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REVIEW ARTICLE

The evaluation and treatment of nocturia: a consensus statement

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What's known on the subject? and What does the study add?
Nocturia is currently defined by the International Continence Society (ICS) as the complaint that an individual has to wake at night one or more times to void. It is, however, an underreported, understudied, and infrequently recognized problem in adults. Many factors may contribute to nocturia which are treatable, yet patients do not seek care or the condition may not be identified by providers.

This paper aims to help healthcare providers better serve patients who are experiencing nocturia by summarizing current research, clinical approaches, and treatment options. The results of the conference provide a balanced evaluation of the full treatment armamentarium capable of meeting the needs of patients with the manifold causes of nocturia such as nocturnal polyuria, overactive bladder, or benign prostatic hyperplasia.

KEYWORDS nocturia, nocturnal polyuria, consensus, multifactorial

INTRODUCTION

Nocturia is currently defined by the ICS as the complaint that an individual has to wake at night one or more times to void [1]. Evidence suggests that most people with <2 voids/night generally have only minimal bother from the condition. Only when ≥2 voids/night occurs on a regular basis is nocturia likely to have more serious consequences for the patient [2]. For example, patients with LUTS, which encompass voiding, post-voiding, and storage symptoms (including nocturia), report that nocturia of ≥2 voids/night is one of their most bothersome symptoms. A recent population-based study of LUTs in Finland suggested that moderate or major bother are only reported by those with ≥3 voids/night [3].

Nocturia is an underreported, understudied, and infrequently recognised problem in adults [4]. Many factors can contribute to nocturia, which may be part of the reason this condition has been largely overlooked or considered only as a symptom of some other disorder. However, nocturia can legitimately be considered a clinical entity in its own right that requires careful diagnostic evaluation.

Nocturia may exact a range of detrimental effects because of the associated sleep fragmentation experienced by patients on a

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regular basis. These effects include: reduced health-related quality of life (HRQL), mood disturbance, reduced productivity at work, poorer overall health, and increased falls and fractures [5,6]. Some studies suggest that the degree of bother associated with nocturia is significantly related to sleep status and attendant deficits rather than nocturnal voiding frequency per se [7]. However, despite these effects many people with nocturia do not seek help from a healthcare provider [8]. Patients may not recognise nocturia as a medical condition amenable to treatment. They may simply view it as an unavoidable aspect of ageing, or may be embarrassed or reluctant to discuss symptoms involving urination.

This consensus opinion paper aims to help physicians and other healthcare providers better serve patients with nocturia by summarizing current research, clinical approaches, and treatment options.

METHODS

In April, 2010, an interdisciplinary conference on nocturia was convened by the New England Research Institutes, Inc. (NERI), in Cambridge, MA, USA. The goal of the 2-day conference was to generate a consensus on the current state and direction of the field of nocturia as it pertains to clinical decision-making for primary care providers, urologists, and other health professionals. Nine panellists were selected on the basis of research or clinical expertise in nocturia or nocturia-related symptoms, as well as their position as 'thought leaders' in this field. The panellists represented a wide range of disciplinary backgrounds, including urology, urogynaecology, psychometrics, and sleep physiology. Full attendance at the conference was required.

Panellists presented prepared findings on the first day of the conference. Every member of the panel received equal time to present and to respond to questions from other panel members. All panel members were required to submit their presentations before the meeting for scrutinising by representatives of the Boston University School of Medicine Department of Continuing Medical Education (BU CME) to assure that the materials and conference met standards set forth by the Accreditation Council for Continuing Medical Education. The meeting itself was not CME accredited, but the NERI conference organizers felt it was important to enlist an independent entity to review all materials for bias and balance before the conference, as well as having a BU CME representative present during the conference.

On the second day of the conference, panellists discussed each of the subject areas presented the previous day until a consensus was reached and articulated. Panellists reviewed all key clinical studies relevant to each area, familiarity with the literature, and personal clinical experience. A summary of findings from the conference was provided to all panel members for review and approval after the conference, and these findings provided the basis for the collaborative writing of this paper.

RESULTS

Epidemiology of nocturia

Nocturia is most commonly thought of as a problem affecting older men. However, evidence strongly suggests that nocturia affects a large proportion of adults of both genders and in all age ranges. A recent meta-analysis of 43 articles relevant to nocturia prevalence concluded that nocturia is common across diverse populations [9]. It is most prevalent in older people, but also affects a significant proportion of younger individuals. using the more clinically relevant criterion of ≥2 voids/night, this analysis found the following prevalence rate ranges:

- Men aged 20–40 years: 2–17%
- Women aged 20–40 years: 4–18%
- Men aged >70 years: 29–59%
- Women aged >70 years: 28–62%

Burgio *et al.* [10] reported an overall prevalence of 58.5% among older adults, with a greater proportion of men (63.2%) than women (53.8%) having ≥2 voids/night. In general, samples considering all adults or only younger adults have shown a higher prevalence of nocturia in women [11], whereas samples of older adults typically show a higher prevalence among older men

'Nocturia is most commonly thought of as a problem affecting older men'

[12]. This is possibly due to the influence of bph, which is a risk factor for nocturia that rises significantly with age among men but is not a relevant factor for nocturia in women.

