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Nocturia: aetiology and treatment in adults

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Abstract | Nocturia is an extremely common condition that has major sequelae for affected patients. Through disruption of sleep, nocturia impairs quality of life and worsens health outcomes, and is associated with a variety of morbidities including diabetes, coronary artery disease, obstructive sleep apnoea, obesity, metabolic syndrome, and depression. Unsurprisingly, several studies have also linked nocturia with reduced survival. Nocturia is not simply a consequence of lower urinary tract disease; rather, it is a multifactorial disorder that is often a manifestation of an underlying renal or systemic disease. Through the use of the frequency volume chart, clinicians can accurately quantify nocturia and determine its aetiology. Evaluation of quality of life and sleep using simple measures is essential in order to assess the impact of nocturia on a patient. Numerous treatment options for nocturia exist, but most are associated with minor benefit or lack sufficient evidence supporting their use. By systematically analysing an individual's causes of nocturia, clinicians can design appropriate treatment strategies to most effectively treat this condition.

The International Continence Society (ICS) defines nocturia as "the complaint that the individual has to wake at night one or more times to void" (REF. 1). This waking is preceded and followed by the intention to sleep. Although a patient with one nightly void is considered to have nocturia, two or more episodes are generally considered as being clinically significant, as this threshold is the one that is associated with reduced quality of life and survival[2,3].

Nocturia is a widespread condition that has a major impact on the lives of affected patients, but is widely misunderstood by patients and physicians alike[4]. One study in Taiwan reported that only 25% of women with two or more nocturnal voids sought medical advice; many did not seek treatment because of their perception that nocturia is a normal part of ageing or that it is untreatable[5]. Of the women that did see a physician, only 63% were offered treatment, perhaps suggesting that physicians are also unfamiliar with nocturia and its treatment options. Remarkably, nocturia is still the most common of the lower urinary tract symptoms (LUTS) to present at urology clinics, accounting for 33% of all LUTS-related chief complaints[6]. Clearly, nocturia is a problem that many clinicians will encounter in practice and must be prepared to manage.

This Review discusses the clinical relevance of nocturia and the necessity for treatment. It provides a contemporary approach to the management of a patient with nocturia, with various aetiologies being described, alongside the appropriate diagnostic tools to identify them. The most recent data regarding treatment options are described, followed by methods to tailor treatment strategies for individual patients.

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Burden of nocturia

An analysis of 43 articles reporting nocturia prevalence in community-based populations revealed that nocturia tends to increase in prevalence with age, but is still a considerable problem in younger populations. In the studies reviewed, up to 60% of the elderly (aged >70 years) and 15–20% of young adults (aged 20–40 years) experienced two or more nightly voids[4]. Young women were more likely to have nocturia than young men, but rates were equal between genders in older populations[4]. Black and Hispanic populations have also been reported to be at increased risk of nocturia compared with white populations[7].

Quality of life

Nocturia is the most bothersome of all of the LUTS and is the most strongly associated with reduced quality of life, as evaluated by health-related quality of life questionnaires[8–10]. Specifically, two or more voids per night is associated with reduced quality of life[2]. An improvement in nocturia has a profound beneficial effect on quality of life[11].

Nocturia is associated with daytime fatigue, poor concentration and decreased mood, problems that can result in many issues including decreased work

Key points

- Nocturia remains underreported and undertreated, despite its prevalence and association with significant morbidity and mortality
- Nocturia has multiple aetiologies, including overproduction of urine (global polyuria and nocturnal polyuria), reduced bladder storage capacity, sleep disorders and a combination of these conditions
- The frequency volume chart, Nocturia Quality of Life questionnaire and the duration of the first uninterrupted sleep period should be used in the assessment and follow-up monitoring of each patient
- Management strategies should be targeted to each patient's specific aetiology of nocturia; some patients might require multicomponent therapies

performance and even motor vehicle accidents[12]. Depressive symptoms are also more common in individuals with nocturia, especially among those who also report sleep disturbances[13].

Sleep quality. Patients often subjectively report impairment in sleep as a result of nocturia. In the analysis of a 2003 National Sleep Foundation survey conducted in a representative sample of the United States population, nocturia was a self-reported cause of sleep disturbance every night or almost every night in 53% of the study population (aged 55–84 years); it was over four times as prevalent as the next most frequent cause (pain)[14].

The perception that nocturia is associated with sleep disturbances has been supported by both objective measures of sleep quality and clinically validated questionnaires. Nocturia is associated with decreased sleep efficiency (defined as the duration of time spent asleep divided by duration of time of intended sleep), decreased total sleep time, decreased proportion of rapid eye movement (REM) sleep, increased arousal during sleep and longer periods of hypoxaemia[15,16]. Subjectively, patients with nocturia are sleepier, as measured by the Epworth Sleepiness Scale score, and suffer from reduced sleep quality, as measured by the Pittsburgh Sleep Quality Index, compared with individuals without nocturia[15,16]. Thus, it might be prudent for clinicians to consider nocturia when a patient's primary complaint is poor sleep.

