morbidities which may ultimately have a much greater impact on overall health.

A urological approach to the management of nocturia

Given the multi-factorial nature of nocturia it must be clear by now that a more holistic approach to the patient with nocturia is mandatory. That said, the urological assessment and treatment of a patient with nocturia will inevitably focus predominantly on those remediable urological conditions which will diminish or mitigate episodes of nocturia. In patients presenting with LUTS suggestive of bladder outflow obstruction, nocturia is thought to

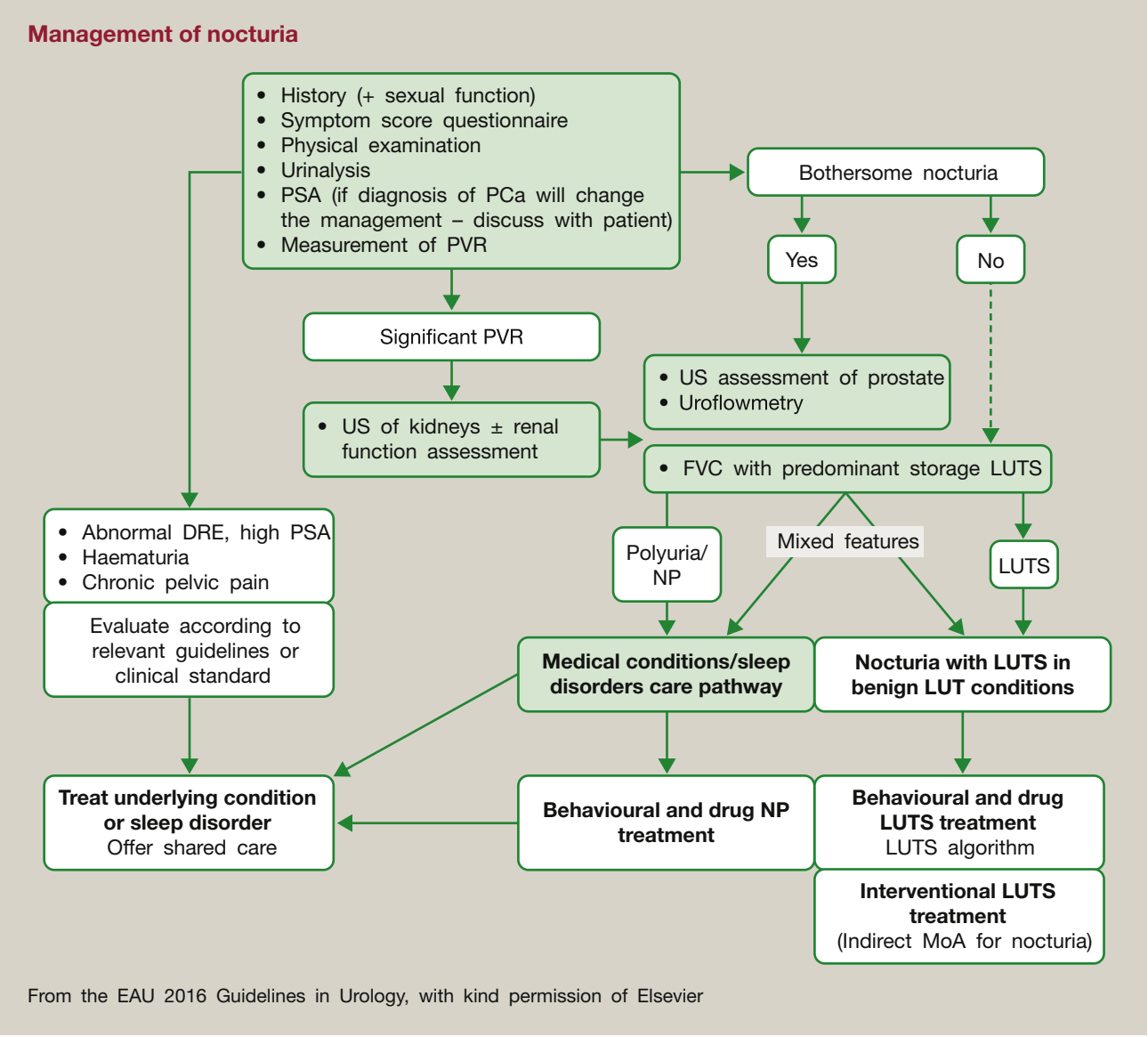

Figure 1

be contributed to by a combination of large post-void residuals, detrusor activity, low functional bladder capacities and nocturnal polyuria. The key to optimum outcomes here is to address all these facets relating to the LUT while additionally identifying concomitant medical co-morbidities which can subsequently be addressed by a multidisciplinary team approach (Figure 1). Many of the interventions aimed at addressing specific LUT pathologies have not always proven to be of particular value which may ultimately strengthen the argument for a multi-disciplinary approach to the management of nocturia.

Nocturia and the overactive bladder

Nocturia is a common association with an overactive bladder. A reasonable assumption would therefore be that antimuscarinics would have a significant role in reducing episodes of nocturia. The evidence is not that clear however. Theoretically their effect might only be significant should the episodes of nocturia be associated with urgency (as there is no direct effect on nocturnal polyuria). While some studies have demonstrated statistically significant reductions in the episodes of nocturia – their clinical significance is far less clear and many researchers regard the improvements as having doubtful clinical significance.