Burgio *et al.* [10] also reported a higher prevalence of nocturia in both male and female african-americans. This finding corroborates an earlier report from the boston area community health (bach) study, which found that african-americans had a nearly 90% greater odds of reporting nocturia than whites, even after controlling for socio-demographic factors [13]. Further research to elucidate the reasons for these disparities

remains to be conducted. Possible explanations include: the higher prevalence among african-americans of conditions associated with nocturia (diabetes mellitus, hypertension, obesity, and cardiovascular disease); factors not measured in existing studies, e.g. Rates of sleep apnoea (higher among african-americans); or the influence of sickle-cell trait (which can cause renal deficits) [2,9,10].

Predictors and risk factors: nocturia is a multifactorial condition

Nocturia has many possible contributing causative factors, attention to which may be relevant to achieve a clinically meaningful reduction in night-time voids. While an association between these risk factors and nocturia has been established, estimates of the proportion of patients with nocturia who are in fact affected by each underlying factor are not well-established. In addition, the causal direction between nocturia and some of these factors can point either way. For example, the risk of nocturia may be higher among individuals who are depressed, yet depression may be initiated or exacerbated by the sleep disruption that accompanies nocturia. Potential causes of nocturia can be categorized as arising from: bladder storage problems; nocturnal polyuria (NP); 24-h (global) polyuria; and sleep disturbance (Table 1) [14,15].

Although the range of possible causative factors in nocturia is large and often overlapping, some are more common than others. A recent population/questionnaire-based survey of nocturia found that the most common predictive factors of nocturia in men were: urgency of urination; BPH; and sleep disruption (as manifested by snoring) [16]. In women, urgency, obesity, and snoring were predictive. Other associations included: history of prostate cancer and antidepressant use in men, and coronary artery disease and diabetes in women.

> 'Although the range of possible causative factors in nocturia is large and often overlapping, some are more common than others'

In a multi-institutional study NP was the most important contributor to nocturia [17]. As with other components of LUTS, there appears to be some longitudinal variability associated with nocturia with ≈10% of women reported to have spontaneous improvement or resolution of bothersome nocturia [18].

Obesity is a common co-morbidity in western society and has been implicated with the entire spectrum of LUTS, including nocturia. Asplund [19] assessed 10 216 older subjects in Sweden and found that nocturia events increased in parallel with body mass index. Additionally, night-time food ingestion with corresponding decreases in diurnal calorific ingestion was associated with increasing nocturic frequency. The author concluded that nocturnal frequency actually might contribute to an increasing risk of obesity.

Incorrect arginine vasopressin (AVP) levels have also been implicated in NP. NP syndrome, associated with decreased or undetectable levels of AVP, is characterized by increased night-time urinary output. This syndrome is especially prevalent in the elderly, perhaps approaching 4% [20]. Depressed AVP levels may be due to either a primary pituitary disorder or a physiological response to increased return of free water into the circulation associated with resolution of lower extremity third-space fluid upon achieving the recumbent position during sleep.

To better appreciate the deleterious effects of nocturia, it is important to understand the effects of disrupted sleep. Restrictions in total sleep time correlate with increased daytime fatigue and decreased daytime alertness, both of which may pose risks, e.g. falls, depressed mood, cognitive impairment, and decreased HRQL, outcomes that are particularly salient for older adults. Because nocturia routinely disrupts the nocturnal period and has been associated with relatively poor quality sleep, it is likely to affect sleep architecture and may effect waking daytime functioning.

Inadequate sleep duration, as may accompany nocturia, is also associated with increased mortality [21], as well as morbidities such as hypertension, obesity, and glucose intolerance [22]. Population-based data suggest that although insomnia is related to factors such as physical pain and depressed mood, nocturia represents an independent risk factor for compromised sleep quality [23].

Such observational data are consistent with the outcomes from experimental studies of

TABLE 1 Potential causes or associated risk factors for nocturia [88,89]

Bladder storage problems	• Reduced functional bladder capacity (i.e. extrinsic compression from uterine fibroids, urogenital prolapse, ovarian tumour)
	• Bladder pain syndrome
	• BOO (i.e. BPH, BPO)
	• Nocturnal DO
	• Neurogenic bladder
	• Cancer of bladder, prostate, or urethra
	• Learned voiding dysfunction
	• Bladder or ureteric calculi
	• DO (idiopathic or neurogenic)
	• OAB
	• Voiding problems and postvoid residual urine (i.e. uterine fibroids, urogenital prolapse, urethral stricture, detrusor failure)
	• Urogenital ageing (i.e. atrophy caused by oestrogen deficiency)
NP	• Congestive heart failure
	• Obstructive sleep apnoea
	• Peripheral oedema (i.e. venous stasis, hepatic failure)
	• Excessive evening fluid intake
	• Circadian defect in secretion or action of AVP
24-h polyuria	• Diabetes mellitus
	• Diabetes insipidus
	• Primary polydipsia
Sleep disturbance	Primary sleep disorders
	• Insomnia
	• Sleep apnoea
	• Periodic leg movements
	• Narcolepsy
	• Arousal disorders (i.e. sleepwalking, nightmares)
Other potential factors	Medical disorders
	• Cardiac failure
	• Chronic obstructive pulmonary disease
	• Endocrine disorders
	Neurological conditions
	• Parkinson disease
	• Dementia
	• Epilepsy
	Psychiatric conditions
	• Depression
	• Anxiety
	Chronic pain disorders
	Alcohol or drug use (consumption or withdrawal)
	Medications (i.e. corticosteroids, diuretics, β-adrenergic antagonists)