The early hours of sleep, during the first two sleep cycles, include a majority of the night's deep sleep, or slow-wave sleep (SWS)[17]. SWS is important for glucose and metabolic regulation. Interruption of SWS (without a change in total sleep time) results in reduced insulin sensitivity, impaired glucose tolerance, and increased plasma glucose levels[18,19]. Disruption of REM sleep has a less clear effect on glucose homeostasis, with studies reporting conflicting results[19–21]. Decreased SWS is associated with depression, obesity, type 2 diabetes mellitus, and hypertension[22,23].

As a patient's first nocturnal void often occurs 2–3 h after sleep onset, it is intuitive that nocturia disrupts SWS[24]. Adults who wake early to void during their first two sleep cycles spend 34% less time in SWS than adults who sleep undisturbed through two sleep cycles[25]. Furthermore, disruption in sleep continuity throughout the night can also reduce SWS. Despite equivalent total sleep times, patients who experience repeated awakenings during the night spend less time in SWS than patients with uninterrupted sleep[26]. Likewise, adults with at least two episodes of nocturia spend 35% less time in SWS compared with those without nocturia[25]. Although no direct evidence is currently available, nocturia might put patients at an increased risk of depression, type 2 diabetes and metabolic syndrome by disrupting SWS.

Because the initial hours of sleep are vital to overall sleep quality, interest has been growing in the time to first void after sleep onset, or the first uninterrupted sleep period (FUSP). The duration of FUSP is drastically reduced with increasing severity of nocturia[27]. A shorter FUSP is associated with increased daytime dysfunction and decreased sleep quality, sleep efficiency and total sleep duration[28]. Under treatment conditions, a longitudinal increase in FUSP over time is strongly associated with improvements in most Pittsburgh Sleep Quality Index (PSQI) subscales[29]. As the PSQI is a clinically validated tool for measuring sleep quality, this finding supports FUSP as a useful proxy for sleep quality[30]. Not only has FUSP been shown to correlate with sleep quality, it also seems to predict health outcomes. Prolonging the FUSP in patients with nocturia has been shown to reduce random blood glucose concentration after >3 months of follow-up[31]. Thus, FUSP can be used as a simple, valuable metric for both health and sleep quality in patients with nocturia.

Morbidity and mortality

Many studies have shown nocturia to be associated with increased mortality[3,32–35]. Data from the Third National Health and Nutrition Examination Survey found nocturia to predict mortality, especially in adults aged <65 years[3]. Another study demonstrated that mortality was higher in patients with known coronary heart disease (CHD) and nocturia than in those with known CHD without nocturia[33]. The Krimpen study, however, found that the increased mortality seen in patients with nocturia was explained by confounding variables, most importantly age[36]. A recent meta-analysis determined that nocturia of two or more voids increased risk of mortality by 22%, and three or more voids increased the risk of mortality by 46%[34]. The study also confirmed that this mortality risk was especially profound in young adults.

Various reasons might explain an increased mortality risk in patients with nocturia. For example, nocturia increases the risk of falls and fractures in the elderly[35,37,38]. In addition, shorter duration of sleep and poor sleep quality are associated with increased all-cause mortality[39,40]. Reduced sleep efficiency predicts increased mortality in healthy older adults[40]. Excessive daytime sleepiness, greater night time wakefulness and poor subjective sleep quality are also associated with an increased risk of frailty or death[41].

Nocturia is linked to numerous morbidities that might also contribute to its association with an increased risk of mortality. These include urinary urgency, benign prostatic hyperplasia (BPH), prostate cancer, snoring, obesity, obstructive sleep apnoea (OSA), diuretic use, coronary artery disease, diabetes, metabolic syndrome, parity and menopause in women, low testosterone in

men, black or Hispanic race, depression, antidepressant use, and restless legs syndrome[7,13,42–45]. Nocturia has been suggested to presage the future development of CHD in younger men, although a meta-analysis did not confirm these findings[32,46].

Nocturia is a complex process implicated in various diseases. With some of these conditions, the direction of the relationship with nocturia is yet unknown. BPH and OSA, for example, are known to directly cause nocturia; the relationship with other diseases is less clear. Nocturia might be a symptom of these morbidities and/or a risk factor for their subsequent development. Nevertheless, nocturia can evidently be used as a clinical predictor of current and future disease.

Physiology of arginine vasopressin

Before discussing the various aetiologies of nocturia, it is important to understand the physiology of urine production. Arginine vasopressin (AVP) is the hormone at the centre of water balance. It maintains normal serum osmolality by regulating excretion of water in the urine. For example, dehydration leads to increased serum osmolality as water is lost. The increase in osmolality activates osmoreceptors in the hypothalamus, which then signal release of AVP from the posterior pituitary gland[47]. AVP acts on V2 receptors in the late distal tubule and collecting ducts of the kidney to stimulate membrane intercalation of aquaporins, channels that increase the kidney's permeability to water. AVP thus allows reabsorption of water and reductions in both urine volume and serum osmolality. In the absence of AVP, water is not reabsorbed and diuresis occurs. Some factors that antagonize AVP and promote water diuresis include prostaglandin E2, atrial natriuretic peptide (ANP), hypercalcaemia, hypokalaemia and lithium[48].

