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# A practical approach to the management of nocturia

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## Funding information

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## Summary

**Aim:** To raise awareness on nocturia disease burden and to provide simplified aetiological evaluation and related treatment pathways.

**Methods:** A multidisciplinary group of nocturia experts developed practical advice and recommendations based on the best available evidence supplemented by their own experiences.

**Results:** Nocturia is defined as the need to void  $\geq 1$  time during the sleeping period of the night. Clinically relevant nocturia ( $\geq 2$  voids per night) affects 2%-18% of those aged 20-40 years, rising to 28%-62% for those aged 70-80 years. Consequences include the following: lowered quality of life; falls and fractures; reduced work productivity; depression; and increased mortality. Nocturia-related hip fractures alone cost approximately €1 billion in the EU and \$1.5 billion in the USA in 2014. The pathophysiology of nocturia is multifactorial and typically related to polyuria (either global or nocturnal), reduced bladder capacity or increased fluid intake. Accurate assessment is predicated on frequency-volume charts combined with a detailed patient history, medicine review and physical examination. Optimal treatment should focus on the underlying cause(s), with lifestyle modifications (eg, reducing evening fluid intake) being the first intervention. For patients with sustained bother, medical therapies should be introduced; low-dose, gender-specific desmopressin has proven effective in nocturia due to idiopathic nocturnal polyuria. The timing of diuretics is an important consideration, and they should be taken mid-late afternoon, dependent on the specific serum half-life. Patients not responding to these basic treatments should be referred for specialist management.

**Conclusions:** The cause(s) of nocturia should be first evaluated in all patients. Afterwards, the underlying pathophysiology should be treated specifically, alone with lifestyle interventions or in combination with drugs or (prostate) surgery.

## 1 | INTRODUCTION

Nocturia is a highly prevalent lower urinary tract symptom (LUTS), defined by the International Continence Society (ICS) as "the complaint that the individual has to wake at night one or more times to void ... each void is preceded and followed by sleep."<sup>1,2</sup> Nocturia equally affects

men and women of all ages, with higher rates in older populations.<sup>3-5</sup> It is associated with falls and fall-related injuries, primarily in the elderly but also in younger age groups, reduced quality of life (QoL), mainly due to fragmented sleep, and an increased prevalence of depressive symptoms, particularly in younger men and women.<sup>5-13</sup> Nocturia also places a considerable economic burden on the individual and healthcare services, in

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terms of direct (falls and fractures), indirect (decreased work productivity and activity levels) and intangible costs (reduction in QoL).<sup>5,14</sup>

Although very common, nocturia remains an underreported, undertreated and poorly managed medical and social problem in adults.<sup>15,16</sup> Nocturia was oftentimes considered a symptom associated with functional issues, such as overactive bladder syndrome (OAB) and/or benign prostatic hyperplasia (BPH), with treatments focused on increasing bladder capacity and/or lowering bladder outlet obstruction. However, because nocturia is often associated with nocturnal polyuria—the overproduction of urine during the night—such treatments will not be effective for all patients and appropriate patient selection is essential.<sup>17-19</sup> As such, it is essential that physicians and other healthcare professionals understand the aetiology, burden and the most effective methods for diagnosing, assessing and treating nocturia. The treatment of nocturia should be according to its causative factors and aetiology where possible, as recommended in the European Association of Urology guidelines on the treatment of male LUTS<sup>20</sup>; however, specific guidelines for nocturia have not yet been published as a journal article.

### 1.1 | Aim

The aim of this expert paper was to raise awareness and increase recognition of nocturia as a medical condition and provide straightforward, practical recommendations for its diagnosis and management.

## 2 | METHODS

The paper was developed by a multidisciplinary group of experts on nocturia, including urologists, general practitioners and a geriatrician with a special interest in nocturia. A non-systematic review of the relevant literature retrieved in the PubMed/Medline database was undertaken, which was supplemented by studies identified by the authors. All recommendations were based on the best available evidence combined with the authors' experiences in managing nocturia. The authors intend that the recommendations and practical advice provided herein will improve confidence in the management of nocturia and help define when specialist referral is appropriate.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Terminology

In 2002, the ICS defined nocturia as *the need to void one or more times during the night, with each void preceded and followed by sleep*.<sup>1,2</sup> This definition is currently a topic of debate<sup>21,22</sup>; however, nocturia often only becomes clinically relevant when it causes comorbidities or bother for the patient. Nocturia once per night has been reported to occur in up to 18.2% of healthy women aged 18-30 years, but with low associated bother to the individual.<sup>23</sup> A more clinically relevant definition of nocturia is "≥2 voids per night," as at this point it would become bothersome for most individuals.<sup>13,24</sup> It should be recognised, however, that perceptions of what frequency is bothersome may

#### What's known

- A non-systematic review of the relevant literature was undertaken, supplemented by studies identified by the authors. All recommendations were predicated on the best available evidence combined with practical insights from the authors' extensive experiences in managing patients with nocturia.

#### What's new

- Nocturia is a bothersome and serious medical condition affecting men and women of all ages, which can negatively impact quality of life and increase morbidity and mortality. Frequency-volume charts are essential for accurate assessment. Treatment should be tailored to the individual patient based on the underlying pathophysiology, with lifestyle interventions always considered. Medical therapies, such as desmopressin in patients with idiopathic nocturnal polyuria, can provide effective and safe relief for patients with persistent bother.

vary considerably between individuals. Nocturnal polyuria has been defined as a nocturnal urine output of >20% of a 24-hour urine volume in younger adults, and >33% in older adults (morning void being included in nocturnal urine output).<sup>2</sup>