healthy younger and middle-aged people who have been temporarily deprived of sleep, either partially or totally. These studies have consistently found a range of deficits arising from disrupted sleep, including: [24–26]

- Reduced glucose tolerance
- Reduced thyrotrophin concentrations
- Raised evening cortisol concentrations
- Greater sympathetic nervous system activity
- Decreased plasma levels of leptin and concomitant increases in plasma levels of ghrelin (which may skew appetite regulation and promote obesity)

In addition to the adverse effects of reduced sleep durations, nocturia may be associated with sleep apnoea. Community-based elderly populations who have higher levels of sleep disordered breathing (>25 breathing events/h), have nearly double the number of nocturia episodes compared with those with low rates of sleep apnoea [27]. Nocturia episodes in these individuals can be at least partially ameliorated by continuous positive airway pressure treatment for sleep apnoea [28].

Impact on HRQL and overall health

Nocturia affects multiple domains of health, especially for older persons. These domains include HRQL, healthcare costs, increased morbidity, missed diagnoses, and inappropriate treatment.

Nocturia carries a high burden of personal distress, discomfort, and even disability. Among men, nocturia is the 'most bothersome' LUT [29]. Affected persons describe their nocturia as 'debilitating, frustrating, distressing, and puzzling',

particularly in its perceived unpredictability [2]. Older persons experience a diminished self-image, feel prematurely 'old', and worry about nocturia causing night-time falls [30]. Bother from nocturia is related to the frequency of episodes; in a population-based study, any degree of bother was associated with ≥2 voids/night, and moderate-to-severe bother with ≥3 voids/night [3]. Notably, in nearly all nocturia epidemiological and treatment studies, frequency is characterized as 'episodes per night' without consideration of the time a person spends in bed. The impact and burden of 3 voids/night is likely to be greater in persons who typically sleep for 6 h vs those who sleep for ≥8 h. Nocturia also has significant effects on the bed-partners and caregivers of affected older persons. This may ultimately lead to sleeping in separate beds, which can have powerful symbolic significance within a relationship. Caregivers of patients with dementia and nocturia have significantly higher rates of depression and chronic illness [31].

The fear of falling experienced by many older persons with nocturia is well-founded: most night-time falls are associated with bathroom trips, vs only 20% of daytime falls [32]. Nocturia increases the risk of an incident fall 25% over 3 years [33]. Fall risk increases with nocturia frequency; the odds ratio (OR) for a fall increases from 1.84 with 2 voids/night, to 2.15 with 3 voids/night [23]. Significantly, nocturia is associated with injurious falls, and greater risk is associated with higher nocturia frequency. The OR for a hip fracture is 1.36 in older men having ≥2 voids/night, and 1.80 having ≥3 voids/night [34].

'Moderate-to-severe nocturia is associated with significant increases in healthcare costs'

Nocturia may be the herald symptom of significant underlying medical conditions and problems, which, if overlooked, can result in significant morbidity and even mortality. Patients may report nocturia more than other symptoms of an underlying condition because of its bothersome nature, a 'window of opportunity' to identify other conditions. Therefore, the complaint of nocturia should prompt not only an evaluation of its possible medical causes, but also screening and evaluation of the patient for previously unrecognized comorbidity. Medical causes of nocturia to consider include not only cardiovascular disease and sleep apnoea, but also moderate alcohol consumption, restless leg syndrome, poor night-time glycaemic control in persons with diabetes, and other causes of primary sleep disturbance (e.g. pain and Parkinson disease).

Failure to consider the medical causes of nocturia can also lead to treatments that have scant evidence for efficacy and/or associated risks (see relevant sections on pharmacological treatment later in this article). Misdirected pharmacological therapy also increases the chance of polypharmacy. Over 40% of older men and 57% of women already take five or more medications, and ≈11% of all older persons take 10 or more; moreover, up to 25% of medications taken by older persons may be inappropriate [35]. Polypharmacy results in higher risk of adverse reactions and drug interactions, as well as decreased adherence and higher healthcare costs.

Economic impact

Moderate-to-severe nocturia is associated with significant increases in healthcare costs. Among persons with ≥3 voids/night, nocturia is associated with higher total medical costs, greater number of hospitalization days, higher inpatient medical costs, and higher outpatient medical costs [36]. Such costs are not limited to older adults.