Secretion of AVP is primarily regulated by serum osmolality, but a natural diurnal fluctuation in AVP also occurs. In adults without nocturia, AVP levels peak at night. Adults with nocturnal polyuria do not have this nocturnal increase in AVP[49]. AVP has an integral role in nocturnal urine production, making it an appropriate target in nocturia treatment.

Aetiologies of nocturia

Traditionally, nocturia was considered a symptom of lower urinary tract disorders, such as BPH and overactive bladder (OAB). We now understand that nocturia can also be a manifestation of renal or systemic disease, and that the nocturnal overproduction of urine — nocturnal polyuria — is a major contributor[50].

The classification of nocturia by aetiology is important for understanding the multifactorial nature of the disorder and targeting treatment towards the underlying pathophysiology in each patient. In simple terms, the causes of increased nocturnal urinary frequency can be classified as one of the following, or a combination thereof: increased production of urine; decreased storage of urine; or voiding because one is already awake. These groups can be more specifically categorized into global polyuria, nocturnal polyuria, reduced bladder capacity, sleep disorders and mixed disorders.

Global polyuria

Global polyuria is the overproduction of urine throughout the day and night. As urine volume exceeds the capacity of the bladder, both daytime and nocturnal urinary frequency occur.

Causes of global polyuria include uncontrolled diabetes mellitus, diabetes insipidus and primary polydipsia. Diabetes insipidus can be caused by either deficiency of AVP (central diabetes insipidus) or insensitivity of the kidney to AVP (nephrogenic diabetes insipidus)[48]. Acquired causes of nephrogenic diabetes insipidus include hypercalcaemia, chronic kidney disease and intake of certain medications (for example, diuretics, selective serotonin reuptake inhibitors, calcium-channel blockers, tetracyclines and lithium)[48,51]. Primary polydipsia is an excessive intake of water that is caused by either psychiatric illness (psychogenic polydipsia) or a rare abnormality of the thirst mechanism (dipsogenic polydipsia)[52].

Nocturnal polyuria

Nocturnal polyuria is the overproduction of urine at night. Patients with nocturnal polyuria do not necessarily suffer from concomitant daytime urinary frequency.

Nocturnal polyuria occurs in patients with increased levels of ANP (for example, those with OSA or congestive heart failure (CHF)), patients with peripheral oedema (for example, those with venous insufficiency, CHF, liver failure, chronic kidney disease and nephrotic syndrome), patients with impaired circadian rhythm of AVP, patients with excessive nocturnal fluid intake, and patients on diuretics[51].

OSA involves respiratory effort against a closed airway, resulting in hypoxaemia and secondary pulmonary vasoconstriction[53]. The latter causes right atrial dilation and release of ANP, which increases glomerular filtration rate of the kidneys by dilating the afferent arterioles, and inhibits reabsorption of sodium in the collecting ducts[54]. ANP thus promotes natriuresis and urine production. More recent data in rat models suggest that OSA might also contribute to nocturia through effects on the bladder: oxidative stress from hypoxic episodes resulted in detrusor instability, reduced bladder compliance and increased spontaneous contractions[55].

As patients with peripheral oedema lie supine at night, interstitial fluid can redistribute into the intravascular compartment; this additional water load on the kidney results in increased urine production[51].

An impaired circadian rhythm of AVP is also implicated in nocturia. Overnight secretion of melatonin and AVP is higher in patients without nocturia than in those with nocturia[49,56]. Night-shift workers have been shown to have an increased frequency of nocturia, although this finding might be the result of decreased nocturnal bladder capacity rather than increased nocturnal polyuria[57].

Reduced bladder capacity

Reduced bladder capacity creates a mismatch between urine production and storage capacity. Reduced bladder capacity can be constant or only nocturnal, resulting in either daytime frequency or nocturia, respectively. These various aetiologies can diminish bladder capacity by

physically reducing space in the bladder (for example, in patients with a high postvoid residual volume of urine caused by incomplete emptying) or by stimulating voids at volumes lower than total bladder capacity.

Causes of reduced bladder capacity include BPH, neurogenic bladder, idiopathic nocturnal detrusor overactivity, cystitis (bacterial, interstitial, tuberculous or radiation cystitis), bladder cancer, prostate cancer, urethral cancer, ureteral calculi, bladder calculi, extrinsic compression, urogenital prolapse, learned voiding dysfunction, anxiety disorders, and medications (for example, β-blockers)[51,58]. Although such conditions affecting bladder capacity can exacerbate nocturia, when or how these conditions cause daytime versus night-time urinary frequency has never been demonstrated.

As defined by the ICS, OAB is a clinical diagnosis made on the basis of the symptoms of urgency, with or without urge incontinence, usually with urinary frequency and nocturia[59]. Detrusor overactivity is diagnosed via urodynamic studies that measure involuntary detrusor contractions during the bladder filling phase. OAB is often — but not always — associated with detrusor overactivity[60]. In women with OAB, nocturia correlates with detrusor overactivity[61,62]. Patients with OAB and detrusor overactivity diagnosed using daytime urodynamic studies were found to experience increased nocturnal detrusor overactivity compared with healthy controls or patients with insomnia[63]. Furthermore, these episodes of nocturnal detrusor overactivity occurred during the 10 min preceding the nocturnal void. Thus, nocturnal detrusor overactivity probably has a role in nocturia among patients with OAB.