### 3.2 | Epidemiology of nocturia

Nocturia is one of the most bothersome LUTS according to most epidemiological studies.<sup>7,25,26</sup> The prevalence of nocturia is high and broadly similar in men and women, affecting 28%-93% of those aged 40 years or older.<sup>27-29</sup> The prevalence varies depending on the definition (from 1 to 3 voids per night). A review of 43 epidemiological studies reported prevalence rates of 11%-35% for ≥1 void per night and 2%-17% for ≥2 voids per night for men aged 20-40 years, whilst for women in the same age group, rates of 20%-44% for ≥1 void per night and 4%-18% for ≥2 voids per night were reported.<sup>27</sup> The prevalence of nocturia in the community increases with age, with rates of 29%-59% for men aged 70-80 years and of 28%-62% for women of the same age (≥2 voids per night).<sup>27</sup> Other studies have reported rates of 16% in men and 21% in women aged over 20 years (≥2 voids per night),<sup>29</sup> and 34% for men and 28% for women (>2 voids per night) aged over 40 years.<sup>28</sup> In another study, reporting a prevalence of 34% in women aged >40 years, it was found that 40% of those with nocturia had no other urinary tract symptom.<sup>26</sup>

In terms of incidence, a recent meta-analysis of 13 studies reported a rate of 0.4% per year among adults (men and women) aged <40 years, 2.8% per year among those aged 40-59 years and 11.5% per year among those aged ≥60 years (≥1 void per night).<sup>30</sup>

### 3.3 | Evaluating patients with nocturia

Numerous underlying factors may contribute to nocturia, and one or several of these factors may be present in an individual (eg, nocturnal

polyuria is very frequently associated with a LUTS/BPH in men or an OAB in women).<sup>18</sup> The multifactorial pathophysiology of nocturia may partly explain why it has not received appropriate attention as a distinct medical presentation.<sup>19,31</sup> The pathophysiological mechanisms for nocturia can be broadly separated into three main causes: (i) reduced bladder capacity, (ii) increased fluid intake and (iii) increased diuresis, with certain medications and behavioural factors exacerbating the condition (Figure 1).<sup>18,19,28,31-34</sup> It has been observed that patients with  $\geq 2$  voids per night have higher nocturnal voided volume, based on increased sodium excretion and lower functional bladder capacity, whilst those with 1 void per night present with lower bladder capacity.<sup>35</sup> The possible pathophysiological factors involved in nocturia in men and women are broadly similar, with the exception of prostate-related issues in men and oestrogen deficiency in women, the latter with an uncertain but possible marginal role in the development of nocturia.<sup>36</sup>

### 3.3.1 | Reduced (nocturnal) bladder capacity

Reduced bladder capacity, whether functional or anatomic, encompasses all the conditions associated with storage dysfunction and storage symptoms. Nocturia occurs when the bladder capacity is exceeded by the amount of urine entering the bladder during the night.<sup>33</sup> Reduced bladder capacity may indicate detrusor overactivity (primary [idiopathic] or secondary, eg, due to neurogenic bladder dysfunction),

overactive bladder without detrusor overactivity, postvoid residual urine due to bladder outlet obstruction, chronic pelvic/bladder pain syndrome, detrusor underactivity or dysfunctional voiding, reduced nocturnal bladder capacity (occurring during sleep) or perhaps lower urinary tract infection.<sup>18,26,33,37</sup>

### 3.3.2 | Increased fluid intake

Excessive fluid intake can lead to nocturia, and this intake can occur either throughout the 24-hour period or specifically in the evening/night.<sup>32</sup> Fluid intake in the evening or night can often have behavioural and lifestyle causes, and such intake is also often associated with the consumption of diuretic beverages (such as caffeine or alcohol).<sup>18</sup> Excess fluid intake can also have a number of other causes including iatrogenic, psychogenic and dipsogenic reasons.<sup>32</sup>

### 3.3.3 | Increased diuresis

#### Global polyuria

Global polyuria is defined as a daily excreted urine volume  $>40$  mL/kg body weight,<sup>33</sup> which equates to  $>2800$  mL/24 hours for a reference person with a body weight of 70 kg. It can be seen in patients with diabetes insipidus, diabetes mellitus, increased fluid intake, hypercalcaemia or primary polydipsia, or it can be drug-induced.<sup>33</sup>