Nocturia and bladder outflow obstruction

Nocturia has been assessed as the most bothersome of symptoms in men with BPH. Outflow obstruction impairs the ability of the bladder to empty and increases post-void residuals. The medical treatment of outflow obstruction consists of combinations of alpha-blockers (which relax smooth muscle) and 5-alpha reductase inhibitors (which reduce the volume of the prostate). While bladder emptying invariably improves, the impact on nocturia is less clear. Some studies have shown reduction in episodes of nocturia but others have failed to reach statistical significance. Standard surgical interventions (such as TURP) are designed to improve obstructive symptoms. The impact of surgery on storage symptoms such as nocturia (as with medical

treatment) is however substantially less clear. Most surgical interventions are associated only with a modest reduction in episodes of nocturia and some have speculated that its principal role is in the de-afferentation of those neurons responsible for initiating involuntary detrusor contractions. Episode reductions of between 0.8 and 1.6 have been described. More recent studies have suggested that surgery for BPH may improve symptoms more than previously thought and more rapidly than previously suggested. Alternatives to outflow obstruction management include intermittent self-catheterization. Large post-void residuals last thing at night can effectively be managed with a once nightly catheter such that residuals are emptied and the functional bladder capacity returned towards normal.

Nocturia and nocturnal polyuria

One of the reasons why treatments traditionally focused at managing bladder outflow obstruction and over-active bladders have singularly been disappointing is that the majority of patients presenting with nocturia have a significant contribution from nocturnal polyuria. It is the single most common cause of nocturia in the urological patient. If this remains undiagnosed then other treatments remain largely ineffective. There are a wide number of causes for nocturnal polyuria. They range from the simple - excessive fluid intake before bed (which would normally respond to simple fluid restriction) to a blunting of the normal circadian rhythm of anti-diuretic hormone release. A variety of cardiovascular pathologies (perhaps mediated by ANP rises) also impact on nocturnal polyuria. As such, anti-diuretic therapy has a significant role to play in those who have failed more conservative approaches. Desmopressin (a synthetic analogue of AVP) is currently the only widely available anti-diuretic drug. It has roles in the management of diabetes insipidus, primary nocturnal enuresis as well as nocturnal polyuria. In those with nocturnal polyuria (and not responding to fluid restriction) it effectively mitigates the insufficient release of endogenous AVP. Desmopressin is both more powerful and has a longer lasting diuretic action than AVP. It stimulates water resorption in the distal and collecting tubules of the kidney. It effectively reduces urine output and delays the need to void. It has a rapid onset of action and is highly effective. However, its principal side-effect is that of hyponatraemia. Its administration therefore requires measuring sodium levels pre-treatment and then thereafter. As a result, anti-diuretic treatment in those over 65 years of age is not recommended. Caution is advised with DDAVP administration. Medication is contraindicated where cardiac insufficiency is present or in other conditions in which diuretic agents are prescribed. Particular care should be ensured to prevent fluid overload in those patients with electrolyte imbalances as well as those at risk of raised intracranial pressure. A careful review of concomitant medication is essential. Tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine may have additional anti-diuretic effects which might potentiate the adverse effects of therapy. Likewise, the ubiquitous use of NSAID medications (which similarly may induce water retention and hyponatraemia) represents another potential contraindication. Drugs which slow intestinal transit time can increase plasma concentrations of orally administered DDAVP and so increase the risk of water retention and hyponatraemia.

Conclusion

Nocturia is a unique symptom often associated with lower urinary tract dysfunction. Uniquely, however, nocturia may arise purely as a result of pathologies unrelated to the urinary tract. While a urological approach to management will inevitably focus on reducing the impact of bladder overactivity and aim to encourage complete bladder emptying, it also acknowledges the significant impact that nocturnal polyuria has on night time voiding and the wide variety of medical co-morbidities which may impact directly or indirectly on this. Management is aimed at addressing the underlying medical pathologies and by either obtunding the diuresis pharmacologically (antidiuretic pharmacotherapy) or by encouraging a diuresis before patients retire to sleep. While reducing the number of episodes of nocturia is important, delaying the time to first awakening may ultimately be of greater significance (allowing the individual to benefit from the more restorative aspects of deep slow-wave sleep) than a number reduction in episodes of nocturia alone. ◆

REFERENCES

1 Lane T. Nocturia – the Cinderella of LUTS. *Urol News* 2014; **18:** 7–9. March-April.
2 Nocturia – causes, consequences and clinical approaches. Editors: Weiss et al Springer (Publisher) ISBN 978-1-4614-1155-0.
3 van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the standardisation subcommittee of the ICS. *Neurourol Urodyn* 2002; **21:** 179.
4 Tikkinen KA, Johnson TM, 2nd, Tammela TL, et al. Nocturia, frequency, bother and quality of life: how often is too often? A population based study in Finland. *Eur Urol* 2010; **57:** 488–98.