BPH causes nocturia owing to low bladder functional capacity from elevated postvoid residual volume and detrusor overactivity. Greater bladder outlet obstruction is associated with increased detrusor overactivity in men with BPH, suggesting that the outflow obstruction might lead to changes in bladder structure and function over time[64,65].

Sleep disorders

The relationship between nocturia and sleep disruption is bidirectional[66]. As discussed earlier, nocturia interferes with sleep. It also seems that sleep fragmentation predisposes to nocturia. When patients awaken for any reason, they might be more likely to void out of convenience or habit rather than owing to an urge[67].

Examples of conditions disturbing sleep are primary sleep disorders (for example, insomnia), secondary sleep disorders (for example, CHF), psychiatric disorders (for example, depression), chronic pain and medication or drug use[68].

Mixed disorders

Some patients with nocturia will fit neatly into the categories discussed above; others will have multiple causes of nocturia. In a review of 194 patients with nocturia, 36% had a mixed aetiology of both nocturnal polyuria and reduced bladder capacity[69]. Thus, the aetiology of nocturia can be multifactorial even in the context of one patient.

Evaluation of nocturia

Practitioners should actively seek and evaluate nocturia, as it is often underreported and undertreated[5]. As with any other medical encounter, the evaluation of nocturia should begin with a complete history and physical examination. Special attention should be given to the number of nightly voids, fluid intake, associated LUTS, symptoms of urinary tract infection, obesity, snoring, peripheral oedema, sleep quality, degree of bother, medical history and medications. If indicated, urinalysis, blood chemistry and further mechanistic testing (for example, urodynamic studies) can be performed[70].

Frequency volume chart

The mainstay of any nocturia work-up is the frequency volume chart (FVC)[1], which is a compendium of the timing and volume of voids (TABLE 1). Owing to intrapatient variability, the FVC is recommended to span 3 days for a good balance between accuracy and patient compliance, but this duration can be adjusted on an individual basis[71]. An analysis of the information in the FVC can be used to identify the underlying pathophysiology of each patient's nocturia (TABLE 1).

Global polyuria is defined as a 24-h urine volume exceeding 40 ml/kg body mass. Primary polydipsia, central diabetes insipidus, and nephrogenic diabetes insipidus can be distinguished using an overnight water deprivation test and renal concentrating capacity test[58]. The ability to concentrate urine after overnight water deprivation proves that a patient can both produce AVP and respond to AVP at its site in the distal nephron, indicating a diagnosis of primary polydipsia. If overnight concentration of urine does not occur, patients receiving a congener of AVP (for example, desmopressin) will concentrate their urine if the kidneys are normally responsive to AVP, providing a diagnosis of central diabetes insipidus. Failure of urine concentration despite exogenous desmopressin administration is indicative of a diagnosis of renal or nephrogenic diabetes insipidus[47].

Reduced bladder capacity can be global or nocturnal. A global reduction in bladder capacity is indicated by a low maximum voided volume (MVV), the largest single voided volume over a 24-h period (TABLE 1). A nocturnal reduction in bladder capacity is diagnosed if nocturia occurs at volumes less than the maximum bladder capacity, and is identified using the nocturnal bladder capacity index (NBCi), which is calculated as the actual number of voids (ANV) minus the predicted number of voids (PNV). ANV does not include the first morning void after waking. PNV is calculated as nocturia index (Ni) (TABLE 1) minus 1. When ANV exceeds PNV, NBCi is >0 and indicates reduced nocturnal bladder capacity relative to the patient's maximum 24-h capacity. NBCi >1.3 has been suggested as the threshold at which reduced nocturnal bladder capacity contributes to nocturia, but a consensus definition is not yet available[72].

Nocturnal polyuria index (NPi) is calculated as nocturnal urine volume (NUV; the total volume of urine voided during the night, including the first morning void) divided by 24-h urine volume. As defined by the

Table 1 | **Summary of the information obtainable from a frequency volume chart**

Term	Definition	Clinical application
24-h urine volume	Total volume voided over 24 h	24-h urine volume >40 ml/kg is diagnostic of global polyuria
NUV*	Total volume of urine voided during the night, including the first morning void	Alternative definitions of NP: • Nocturnal urine production rate >90 ml/h • NUV >0.9 ml/min • NUV >6.4 ml/kg
MVV	Largest single voided volume over 24 h, day or night (thus representative of bladder capacity)	Low MVV indicates reduced global bladder capacity
Ni*	Ni = NUV/MVV	Ni >1 suggests nocturia due to mismatch between production and capacity during sleep
ANV	Number of nocturnal voids, excluding first morning void	Accurate measure of nocturnal frequency (superior to questionnaires)
PNV	PNV = Ni – 1	Used to determine nocturnal bladder capacity
NBCi	NBCi = ANV – PNV	NBCi >0 indicates reduced nocturnal bladder capacity
NPi	NPi = NUV/(24 h urine volume)	NPi >20–33% diagnostic of NP (age dependent)

*An NUV exceeding bladder capacity, or a Ni >1, leads to nocturia. ANV, actual number of nightly voids; MVV, maximum voided volume; NBCi, nocturnal bladder capacity index; Ni, nocturia index; NP, nocturnal polyuria; NPi, nocturnal polyuria index; NUV, nocturnal urine volume; PNV, predicted number of nightly voids.