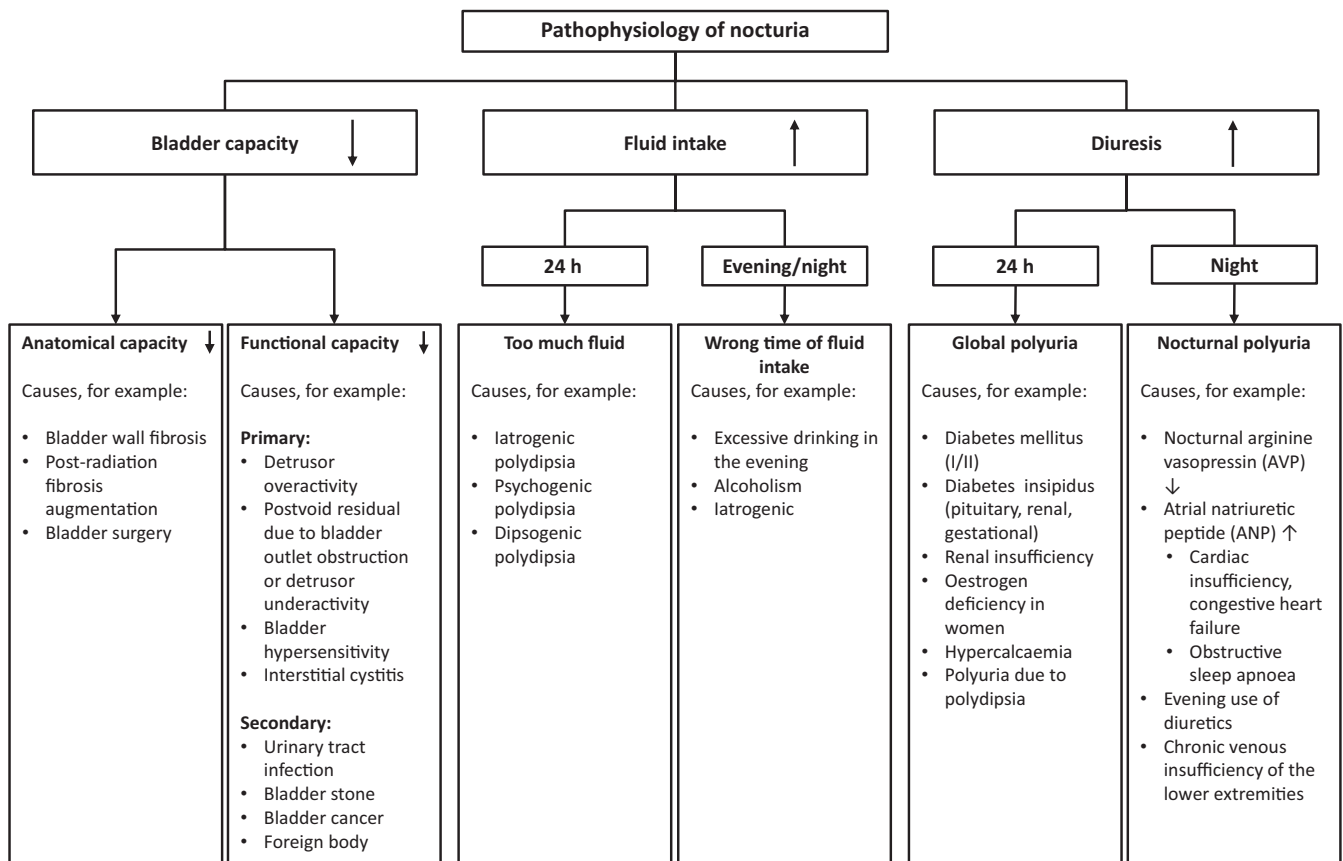


FIGURE 1 Pathophysiology of nocturia (adapted from Oelke et al<sup>32</sup>)

### Nocturnal polyuria

Nocturnal polyuria (night-time urine output >20% of total daily urine output for younger adults or >33% for older adults) is the most frequent cause of nocturia, having been shown in studies to be responsible for up to 88% of cases.<sup>2,38,39</sup> Nocturnal polyuria is thought to result from an abnormality of the circadian rhythm of secretion of the antidiuretic hormone, arginine vasopressin (AVP). It is a heterogeneous condition, in which water diuresis, solute diuresis or a combination of both is the underlying cause.<sup>40</sup> Water diuresis is represented by high free water clearance and low osmolality at night. For solute diuresis, the driving force seems to be increased sodium clearance during the night.<sup>40</sup>

Nocturnal polyuria may be behavioural (excess fluid intake), drug-induced or a part of global polyuria. Systemic diseases such as congestive heart failure, venous stasis in the lower extremities, obstructive sleep apnoea (OSA), renal tubular dysfunction, hepatic failure and hypoalbuminaemia can cause fluid and electrolyte sequestration and, therefore, may also be reasons for nocturnal polyuria.<sup>31,33,41</sup>

### 3.4 | Risk factors and comorbidities

Nocturia ( $\geq 2$  voids per night) has been significantly associated with various risk factors and comorbidities (Table 1).<sup>28</sup> Several epidemiological studies have also reported a positive association between nocturia and erectile dysfunction in diabetic<sup>42</sup> and non-diabetic men.<sup>43</sup>

### 3.5 | Impact of nocturia

Nocturia can have a significant, negative impact on patients' QoL (both mental and physical) and be linked to depression and increased mortality.<sup>5,6,9,13,29</sup> The impact on QoL comes primarily from disturbed sleep caused by nocturia, which can lead to sleep deprivation, especially when there is difficulty in returning to sleep.<sup>5,10</sup> This leads to tiredness and daytime fatigue that can affect daily activities and thereby reduce QoL.<sup>5,10</sup> Nocturnal voiding can negatively affect the occurrence and length of deep, restorative (N3)

sleep, often considered the most restorative stage of sleep.<sup>44</sup> Long-term loss of N3 sleep as occurs in nocturia could have potentially deleterious impact on daytime alertness, health and well-being.<sup>44,45</sup> The negative effect of nocturia on sleep outcomes appears to be stronger in adults aged >65 years.<sup>46</sup> As nocturia causes activity at night when a patient may not be fully awake, it is also an important cause of falls and fall-related fractures in the elderly population.<sup>5,8</sup> A population-based epidemiologic survey also found a strong association of nocturia with depression in both men and women, with a significant trend in increased odds of depression with more voids nightly.<sup>13</sup> The magnitude of this association was larger in younger age groups, especially among women aged <50 years.<sup>13</sup> Nocturia ( $\geq 2$  voids per night) has been found to increase the mortality risk by 54% in men (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.18-2.00) and by 28% in women (HR 1.28, 95% CI 1.04-1.57).<sup>29</sup> Interestingly, the magnitude of the association was greater in men and women <65 years. There was a significant trend for increased mortality risk with increasing number of nocturnal voiding episodes. Potential underlying mechanisms for this association included sleep disruption and subsequent development of related comorbid conditions.<sup>29</sup>

An increasing number of epidemiological studies have shown a strong association between sleep deprivation and adverse metabolic traits, including obesity, type 2 diabetes and arterial hypertension, with experimental evidence suggesting distinct pathophysiological mechanisms by which insufficient sleep impairs metabolic health.<sup>47</sup> Each of these metabolic diseases is likely to be associated with an increased risk for premature death.<sup>47</sup> A meta-analysis of 16 studies involving 1 382 999 people reported <7 hours of sleep to be associated with an increased risk of all-cause mortality (relative risk [RR] 1.12, 95% CI 1.06-1.18;  $P < .01$ ), although >8 hours of sleep was also associated with an increased risk of death (RR 1.30, 95% CI 1.22-1.38;  $P > .0001$ ), perhaps due to socio-economic factors and/or comorbidities.<sup>48</sup>