As noted earlier, 15–20% of young adults report ≥2 voids/night. Some evidence suggests that younger workers, specifically, may experience more troubled sleep and associated problems than older adults [37]. Whether caused by, or simply exacerbated by, nocturia, these sleep interruptions may erode the general state of health and well-being. These negative effects of nocturia may be particularly difficult for younger patients because they are more likely to have active lifestyles and demanding work schedules. As younger adults are more commonly engaged in the workforce than older adults, nocturia can be expected to exert a disruptive economic impact disproportional to the prevalence of this condition relative to that of older adults.

The impact of nocturia on work productivity was recently estimated using prevalence data from the BACH Study and data from the USA Bureau of Labor Statistics [38]. Subjects reporting nocturia had greater impairment in productivity as measured by the Work

TABLE 2 Based upon analysis of the 24-h FVC, the patient may have

Reduced voided volume (indicating a reduced capacity of the bladder to store urine) either globally or exclusively during the hours of sleep (low nocturnal bladder capacity).
Excessive urine production during the day and night (polyuria, where 24 h urine volume is >40 mL/kg [42])
Excessive urine production specifically at night where 24 h urine output remains normal (NP, see above)
Combinations of the above ('mixed aetiology')

Productivity and Activity Impairment questionnaire (14% vs 5%; 0% maximum productivity, 100% total loss of work productivity). The study concluded that the annual cost to the USA society resulting from loss of productivity from nocturia in the population aged <65 years is ≈$61 billion/year, and $1.5 billion/year for people aged ≥65 years due primarily to the cost of treating complications of falls in older adults.

CLINICAL ASPECTS

Evaluation of patients with nocturia

Although nocturia is common in the general population and may be bothersome or even distressing to patients, it may not be the initial complaint of patients. Clinicians need to be alert to the possibility that their patients are affected by nocturia but may be reluctant to discuss it. Asking patients about nocturia, and LUTS in general, may help them talk more openly about symptoms related to night-time voiding and to what degree they are bothered about it. Given the multi-factorial nature of nocturia, initial assessment involves taking a thorough history to more clearly understand the patient's symptoms. Questionnaires are useful in quantifying the effect of nocturia on daily functioning [39,40]. Patients should be evaluated for underlying disease states, cardiovascular conditions, and consumption of liquids (including, specifically, those containing alcohol and caffeine). Urine analysis, urine culture, and cytology should also be carried out; abnormalities in any of these should be further evaluated with cystoscopy or urography where clinically appropriate.

An important causative factor in nocturia may be NP, typically defined as a nocturnal urinary output >20% of the daily total in young adults and >33% in older adults. NP is present in up to 83% of the general population with nocturia and, as such, clinicians should be alert to the fact that this overproduction of urine at night may be a key contributory factor in their patients, even among those with an overactive bladder (OAB) or benign prostatic obstruction (BPO) diagnosis [41]. NP is often missed during the evaluation and diagnosis of nocturia, which may interfere with a clinically significant improvement in nocturia for these patients.

A key tool in the evaluation and diagnosis of nocturia is the frequency-volume chart (FVC), in which patients record the volume and timing of daytime and night-time voids for 1–3 days. The voiding patterns revealed by FVC data can provide clinicians with invaluable guidance regarding aetiology and treatment (Table 2). The use of FVCs is additionally recommended because of demonstrated discrepancies between nocturnal voiding data obtained using FVCs and data obtained from subjective questionnaires such as the IPSS [43].

The multifactorial nature of nocturia suggests that for many patients, nocturia treatment may involve multiple incremental therapeutic manoeuvres to obtain a clinically meaningful benefit [16].

Nocturia and OAB

Nocturia is often confused with LUTS and assumed to be a symptom of OAB or BPO. Not all patients with OAB or BPO have nocturia and the relationship between nocturia and OAB is not well understood. There are several reasons for this that relate to the definition of both conditions. Firstly, for nocturia, there are no validated nocturia instruments that determine:

1) why the patient was awakened,
2) why he or she voided (i.e. out of convenience, habit, urge, or urgency), and
3) whether the patient fell back asleep.

Secondly, the definitions of urgency (the *sine-qua-non* symptom of OAB) and OAB itself are the subject of debate. For example, using very strict criteria for OAB, Tikkinen [44] found a prevalence of only ≈8% compared with the oft-quoted 16–17%.Thirdly the symptoms of OAB have a wide differential diagnosis that must be considered.

Nonetheless, clear associations between OAB and nocturia exist. In a Finnish population-based study of 6000 participants, Tikkinen [44] reported that 17% of patients with nocturia reported OAB. Conversely, 80% of patients with OAB reported nocturia. Furthermore, there was a direct relationship between the number of nocturnal voids and the prevalence of OAB ($P < 0.001$). Nocturia and OAB increased with age ($P < 0.001$) and this relationship persisted across age groups.