ICS, nocturnal polyuria is an NPi of >33% in adults aged >65 years (a definition known as the NP33 definition) and >20% in adults aged <25 years, assuming the total 24-h urine volume is normal, with gradations for intermediate age groups[1]. Thus, nocturnal polyuria is defined as a nocturnal overproduction of urine relative to overall daily urine production. Other proposed definitions of nocturnal polyuria include nocturnal urine production >90 ml/hr (NUP90), NUV >6.4 ml/kg and NUV >0.9 ml/min[73].

Recent data indicate that nocturnal polyuria can be caused by water diuresis, sodium diuresis or a combination thereof[74]. Thus, an analysis of urine and a renal function profile might be a useful adjunct to the FVC in patients with nocturnal polyuria in order to further determine each patient's pathophysiology. However, utilizing such an analysis to dictate treatment decisions is not yet ready for everyday clinical application.

Revising the definition of nocturnal polyuria. The ICS NP33 definition is currently a topic of debate. Up to 70% of men aged 50–78 years without nocturia meet the criteria for nocturnal polyuria as defined by NP33 (REF. 75). In a meta-analysis of studies comparing mean nocturnal voiding frequency in patients with and without nocturnal polyuria as defined by NP33, a mere difference of 0.6 nightly voids was found between the two patient groups[50]. If nocturnal polyuria were instead defined as NUP90, significantly fewer patients with nocturia would be considered to have nocturnal polyuria[75]. It seems that —owing to its low specificity — the NP33 definition might overestimate the prevalence of nocturnal polyuria. Therefore, some authors have suggested that the cut-off should be raised to an NPi of >53%, and many others have recommended that nocturnal polyuria should be defined on the basis of total volume of nocturnal voids, rather than as a proportion of daily urine production[73,76].

Severity of nocturia

Assessing the severity of nocturia is an important aspect of the evaluation of the patient. The FVC provides the number of nightly voids, but it does not illustrate the impact of these voids on the patient. The Nocturia Quality of Life questionnaire (N-QoL) is a validated tool that evaluates sleep, energy, degree of bother and global quality of life[70,77,78]. Other validated quality of life and symptom questionnaires can also be useful but do not measure the impact from nocturia specifically. N-QoL and FUSP can be used alongside the FVC in the primary assessment of patients with nocturia.

Management of nocturia

General treatment strategies for any patient with nocturia include night time fluid restriction, voiding before sleep and dietary modifications (for example, avoiding caffeine and alcohol). A behavioural modification program that provided the patient with a basic understanding of urine physiology, advice on regulation of fluid intake and a personalized discussion with a nurse practitioner significantly improved nocturia and quality of life[79]. For some patients, such treatment is sufficient. Most patients, however, will require further intervention designed with their individual disease pathophysiology in mind (BOX 1).

Nocturnal polyuria

The goal of therapy for nocturnal polyuria is to reduce nocturnal production of urine. The specific aetiology of a patient's nocturnal polyuria should first be identified, in order to allow treatment of the underlying disease, rather than simply treating the manifesting nocturia. Examples of disease-specific interventions include compression stockings and evening leg elevation for peripheral oedema, continuous positive airway pressure (CPAP) for OSA, optimal management of chronic diseases such as CHF, and adjustment of choice and timing

Box 1 | **Treatment strategies for various aetiologies of nocturia***

Nocturnal polyuria
- Desmopressin
- Diuretics in the afternoon
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Continuous positive airway pressure (in patients with obstructive sleep apnoea (OSA))
- Compression stockings and evening leg elevation (in patients with peripheral oedema)

Reduced bladder capacity
- Behavioural therapy: pelvic floor muscle training; delayed voiding; urge suppression (in patients with overactive bladder (OAB))
- α1-adrenergic blockers (in patients with benign prostatic hyperplasia (BPH))
- Phosphodiesterase inhibitors (in patients with BPH)
- 5α-reductase inhibitors (in patients with BPH)
- NSAIDs (in patients with BPH)
- Transurethral resection of prostate or related surgeries (in patients with BPH)
- Antimuscarinics (in patients with OAB)
- β3-adrenergic agonists (in patients with OAB)
- Percutaneous tibial nerve stimulation (in patients with OAB and neurogenic detrusor overactivity)
- Intradetrusor botulinum toxin A (in patients with OAB) and intraprostatic botulinum toxin A (in patients with BPH)
- Phytotherapies: *Pygeum africanum*, Cernilton (in patients with BPH)

Global polyuria
- Water restriction and psychotherapy (in patients with psychogenic polydipsia)
- Desmopressin (in patients with central diabetes insipidus)
- Removal of offending medications (in patients with acquired nephrogenic diabetes insipidus)
- Thiazide diuretics and indomethacin (in patients with partial nephrogenic diabetes insipidus)
- Glycaemic control (in patients with diabetes mellitus)

Sleep disorders or disruptions
- Behavioural therapy: reducing time in bed and maintaining a regular sleep schedule
- Melatonin
- Sedative-hypnotic drugs

Mixed disorders

Various combinations of the above options

*General strategies for any patient with nocturia should also include behavioural modifications such as night-time fluid restriction, voiding before sleep, avoiding caffeine and alcohol, and education about nocturia and voiding.

of medications. In patients with OSA, CPAP reduces nocturnal frequency, NUV and NPi, and improves sleep quality and quality of life[80–82].