The impact of nocturia has considerable pecuniary implications for patients and the health service. It was estimated that hospitalisations across the EU due to hip fractures associated with nocturia cost approximately €1.0 billion in 2014.<sup>5</sup> In addition to these direct costs, indirect costs arise from decreased work productivity and activity levels, with lost productivity at work in the EU region in 2014 due to nocturia estimated to have cost €29.0 billion.<sup>5</sup> In the USA, the annual direct costs due to nocturia-associated falls were estimated to be approximately \$1.5 billion and the indirect costs were expected to be \$61 billion in 2014.<sup>5</sup>

### 3.6 | Clinical presentation and evaluation

Many patients may not recognise nocturia as a medical condition amenable to treatment or they may be embarrassed or reluctant to discuss symptoms,<sup>15,49,50</sup> so there is an onus on the physician to broach the topic to avoid delays in diagnosis and treatment.<sup>51</sup> In one survey, in 66.4% of women with <3 nocturnal voids, nocturia was perceived to be a minor problem, and 60.7% assumed it was part of the ageing process,

**TABLE 1** Independent significant risk factors for nocturia ( $\geq 2$  voids)<sup>28</sup>

Both genders	Men	Women
<ul style="list-style-type: none"> <li>Age</li> <li>Hispanic and Black ethnicity</li> <li>Diabetes mellitus or insipidus</li> <li>Arthritis</li> <li>Asthma</li> <li>High blood pressure</li> <li>Anxiety</li> <li>Depression</li> <li>History of bed-wetting in childhood</li> </ul>	<ul style="list-style-type: none"> <li>Prostatitis</li> <li>Prostate cancer</li> </ul>	<ul style="list-style-type: none"> <li>High body mass index</li> <li>Heart disease</li> <li>Inflammatory bowel disease</li> <li>Recurrent urinary tract infection</li> <li>Uterine prolapse<sup>a</sup></li> <li>Hysterectomy</li> <li>Postmenopausal</li> </ul>

<sup>a</sup>Generally considered to be associated with overall urogenital prolapse or pelvic floor dysfunction.

which prevented them from seeking treatment.<sup>15</sup> Of those women who had consulted a doctor, 37.2% were not offered any treatment.<sup>15</sup> In another population-based study of 8659 patients, it was reported that it took, on average, 51 weeks for the patient to have a first consultation after the onset of nocturia, with a further 12 weeks to make a diagnosis, and another 37 weeks from diagnosis until first prescribed treatment.<sup>16</sup> The overall time from the onset of symptoms to beginning treatment was nearly 2 years (mean 105.5 weeks).<sup>16</sup> In this study, the most common reason for seeking medical help was worsening of symptoms (severity or frequency). Urinary incontinence, tiredness, fear of other (serious) underlying diseases and recommendation of a friend or relative were other important reasons to consult a doctor.<sup>16</sup> This study implied that there should be greater awareness and screening for nocturia, even in the absence of other urinary symptoms.

A thorough assessment of nocturia and its possible causes is crucial before treatment initiation (Table 2; also see Checklist available as online material).<sup>32,52-54</sup> The evaluation of a patient should begin with taking a thorough history to assess, understand and discriminate LUTS in general and nocturia in particular.

Frequency-volume charts (FVCs) are the cornerstone of initial assessment and are pivotal in determining the type of nocturia and associated causes (Figure 2)<sup>32</sup> (example available as online material; see also [www.opstaanomteplassen.be](http://www.opstaanomteplassen.be) and Everaert et al<sup>56</sup>).

**TABLE 2** Assessment of patients with nocturia<sup>32,53-55</sup>

- Patient history
  - Fluid consumption, alcohol and caffeine intake, urinary symptoms (including voiding, urgency and frequency), sleeping habits, medical history, symptoms of obstructive sleep apnoea (consider using the Epworth Sleepiness Scale or STOP-BANG<sup>54</sup>)
- Review current medication to identify drugs that may contribute to nocturia
  - for example, calcium channel blockers such as amlodipine or nifedipine
  - diuretics such as furosemide or torasemide
- Physical examination
  - Blood pressure, digital rectal examination of the prostate in men/pelvic examination in women, checking for oedema of the lower extremities, checking genitalia for any abnormalities (eg, for phimosis, meatal stenosis or cancer), abdominal examination including palpation of the bladder to rule out urinary retention
  - Determine whether patient is overweight/obese—measure weight/body mass index and/or waist circumference
- Frequency-volume chart (in all cases)
  - Minimum of 3 days
- Investigations
  - Urinalysis (in all cases) with urine culture if urinary tract infection suspected, serum electrolytes and creatinine, serum glucose/HbA1c, serum lipid profile
- Prostate specific antigen (PSA) for prostate cancer (if clinically relevant) and estimation of prostate size
- Additional tests, including (if required)
  - Cystoscopy
  - Specific cardiology tests (eg, electrocardiography, echocardiography, magnetic resonance imaging of the chest or coronary angiography)
  - Measurement of PVR as evaluated by transabdominal ultrasonography, a bladder scan or catheterisation