In an earlier study, Tikkinen *et al.* [16] reported an incidence of OAB in 8% and 9% of men and women respectively using the symptom urgency as the marker of OAB. These data suggest that OAB is no more common in patients with nocturia than in the general population. In contrast, several authors have reported an incidence of OAB as high as 33% in patients with nocturia and, conversely a 50% incidence of nocturia in those with OAB [45–47].

In an observational study of women with OAB who underwent urodynamics, Matharu *et al.* [48] reported that in women aged >40 years, the incidence of detrusor overactivity (DO) increased with increasing self-reported nocturia; i.e., the more night-time voids, the greater the chances of having DO.

Indirect evidence that OAB plays a relatively minor role in the genesis of nocturnal voids comes from studies showing that OAB medications are not effective in reducing night-time voids [49,50]. Although, these studies do suggest that antimuscarinics reduce the number of night-time voids that are due to urgency. For example, Brubaker and Fitzgerald [49], reported that solifenacin reduced nocturnal voids by 36% in patients without NP, while having no effect on overall nocturnal voids.

From the studies cited above, we can conclude that:

1) most patients with nocturia do not have OAB,
2) most patients with OAB do have nocturia,
3) antimuscarinics do not appear to be efficacious for nocturia, and
4) antimuscarinics may be effective for nocturnal voids due to urgency.

Ultimately, to evaluate the relationship between nocturia and OAB better methods are needed to determine whether the patient was awakened by an urge to void or by something else, and why he or she voids once awakened. Thus, a clearer means of distinguishing urgency from a normal urge to void and a broader definition of OAB is needed. The Standardisation Committee of ICS states that: '(Urinary) urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder syndrome.if there is no proven infection or other obvious pathology' [51]. Urgency is defined as '. the complaint of a sudden compelling desire to pass urine, which is difficult to defer'. However, these definitions may be too restrictive, especially insofar as determining the relationship between OAB and nocturia.

In a study designed to define the sensation of urgency, patients were asked to describe, in their own words, what they meant by urgency [52]. The most common answer was, 'If I wait too long, I have trouble getting to the bathroom in time'. In fact, only a few patients described urgency as a 'sudden' event. Based on these data, two distinct types of urgency emerged that may have relevance for determining why a patient voids when awakened from sleep. Type 1 urge was described as an intensification of the normal urge to void and occurred in 69% of patients with OAB, and type 2 (31%) was a sudden precipitous urge that is a different sensation from the normal urge, which conformed to the ICS definition. In patients with type 1 urge, the intensity of the urge to void increases over time and culminates in micturition; whereas, in type 2 the patient has little or no warning and must rush to the bathroom. The idea that the urge to void can be graded runs counter to ICS doctrine, but nevertheless has strong scientific support [53–55].

'Most patients initially respond to nocturia by engaging in one or more life-style modifications'

Another confounding factor in the analysis of the relationship between OAB and nocturia is that the ICS definition considers OAB to be a syndrome, with symptoms suggestive of DO (involuntary contractions of the bladder), and recommends that the term OAB be used only 'if there is no proven infection or other obvious pathology'. This definition has profound effects on research methodology because, in fact, there are many conditions in the differential diagnosis of OAB symptoms that should, theoretically, be exclusion criteria. In practice though, most studies do not include such exclusion criteria (Fig. 1) [56]. In conclusion, understanding the relationship between nocturia and OAB requires considerable future research, involving the following steps: the definitions of nocturia, OAB and urgency need to be better defined and studies are needed to determine the reasons why patients arise from sleep to void, whether it is because of a bladder sensation or something else.

MANAGEMENT

Lifestyle changes and supplements

Most patients initially respond to nocturia by engaging in one or more life-style modifications (Table 3). These techniques usually enable patients to manage their symptoms initially. However, as nocturia progresses, these modifications lose their effectiveness and many patients then turn to supplements of one sort or another or eventually seek medical intervention.

Many patients try herbal supplements to limit their nocturia. Supplements are attractive because:

- They are perceived as 'natural'
- They are easy to obtain (available in most drug stores and over the internet)
- No doctor input is needed
- They are relatively inexpensive
- They are perceived to be safe, i.e. without side effects (mainly because they have never been adequately tested)

In the USA, 50–90% of men have tried supplements before seeking medical treatment for their LUTS/BPH [57].

Several plant-based extracts are currently on the market as supplements purporting to

FIG. 1.
OAB was found to be idiopathic in only 5% of men. The following differential diagnoses were reported.