Diuretics taken in the afternoon can facilitate redistribution and diuresis of fluid accumulated in the interstitial space, thus preventing this same effect from occurring during the night. A randomized controlled trial (RCT) of 49 men with neither current diuretic use nor CHF demonstrated that mean nocturnal voids decreased by 0.5 with an afternoon dose of furosemide and did not change with placebo[83]. Although limited data are available, afternoon diuretics might be effective for nocturnal polyuria. Patients with nocturnal polyuria who are already taking diuretics should be advised to take the dose in the afternoon rather than at night.

By inhibiting prostaglandin synthesis, NSAIDs may improve nocturia. Prostaglandins increase detrusor muscle tone and promote diuresis by increasing glomerular blood flow[84]. In a randomized, placebo-controlled crossover study involving 26 patients with nocturnal polyuria, diclofenac increased FUSP by 18 minutes, decreased mean nocturnal voids by 0.4 and decreased NPi from 44% to 39%[85]. These data suggest that diclofenac is of minor benefit in patients with nocturnal polyuria, but further study is required to determine the efficacy of NSAIDs in this patient group.

Imipramine is an approved treatment for nocturnal enuresis in children, but use of this drug has not been studied in adults with nocturia[86]. Adverse effects include cardiac arrhythmias, hepatotoxicity, CNS depression, drug interactions and possible overdose. Thus, imipramine should not be considered standard therapy for nocturia in adults.

Desmopressin. Desmopressin is a synthetic AVP analogue that promotes water reabsorption and inhibits diuresis[87]. This drug is recommended for the treatment of nocturia by the International Consultation on Incontinence (Grade A recommendation, level 1 evidence), European Association of Urology (Grade A recommendation, level 1b evidence) and International Consultation on Urological Diseases (Grade A recommendation, level 1 evidence)[70,88,89]. A systematic review of 10 RCTs involving 2,191 patients demonstrated that desmopressin is moderately effective[90]. However, four of the trials excluded patients who had adverse effects or no response to desmopressin during an initial titration period, which represents a significant source of bias. Compared with placebo, a dose of at least 100 μg reduced mean nocturnal voids by 0.72 and increased FUSP by >1 h. A dose–response relationship was demonstrated. The beneficial effects were seen at a minimum dose of 25 μg with no additional benefit at doses above 100 μg. Improvements in various quality-of-life scales have also been demonstrated with desmopressin treatment[68]. A long-term study indicated that the efficacy of desmopressin is maintained after 1 year of treatment[91].

The orally disintegrating tablet (ODT) formulation of desmopressin has a higher bioavailability than the standard tablet. Studies suggest that the minimum effective dose is 50 μg for men and 25 μg for women[92,93]. This gender discrepancy is consistent with other studies that found women to be more sensitive to desmopressin, but this effect was consistently not evident in the systematic review mentioned above[78,90,94,95].

Adverse effects of desmopressin. Hyponatraemia and headaches are the most common adverse effects associated with desmopressin[90]. Hyponatraemia occurs in 5.6% of adults treated with desmopressin, but the risk is highest in patients aged >65 years and in those with low baseline serum sodium concentration[90,96]. Baseline serum sodium level should be measured in every patient before commencing desmopressin therapy, and patients with baseline hyponatraemia should be excluded. Desmopressin should be used with caution in patients

aged >65 years owing to the high risk of hyponatraemia. In these patients, measurement of serum sodium level should be repeated within 1 week after initiating or increasing therapy and again at 1 month, with further follow-up monitoring of serum sodium level every 6 months or as needed.

Reduced bladder capacity

Increased bladder capacity can be achieved by reducing bladder outlet obstruction or reducing detrusor overactivity. Most research into treating nocturia caused by reduced bladder capacity has been focused on traditional treatments for BPH and OAB.

Men with BPH and nocturia are often prescribed α1-blockers. An RCT involving 3,047 men with BPH indicated that the α1-blocker doxazosin reduced nocturnal voiding frequency in patients with two or more nightly voids[97]. However, the mean reduction in nightly voids was just 0.77 with doxazosin compared with 0.61 with placebo (P <0.05 for doxazosin versus placebo). Other studies have found similarly modest results with other α1-blockers such as silodosin, terazosin and alfuzosin[98–100]. Evening dosing of α1-blockers might be more effective for reducing nocturnal frequency and improving N-QoL[101]. Tadalafil, a phosphodiesterase type 5 inhibitor also approved for BPH, is similarly associated with a minor reduction in nocturnal frequency[102]. The fact that these drugs offer only minimal improvement indicates that they have limited utility in nocturia therapy.