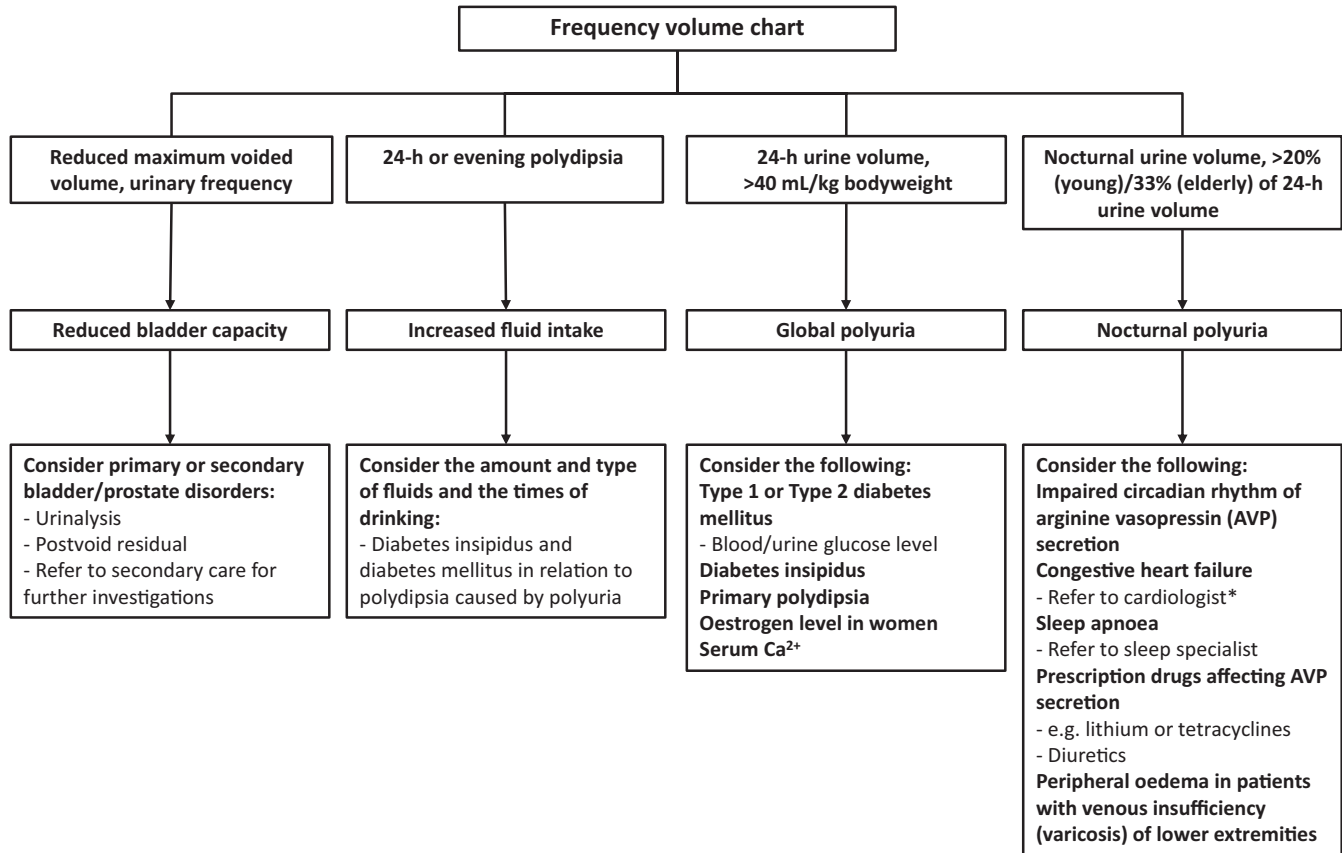
Documentation of the time of voided urine during the night for determination of nocturnal frequency and volume of urine voided during the night (including the volume of the first void after awaking the next morning) for the determination of nocturnal diuresis can discriminate between the major causes of nocturia, can identify the underlying pathophysiology and can determine the sleep pattern of the patient.<sup>32</sup> Analysis of patients' FVCs will reveal many important clues to the aetiology of nocturia, including total 24-hour urine volume (evaluating 24-hour polyuria), nocturnal urine volume (evaluating nocturnal polyuria), voiding frequency and voided volumes (evaluating bladder storage or prostate problems).<sup>36</sup> FVCs also help to target specific non-urologic aetiologies.<sup>33</sup> Use of a screening tool, such as the recently published TANGO (Targeting the individual's Aetiology to Guide Outcomes),<sup>57,58</sup> can also potentially aid in the identification and assessment of non-lower urinary tract comorbidities associated with nocturia. FVCs can be supplemented by bladder diaries, which are especially useful in compliant patients over longer stretches of time and provide an opportunity for patients to add important qualitative details about or associated with their symptoms.<sup>59</sup> FVCs or bladder diaries should be completed for a minimum of 3 days, and it is important that the need for accuracy is explained to the patient before asking them to complete it.<sup>60,61</sup> These self-monitoring approaches also aim to reflect and educate patients on the correct use or timing of fluid intake in managing nocturia.

#### Recommendations on the assessment of nocturia

- The basic assessment should include a detailed history and physical examination. If nocturia is reported, patients should be asked about other lower urinary tract symptoms, fluid intake, medications and comorbid medical conditions.
- Urinalysis (by dipstick or urinary sediment) and measurement of postvoid residual volume should be performed in all cases and followed up with additional tests (eg, uroflowmetry, computer-urodynamic evaluation of bladder function and cystoscopy, etc) as warranted.
- Diagnosis of nocturia and nocturnal polyuria should be based on the results of a FVC and subsequent investigations to discriminate among the potential underlying causes of nocturia (Figure 1).
- FVCs may be supplemented by bladder diaries.
- The patient should be referred to the relevant speciality within secondary care for further investigation (if the primary cause(s) remain unclear or too complicated to treat).