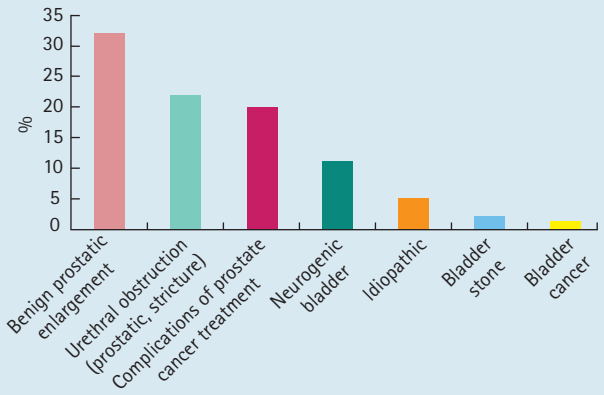


TABLE 3 Life-style modifications to manage nocturia

Pre-emptive voiding
Nocturnal dehydration
Dietary and fluid restrictions (avoidance of caffeinated beverages, alcohol etc.)
Medication timing (diuretics in the mid-afternoon)
Evening leg elevation to mobilize fluids
Use of sleep medications/aides
Use of protective undergarments

TABLE 4
Plant extracts used as supplements for BPH/LUTS [57]

Latin name	Common name
Serenoa repens, Sabal serrulata	American dwarf palm/saw palmetto berry
Pygeum africanum	African plum tree
Hypoxi rooperi	South African star grass
Urtica dioica	Stinging nettle
Secale cerale	Rye pollen
Cucurbita pepo	Pumpkin seed

improve symptoms of BPH/LUTS (Table 4) [57]. The most commonly-used supplement for nocturia symptoms is *Serenoa repens*, saw palmetto berry extract [57]. Because these products are plant extracts and manufacturers use several different extraction processes, there is significant variability in the products being sold. For example, the dosage of saw palmetto berry extract varied from –97% to +140% of the dose stated on the bottle label with half the products having < 20% of the stated dose [58].

Numerous mechanisms of action for saw palmetto berry extract have been proposed. These theories are frequently based upon *in vitro* experiments, usually with cell cultures. However, none of the purported mechanisms of action have been confirmed [59].

The only saw palmetto product that has undergone extensive clinical study is Permixon brand saw palmetto berry extract (Pierre Fabre Medicament, Castres, France). Two meta-analyses of all the published and unpublished trials of Permixon have been undertaken [60,61]. The initial analysis included 13 trials with 2794 patients. The results showed that nocturia was decreased by placebo by 0.69 voids/night while the Permixon treated patients' nocturia episodes were reduced by 1.19 voids/night. Maximum urinary flow rates (Q_{max}) were increased by placebo by 0.51 mL/s and by Permixon by 2.71 mL/s. In that study there was a statistically significant improvement in Q_{max} and reduction in nocturia greater than placebo, although whether these changes have any clinical significance is unclear [60]. The second meta-analysis of Permixon included 17 studies with 4820 patients [61]. As in the first analysis, nocturia was decreased slightly and Q_{max} improved slightly at levels that reached statistical, but perhaps not clinical, significance.

A National Institutes of Health-sponsored, 1-year, placebo-controlled trial of 225 patients evaluating Sabalselect (Indena California, USA) brand saw palmetto berry extract showed no difference in the reduction of LUTS as measured by the AUA Symptom Score [62]. The reduction was 0.72 for placebo and 0.68 for the product. In fact, during the placebo run-in period, there was a reduction of 1.49, which was a greater effect than the product alone. There were minor but not statistically significant improvements in urinary flow rates and BPH impact Index (–0.33 vs –0.09) with the saw palmetto. This trial is important because it was the only non-company sponsored trial in this area and it did not show any efficacy for the herbal product.

Non-antidiuretic pharmacotherapy

In critically reviewing the literature on the subject of non-antidiuretic pharmacotherapy for nocturia, a few issues immediately arise with implications for assessing the efficacy of any given treatment. A 'successful' treatment programme for nocturia should result in a clinically significant (as opposed to statistically significant) reduction in nocturnal awakenings to void and a subsequent positive effect on the negative issues associated with nocturia, yet limited evidence-based medicine exists.

Several studies have explored the efficacy of terazosin, finasteride, or combinations of these drugs in improving nocturia symptoms. For example, the effect of tamsulosin oral-controlled absorption system (OCAS) 0.4 mg. was assessed in a phase 3B pilot study in men with LUTS/BPH and ≥2 voids/night [63]. That study concluded that 'tamsulosin OCAS 0.4 mg was superior to placebo in reducing . . . the mean IPSS nocturia'. However, the 'significant reduction', amounted to a mean change of 3.1 to 2.3 awakenings for placebo and 3.1 to 2.0 for drug. The change in the time to the first awakening to void was not statistically significant. Another representative study was a secondary analysis of IPSS nocturia data from the Veterans' Administration Cooperative Study [64]. The data from 1078

men, aged 45–80 years, with a diagnosis of BPH who completed 12 months of the trial were analysed specifically for reduction in nocturia. There were four arms in the study: terazosin, finasteride, combined terazosin plus finasteride, and placebo. The improvement in the placebo group was from 2.4 to 2.1 voids/night; improvements in the other groups were: terazosin 2.4 to 1.8, finasteride 2.5 to 2.1 and the combined therapy 2.4 to 2.0 voids/night. The authors arbitrarily designated a 50% reduction in nocturia as being a meaningful benefit, and this was statistically significant for comparing response rates by treatment arm (chi-square analysis), but the reality is that there was only a 17% greater improvement for the α-blocker over placebo in this parameter.