Another commonly used medication for BPH is the 5α-reductase inhibitor (5-ARI). Studies have demonstrated either no improvement or clinically insignificant improvements in nocturnal frequency with 5-ARIs compared with placebo[97,99,103]. Similarly, combination therapy with α1-blockers and 5-ARIs provided either no improvement or minor improvement compared with α1-blocker monotherapy[97,99,104]. It seems unlikely that 5-ARIs offer much benefit in nocturia, either as a monotherapy or as part of combination therapy.

NSAIDs are potentially a useful treatment for nocturia associated with BPH. An RCT including 80 men with BPH but without nocturnal polyuria found that the mean number of nocturnal voids decreased from 5.17 to 2.5 with celecoxib and from 5.30 to 5.12 with placebo (P >0.05 for placebo)[105]. Whether NSAIDs are mitigating nocturia as a result of some direct anti-inflammatory effect on the prostate, decreased diuresis owing to inhibition of PGE2-mediated antagonism of AVP, or a combination thereof, is unknown.

Surgical procedures for BPH have also been studied with nocturia as an outcome of interest. Transurethral resection of the prostate (TURP) was found to reduce nightly voids by one and increase FUSP by 35 min from baseline[106]. Compared with tamsulosin, TURP further reduced nightly voids by 0.34 and improved N-QoL, but no difference was found in FUSP between the two groups. In another study, holmium laser enucleation of the prostate decreased nocturnal frequency by 0.6 voids, increased MVV and decreased the proportion of patients with NBCi >1 (REF. 107). In men with BPH characterized by concomitant bladder outlet obstruction and detrusor overactivity identified on urodynamic studies, TURP effectively reduces detrusor overactivity postoperatively[108,109]. Thus by relieving the bladder outlet obstruction, TURP can facilitate a recovery of bladder function, possibly alleviating associated storage symptoms such as nocturia. So surgery might provide a modest benefit but should only be used in patients with nocturia who have other indications for intervention.

Antimuscarinics are the treatment of choice for OAB, but their value in treating nocturia is limited, likely owing to the minimal effect of these medications on voided volumes[110]. In a meta-analysis evaluating use of various antimuscarinics for treating nocturia in 13,247 patients with OAB, most antimuscarinics demonstrated no benefit over placebo[111]. The most efficacious drug was trospium chloride, which reduced the mean number of nocturnal voids by only 0.24 compared with placebo. A 2014 study showed that fesoterodine did not reduce nocturnal frequency in OAB. However, after excluding patients with nocturnal polyuria from the analysis, fesoterodine reduced nocturnal voids, prolonged FUSP and improved sleep quality[112]. Another study demonstrated that fesoterodine produced small but statistically significant diminutions in both OAB-related nocturnal urgency and nocturnal frequency[110]. These data suggest that antimuscarinic monotherapy is perhaps useful for nocturia associated with urgency but without nocturnal polyuria[110,113].

The combination of α1-blockers with antimuscarinics is sometimes used in the treatment of LUTS. In an RCT studying 897 men with BPH and OAB, mean number of nocturnal voids decreased by 0.59 with combination therapy of tolterodine and tamsulosin and by 0.39 with placebo (P <0.05 versus placebo); monotherapy with either drug showed no improvements[114]. Recent studies have obtained more promising results in men already taking α1-blockers[115,116]. Twice-daily add-on imidafenacin, which is a short-acting antimuscarinic, reduced mean number of nocturnal voids by 0.6 and improved FUSP and N-QoL; nocturnal voids increased by 0.1 (P = 0.5227) in the control group taking α1-blocker monotherapy[116]. Combination therapy with α1-blockers and antimuscarinics might provide minor improvement in men with nocturia and urgency.

In patients with nocturia and urgency, behavioural therapy (such as pelvic floor muscle training, delayed voiding and urge suppression techniques) has been shown to be superior to antimuscarinics and placebo[117]. Adding behavioural therapy to current α1-blocker use further reduced mean nocturnal voids by 1.26, compared with a reduction of 0.61 with add-on antimuscarinics[118]. Behavioural therapy might be a more effective treatment than antimuscarinics for nocturia associated with urgency and OAB symptoms.

Mirabegron is a β3-adrenergic agonist approved for the treatment of OAB. In an RCT comparing mirabegron and tolterodine in 314 patients, mirabegron was found to significantly decrease mean nocturnal voids from baseline by an additional 0.39 voids compared with placebo, whereas the reduction seen with tolterodine compared with placebo was not significant[119]. Add-on mirabegron to prior solifenacin therapy has been shown to reduce

nocturia by up to 0.6 episodes per night compared with baseline solifenacin monotherapy[120]. However, another study showed no significant reduction in nocturia using mirabegron compared with placebo in patients with OAB[121]. Although some results from these studies of mirabegron have been promising, further study is required regarding the use of this drug for nocturia associated with OAB. As is the case for antimuscarinics, the effect of mirabegron on nocturia is likely limited by its minimal effect on bladder capacity[122].