### 3.7 | Treatment of nocturia

Treatment should be tailored to the underlying causes of nocturia (Figure 1) and should include lifestyle modifications and, if required, pharmacological therapy (Figure 3).<sup>32</sup> Some medications can precipitate nocturia and, therefore, a medication review is warranted in all patients (see lifestyle modifications, below). It is



**FIGURE 2** Nocturia evaluation algorithm based on frequency-volume chart (adapted from Oelke et al<sup>32</sup>). \*Some patients might not require referral to a cardiologist. The National Institute for Health and Care Excellence (NICE) guidelines for chronic heart failure state that referral of patients to a cardiologist is only necessary for initial diagnosis and patients with severe heart failure or where the condition is not responding to treatment<sup>62</sup>

important that patients are informed about the goals of treatment: to decrease nocturia episodes; to increase total sleep time and quality; to increase QoL; and to diminish associated comorbidities (Table 3).<sup>20</sup>

### 3.7.1 | Medical management

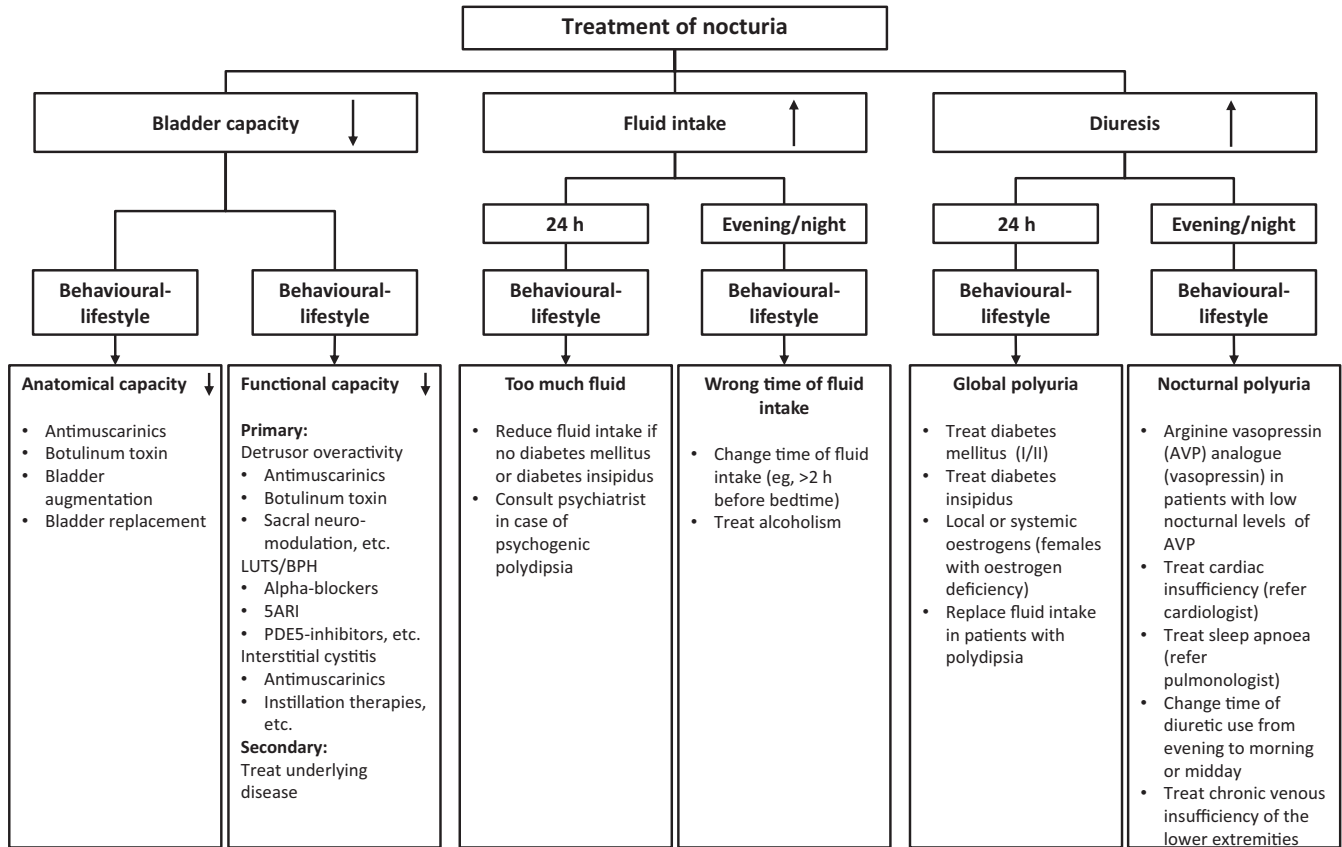
Pharmacological therapies are indicated after failure of lifestyle modifications and behavioural treatments which, however, should be continued together with the drugs. Several pharmacological therapies have been used for the treatment of nocturia, depending on the underlying cause(s), including<sup>32</sup> antidiuretic agents (vasopressin receptor agonists; desmopressin), diuretics, muscarinic receptor antagonists (antimuscarinics),  $\beta_3$ -adrenoceptor agonists (mirabegron),<sup>66</sup> alpha-adrenoceptor antagonists ( $\alpha_1$ -blockers),  $5\alpha$ -reductase inhibitors, phosphodiesterase type 5 inhibitors (PDE5i) and plant extracts. Except for desmopressin in the treatment of patients with nocturia due to nocturnal polyuria,<sup>67-70</sup> the strength of evidence for many of these agents has been classified as low by the International Consultations on Urological Diseases committee.<sup>37,71</sup>

#### Reduced (nocturnal) bladder capacity

The use of antimuscarinics or  $\beta_3$ -agonists (mirabegron) for overactive bladder management and  $\alpha_1$ -blockers,  $5\alpha$ -reductase inhibitors with or without  $\alpha_1$ -blockers, PDE5i or plant extracts for male LUTS/bladder outlet obstruction has been shown to significantly reduce nocturnal voiding frequency in populations where the indicated condition is shown to be present, albeit to limited clinical effects of approximately  $-0.2$  episodes per night on average compared to placebo.<sup>32,33,53,72-74</sup> Emerging evidence has also indicated a role for onabotulinumtoxinA injections in reducing night-time nocturia in patients with overactive bladder without nocturnal polyuria.<sup>75-77</sup>