Antimuscarinic therapy for OAB has also been explored as a treatment approach for nocturia. As nocturia is commonly seen in OAB, it has been assumed that first-line medications for OAB will exert a clinically significant effect. Yet, as antimuscarinics exert no effect on NP, these agents would be expected to exert an effect on nocturia only if the episodes of nocturia awakening were associated with urgency, and even then, antimuscarinics decrease urgency episodes by half at best. This suggests that antimuscarinic therapy may be ineffective except for the group of patients with very severe urgency in whom most voids (counting urgency incontinence episodes as voids) were associated with urgency.

'Antimuscarinic therapy for OAB has also been explored as a treatment approach for nocturia'

In a representative study, Brubaker and Fitzgerald [49] reported on the effect of solifenacin on male and female patients with OAB using pooled data from four 3-month phase III trials. Of the 3032 patients who were randomized, 2534 reported nocturia at baseline and 62% of the patients reporting nocturia were classified as having NP. The baseline number of nocturnal episodes was higher in those patients with NP 2.27–2.33 vs 1.66–1.70 voids/night. In those without NP there was a 'significant' reduction in nocturia which amounted only to a numeric difference of 0.18 net advantage over placebo for the 5 mg dose and 0.08 for the 10 mg dose. For those patients with NP, the reductions were not significantly different from placebo (0.72 and 0.68 voids/night for the 5 and 10 mg doses respectively, vs 0.64 voids/night for placebo).

Using trospium chloride, Rudy *et al.* [65] showed a statistically significant decrease in the mean number of nocturic episodes per night (baseline 2) of 0.57 voids/night for drug vs 0.29 voids/night for placebo, a difference of 0.28 episodes. Zinner *et al.* [66] reported similar results with the same drug.

There has been a group of studies done with tolterodine and with the newer agent, fesoterodine, which seem to characterize the spectrum of results seen with the antimuscarinic agents (Table 5) [67–70].

Rackley *et al.* [50] reported on the median percentage reduction in nocturnal voiding frequency with tolterodine, dividing the nocturnal voids into non-OAB voids, OAB voids, and severe OAB voids. Overall, there was no significant effect over placebo on nocturic episodes, a finding also reported by Nitti *et al.* [71]. However, with night-time dosing, there was a statistically significant improvement in OAB-related nocturnal voids (those associated with urgency). Such results argue for proof of concept for reduction in urgency episodes with antimuscarinic agents and, further, suggest that antimuscarinics potentially offer the most benefit to patients with significant and severe frequent nocturnal urgency without NP, an opinion shared by Brubaker and Fitzgerald [49].

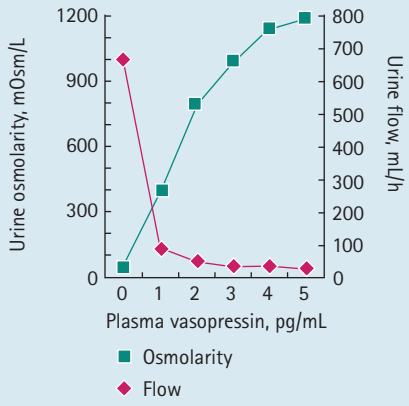
There has been little success in treating nocturia with 5α-reductase inhibitor (5ARI) agents given to patients for relief of symptoms due to BOO caused by prostatic enlargement. There have been occasional reports of statistically significant results from placebo-controlled trials with α-adrenergic blockade, but these results are of doubtful clinical significance. The same can be said for combined therapy with these two types of agents. Statistical success has been achieved in some groups with various antimuscarinic agents, but, again, the clinical significance of these changes in the groups studied is doubtful. Hypothetically, to observe a clinically significant result with any of these agents, one would have to select a group of patients with a lot of nocturia episodes, most of which were due to DO-related urgency. These agents are likely to continue playing a role in reducing symptoms of patients with LUTS attributable to BOO and to OAB.

TABLE 5 Collected results of recent studies with data for effect of fesoterodine on nocturia

References	Treatment	Median % decrease, *P*	Mean decrease in no. voids per night/baseline, *P*
Chapple *et al.* 2005 [67]	Placebo	27	0.32/1.8
	Tolterodine extended release 4 mg	25, NS	0.40/2.0, NS
	Fesoterodine 4 mg	29, NS	0.39/1.9, NS
	Fesoterodine 8 mg	24, NS	0.39/2.0, NS
Nitti *et al.* 2007 [68]	Placebo	25	0.39/2.0
	Fesoterodine 4 mg	33, 0.13	0.58/2.2, 0.42
	Fesoterodine 8 mg	25, NS	0.55/1.9, 0.09
Herschorn *et al.* 2010 [69]	Placebo	25	0.5/2.3
	Tolterodine extended release 4 mg	28, NS	0.6/2.2, NS
	Fesoterodine 8 mg	29, NS	0.6/2.2, NS
Dmochowski *et al.* 2010 [70]	Placebo	no difference in mean nocturnal voids or nocturnal urgency episodes for either	?/2.7
	Fesoterodine (titrated 4–8 mg)		?/2.6

NS, not statistically significant.