In an RCT involving 100 adults with urinary frequency, percutaneous tibial nerve stimulation (PTNS) decreased nocturnal frequency by 0.7 voids from baseline; tolterodine therapy provided similar results[123]. In patients with neurogenic detrusor overactivity from multiple sclerosis or Parkinson disease, PTNS has been shown to significantly improve nocturia and urodynamic parameters such as bladder capacity[124,125]. PTNS should, therefore, be considered in patients with nocturia, especially in those with neurogenic detrusor overactivity.

Results from a systematic review and meta-analysis show that intradetrusor injections of botulinum toxin A improved nocturia by only 0.25 mean nocturnal voids compared with placebo in patients with OAB[126]. Patients treated with intradetrusor botulinum toxin A experienced a higher incidence of adverse effects, including urinary retention and increased frequency and severity of urinary tract infections compared with those who received placebo. Botulinum toxin A might be more useful in treating BPH: a small study involving 10 patients with LUTS suggestive of BPH showed that use of intraprostatic botulinum toxin A was associated with a significant improvement in nocturia from baseline[127]. However, more evidence is needed before intraprostatic injections can be widely recommended.

Several phytotherapies have also been studied in patients with nocturia associated with BPH. *Pygeum africanum* and Cernilton (from *Secale cereale)* have been shown to modestly improve nocturia in this patient group, but saw palmetto (from *Serenoa repens*) was not found to be effective[128–130].

Global polyuria

The treatment of global polyuria should focus on treating the underlying diseases. Removal of offending medications (for example, lithium) and proper management of diabetes mellitus should theoretically improve polyuria and nocturia, since uncontrolled diabetes is associated with nocturia[131]. Primary polydipsia should be treated with water restriction and psychotherapy, if necessary[58]. Central diabetes insipidus is treated with desmopressin as a synthetic AVP replacement therapy, and nephrogenic diabetes insipidus, if partial, can be treated with dietary modifications, thiazide diuretics and indomethacin[47].

Sleep disruption

Sleep and nocturia are intimately linked. Sleep disruption increases the risk of nocturia, and nocturia delivers much of its harm through its effect on sleep. In patients with insomnia and nocturia, behavioural therapy (such as advice to reduce time in bed and maintain a regular sleep schedule) can result in modest reductions in nocturnal urinary frequency[132].

In patients whose primary complaint is disturbed sleep, medications to promote sleep might be an effective treatment for nocturia. Melatonin and rilmazafone (a benzodiazepine with sedative and hypnotic effects) both independently improved quality of life and reduced mean nocturnal voids by 0.8 and 1.0, respectively, from baseline in a study group with various aetiologies of nocturia; no placebo group was included in this study for comparison[133]. However, another study indicated that melatonin, compared with placebo, only minimally reduced nocturia in men with BPH[134].

Mixed disorders

For patients in whom nocturia has multiple causes, a multimodal treatment strategy might be the most appropriate approach. One study evaluated an approach that first identified a patient's aetiologies of nocturia and then implemented an individualized treatment regime consisting of behavioural modification, α1-blockers, antimuscarinics, sedative–hypnotic drugs, or a combination of these treatments. Patients experienced decreased nocturnal urinary frequency, reduced bother from nocturia, and improved sleep quality[135].

Patients with nocturia that is refractory to α1-blocker treatment can benefit from add-on behavioural treatment, desmopressin, antimuscarinics, or sedative–hypnotic drugs, depending on their underlying problem[116,118,136–139]. Results from another study in patients with nocturia suggest that patient adherence to desmopressin given in combination with behavioural therapy is greater than adherence to desmopressin monotherapy[140]. Physicians can use the FVC to uncover an individual's pathophysiology of nocturia and then design multicomponent treatment regimens to most effectively treat each patient.

Monitoring treatment outcomes

After implementing therapy, its efficacy and effect on patients should be assessed. A reduction in nocturnal frequency should be measured with the FVC, rather than as part of a questionnaire. Since a clinically significant reduction in nocturnal frequency is unclear and differs between patients, improvement in nocturia can be assessed with the patient's self-reported bother from symptoms, N-QoL, FUSP and other measures of sleep quality.

Conclusions

Nocturia can have a variety of aetiologies, even in the setting of an individual patient. Despite its implications on quality of life and perhaps mortality, a paucity of effective treatment options are available. This lack of treatment options might be the result of the multifactorial nature of the condition, which makes diagnosis and identification of appropriate treatment of each patient's nocturia challenging.

The current approach to evaluation of a patient with nocturia requires revision. N-QoL and FUSP are useful additions to the FVC for evaluating nocturia and its

severity, but categorizing patients by aetiology is still not a widespread practice. New tools are needed and we need to better utilize the available tools in order to systematically identify the causes of nocturia in each patient. Part of this process might involve crafting a new definition of nocturnal polyuria. Some studies have adopted this systematic approach and demonstrated increased efficacy of particular treatments in subgroups of patients with nocturia. Such research will ideally enable clinicians to more effectively apply existing treatment options according to the pathophysiology of an individual patient's nocturia.

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Author contributions

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Competing interests statement

J.P.W. declares that he serves as consultant for Allergan, Astellas, Elsevier, Ferring, Pfizer, Symptelligence and Vantia. H.D. and A.E. declare no competing interests.