#### Increased diuresis

Desmopressin, a synthetic vasopressin analogue, acts on the  $V_2$  receptors of the distal collecting tubules with the aim of concentrating urine at night.<sup>33</sup> Treatment with a  $V_2$  agonist is useful only in patients with idiopathic nocturnal polyuria with excessive water diuresis, or in patients with central diabetes insipidus, as this is indicative of suppressed vasopressin levels.<sup>40</sup> However, where there is nocturnal sodium diuresis, treatment to restore a normal sodium clearance



**FIGURE 3** Management algorithm for patients with nocturia/nocturnal polyuria (adapted from Oelke et al<sup>32</sup>)

pattern could be indicated as this would act to lower nocturnal urine production.<sup>40</sup>

Desmopressin has shown to be an efficacious and well-tolerated treatment for patients with nocturia due to nocturnal polyuria, with females requiring lower effective doses compared to males.<sup>67-70</sup> Nasal spray, oral tablet and sublingual melt formulations of desmopressin

**TABLE 3** Potentially beneficial lifestyle modifications for patients with nocturia<sup>20,32,52,53,63-65</sup>

- Minimising fluid intake at least 2 h before going to bed, particularly caffeine and/or alcohol
- Restricting total fluid consumption to <2 L/day, if comorbidities allow
- Emptying bladder before going to bed
- Barrier-free access to a toilet or a toilet chair
- Increasing exercise and fitness levels (including pelvic floor exercises, if indicated)
- Reducing dietary salt intake
- Weight loss if overweight/obese
- For patients with peripheral oedema (lower extremities) due to congestive heart failure or chronic venous insufficiency
  - Elevating the legs above the heart level a few hours before going to bed for sleeping
- For patients on diuretics
  - Taking diuretics mid-afternoon, rather than just prior to retiring
  - This should take into consideration the half-life of the specific diuretic (eg, furosemide has a serum half-life of ~1.5 hours and torsemide ~3.5 hours)

have been developed, although not all formulations and doses are available in every country. Each of these has specific pharmacological properties and doses. For example, the sublingual melt formulation has a time to maximum plasma concentration of 0.5-2.0 hours and a serum half-life of around 2.8 hours, meaning that its effect lasts for approximately 8 hours.<sup>78</sup> A once-daily, low-dose, gender-specific formulation of desmopressin has lately become available: 25 µg for women and 50 µg for men.<sup>79</sup> This formulation has the benefit of reducing the antidiuretic activity to a maximum of 3-5 hours during the nightly sleep,<sup>79</sup> whilst also limiting the risk of hyponatraemia, an adverse event associated with higher doses of desmopressin.<sup>67</sup> Desmopressin should be taken one hour before going to bed (with the intention of sleeping) without water (for melt or spray) or with minimal water (for tablet) and with fluid restricted to a minimum until eight hours after dosing; otherwise, fluid retention and/or hyponatraemia may result.<sup>79</sup>

Comparison of 25 µg desmopressin once daily to placebo in 261 women with nocturia (≥2 voids per night) found that desmopressin significantly reduced the mean number of nocturnal voids and increased the mean time to first nocturnal void by 49 minutes compared with placebo at 3 months.<sup>67</sup> Similar efficacy has been demonstrated in a study that investigated 50 and 75 µg desmopressin in men with nocturia (≥2 voids per night).<sup>68</sup> Significant increases in health-related QoL and undisturbed sleep were also observed compared with placebo.<sup>45,68</sup> A further study from Japan evaluating four different doses of orally disintegrating sublingual desmopressin (10, 25, 50 or 100 µg) suggested that woman appear



to be more sensitive to this medication and therefore require a lower dose (25 µg vs 50 µg in men) to achieve clinical improvement.<sup>69</sup> A pooled analysis of three randomised, controlled trials reported that these effects can be maintained and even enhanced over the course of a year.<sup>70</sup>

Hyponatraemia after desmopressin intake, defined as a serum sodium concentration <130 mmol/L but not necessarily associated with symptoms or signs, occurs in 5.0%-7.6% of individuals and has most frequently been observed in patients >65 years of age, especially in women, and individuals with low serum sodium concentration at baseline and higher 24-hour urine volume per body weight.<sup>80,81</sup> For older patients, serum sodium monitoring before starting treatment and in the early phase of treatment (after 4-8 days and at 1 month after initiation) can help to quickly identify hyponatraemic patients.<sup>72</sup> Education of patients and their partners on recognising hyponatraemia should also be undertaken to ensure rapid identification if it occurs. Symptoms or signs of hyponatraemia—usually associated with the degree of decreased serum sodium level—start with nausea, vomiting, headache and lethargy. In rare cases, confusion, decreased consciousness and muscle weakness, spasms or cramps, and seizures or coma can occur. Relevant factors that could affect the sodium level in patients include gender, low baseline serum sodium, reduced kidney function, cardiac or renal comorbidity, polypharmacy with diuretics<sup>80</sup> and injudicious liquid intake.

In contrast to the antidiuretic drug desmopressin, the aim of diuretics for nocturia is to induce diuresis before sleep and to shift the polyuric phase from night-time (sleep) to daytime.<sup>31</sup> This approach may be suitable for patients with nocturia when the underlying cause is unknown,<sup>59</sup> although the overall evidence supporting the use of diuretic therapy is low. Timing of diuretic therapy is important. Patients with nocturnal polyuria as a result of fluid reabsorption in the lower extremities whilst lying down should take their diuretics in the mid-afternoon to release fluid built up during the day; if taken too late in the day, it may inadvertently increase nocturnal polyuria.<sup>72</sup>

### Combined therapy

In cases with a multifactorial aetiology of nocturia, treatment could target the various underlying causes with two or more drugs and, if necessary, in a multidisciplinary setting, but should always involve lifestyle changes and behavioural therapies. The addition of low-dose oral desmopressin 50 µg to the  $\alpha_1$ -blocker tamsulosin has shown to reduce the nocturnal frequency of voids by 64.3% compared with 44.6% when tamsulosin was given alone in patients with signs or symptoms of BPH (with or without nocturnal polyuria).<sup>82</sup> The study also demonstrated that this combination therapy improved the quality of sleep, whilst overall tolerability remained comparable to tamsulosin monotherapy.<sup>82</sup> Similar results have been seen when low-dose desmopressin was added to other  $\alpha_1$ -blockers for men with LUTS/BPH.<sup>83,84</sup> A recently published, double-blind, randomised, proof-of-concept study showed that a combination of desmopressin 25 µg and the antimuscarinic tolterodine provided a significant benefit in nocturnal void volume ( $P = .034$ ) and time to first nocturnal void ( $P = .045$ ) over tolterodine monotherapy in women with OAB and nocturnal polyuria.<sup>85</sup>

### 3.7.2 | Other interventions

Surgical procedures for the relief of bladder outlet obstruction (eg, transurethral resection of the prostate) should not be considered in patients whose primary complaint is nocturia, but may be an option in some patients with LUTS, bladder outlet obstruction and postvoid residual urine who fail medical therapy, assuming that they are good surgical candidates.<sup>71</sup> A comprehensive assessment of the cause(s) of nocturia should be undertaken in all patients considered for surgery.<sup>71</sup>

Nocturia often improves in patients with OSA using continuous positive airway pressure.<sup>41</sup> Patients who undergo uvulopalatopharyngoplasty for their OSA have also seen an improvement in nocturia symptoms.<sup>86</sup>

#### Recommendations on the treatment of nocturia

- Treatment should be tailored to the cause(s) of nocturia in the individual patient.
- Some medications can precipitate nocturia and, therefore, change of the drug or timing of drug use may be warranted.
- Lifestyle and behavioural modifications should be attempted before instigating other treatments, with a trial of up to 3 months, a reasonable time period over which to assess treatment response, unless bother is increasing and intolerable.
- Pharmacological therapies should be introduced after lifestyle modifications have failed or as adjuncts.
- Patients on diuretic therapy should take diuretics during the mid-late afternoon, taking into consideration the half-life of the specific agent.
- Desmopressin is the pharmacologic treatment for nocturia due to nocturnal polyuria with the highest quality evidence to support its use, with a once-daily, low-dose, gender-specific formulation indicated for nocturia due to nocturnal polyuria.
- Diuretics,  $\alpha_1$ -blockers, 5 $\alpha$ -reductase inhibitors, PDE5i, plant extracts, antimuscarinics and the  $\beta_3$ -agonist mirabegron all have potential utility to reduce nocturnal voiding frequency in patients with different causes of decreased functional bladder capacity, although the clinical impact of such treatments appears to be limited.
- Educating patients on the available treatment options and involving them in the decision-making process can help to increase adherence to medication and thereby improve patient functioning and QoL.<sup>87</sup>
- After implementing therapy, its efficacy and effect on patients should be assessed, with consideration given to combining therapies/interventions in the light of an inadequate response.
- Patients with nocturia of undetermined cause not responding to lifestyle and medical therapy should be considered for specialist assessment.

## 4 | CONCLUSIONS

Nocturia is a highly prevalent serious medical condition equally affecting men and women of all ages. It can have a profound impact on QoL and work productivity and can increase the risk of falls, fractures and mortality whilst disrupting the restorative part of sleep. Due to its multifactorial aetiology, nocturia should potentially be viewed as a distinct medical presentation in its own right, albeit one that is a symptom of an underlying disease or misbehaviour. With appropriate assessment and diagnosis, this bothersome condition can be treated successfully. Use of the FVC alongside comprehensive patient evaluation is essential to accurately identify the cause(s) behind nocturia and thereby tailor the optimal management approach. Lifestyle modifications and behavioural interventions are the first step in successfully managing nocturia and should be discussed with every patient. When lifestyle modifications fail or yield an inadequate response, then medical therapies, such as desmopressin, should be introduced. Patients with nocturia not responding to these treatments should be referred to the appropriate specialist based on the underlying aetiology or to a specialist in nocturia when the cause is unknown. As there are currently no separate guidelines on the management of nocturia available, this article could serve as a temporary, evidence-based recommendation on the assessment and treatment of nocturia to guide general practitioners, urologists, gynaecologists or other medical specialties.

## AUTHOR CONTRIBUTIONS

All authors contributed to the evaluation of the relevant literature, consensus on the recommendations, and drafting, critical review and approval of the final manuscript.

## DISCLOSURES

MO has been speaker, consultant and/or trial participant for Apogepha, Astellas, Bayer, GlaxoSmithKline, Ferring, Lilly and Pfizer. SDW has been an advisor and speaker for Astellas; has been a speaker and advisor for and has received a research grant from Medtronic; and has been an advisor to Allergan, Ferring, Lilly, Menarini and Pfizer. MJD has been an advisor, speaker and researcher for Allergan, Astellas, Ferring, Hikma and Pfizer. AG is a scientific consultant for Allergan, Astellas, Ferring and Menarini. MK has received funding for research, conference attendance, lecturing and advice from the pharmaceutical industry including Astellas, Pfizer, Takeda, Bayer, MSD, BI, Lilly, GSK, AstraZeneca and Menarini. MK is Editor-in-Chief of PCCJ and is also on several NHS advisory boards including the Prostate Cancer Risk Management Programme and the Prostate Cancer Advisory Group. SO has been a speaker for Astellas, Ferring and Pfizer. JR has been an advisor and speaker for Astellas, Ferring and Lilly. PVK has acted as advisor and speaker for Astellas, Ferring and Medtronic. KE has received grants and honours as a speaker and advisor for Allergan, Astellas and Ferring.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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