FIG. 2. As the level of plasma vasopressin rises, urine osmolarity increases sharply which, in turn, rapidly reduces the flow of urine and the need to void.



However, other types of therapy will need to be used to achieve a clinically significant reduction in nocturia.

Timed diuretic therapy

Diuretics are often prescribed for peripheral oedema with no particular attention to the time of day at which they would be most effective. In patients with NP owing to reabsorption of third-space lower extremity fluid during recumbency associated with intended sleep, diuretics should be administered during the mid-afternoon to address fluid accumulated over the course of the day, but not so late as to actually exacerbate NP [72,73]. Diuretics (specifically bumetanide and furosemide) have been conferred Level 2 evidence, Grade C recommendation by the Committee for Establishment of the Clinical Guidelines for Nocturia of the Neurogenic Bladder Society [74].

Antidiuretic therapy

For patients whose nocturia is related to NP, either alone or combined with OAB or BPH, treatment that reduces nocturnal urine volumes may be warranted [75]. Assuming that patients have been given advice regarding night-time fluid intake, and other causes of NP have been excluded, then antidiuretic therapy may be an appropriate choice as it can address insufficient secretion of AVP, which results in NP and, frequently, nocturia.

Antidiuretic therapy with the synthetic analogue of AVP, desmopressin, is the only pharmacological therapy which in some countries is indicated specifically for nocturia. Desmopressin is a selective V_2 receptor agonist, and therefore has a greater specificity of action than AVP, avoiding unwanted vasopressor and uterotonic effects associated with V_1 agonism [76]. Desmopressin has a more powerful and longer-lasting antidiuretic action than AVP. It increases reabsorption of water in the distal and collecting tubules of the kidney via its action on the V_2 receptor, and concentrates the urine, decreasing urine production, and postponing the need to void (Fig. 2).

Given the specific antidiuretic action of desmopressin, it is the pharmacological therapy of choice for patients with nocturia where NP is present, and has a grade A level 1 recommendation from the International Consultation on Incontinence [77]. It has a fast onset of action, with urine production decreasing within 30 min of oral administration [78], and can be administered as a tablet or oral lyophilisate ('melt') formulation requiring no concomitant fluid intake. The oral lyophilisate formulation has greater bioavailability than the tablet, allowing lower dosing to achieve equivalent antidiuresis and a well-defined duration of action with different dosages in children with bedwetting [79].

Several randomized placebo-controlled trials have shown the efficacy of oral desmopressin in the treatment of adults with nocturia. A series of 3-week, randomized, double-blind, placebo-controlled trials showed that oral desmopressin (0.1, 0.2 or 0.4 mg tablet) is effective in both men and women aged ≥18 years with nocturia. In these studies, clinical response was defined as ≥50% reduction in nocturnal voids from baseline. In the study of men, 34% of patients had a clinical response with desmopressin, as compared with 3% of patients receiving placebo ($P < 0.001$) [80]; the mean number of nocturnal voids

reduced from 3.0 to 1.7 and from 3.2 to 2.7 respectively ($P < 0.001$). In women results were similar: 46% of desmopressin-treated women had a clinical response, compared with 7% of those on placebo ($P < 0.001$) [81]; the mean number of nocturnal voids was reduced from 2.92 to 1.61 and from 2.91 to 2.36 respectively ($P < 0.001$). In an additional study investigating both men and women, 33% of desmopressin-treated patients had a clinical response, vs 11% with placebo ($P < 0.001$), with the mean number of nocturnal voids decreasing from 3.26 to 2.01 with desmopressin and from 2.8 to 2.42 with placebo ($P < 0.001$) [76]. Long-term studies show that efficacy is maintained and improved during 10–12 months of treatment; a rebound effect is seen when treatment is withdrawn, confirming the association between continued treatment and response [81].

Desmopressin was well tolerated in all studies and treatment-related adverse event rates were similar to placebo during the double-blind phases. Hyponatraemia is the only potentially serious adverse event associated with desmopressin use. Cases are rare and the primary predictor is increasing age. Initiation of desmopressin is therefore currently not indicated for patients aged ≥65 years. The mechanisms behind desmopressin-induced hyponatraemia are well understood, and serum sodium monitoring at baseline and early in treatment in older patients can greatly reduce their risk of developing the condition.

Patients' initial sleep period is significantly prolonged with desmopressin therapy, meaning that important slow-wave sleep (SWS) in the first part of the night is less likely to be interrupted [76]. Van Kerrebroeck *et al.* [76] found that desmopressin-treated patients were significantly more likely to report that they felt fresh in the morning than patients receiving placebo ($P = 0.02$). Furthermore, the proportion of patients who reported nocturia as their most bothersome symptom decreased by >50% with long-term desmopressin treatment [82].

'Most patients diagnosed with BPH or OAB have comorbid NP'

Most patients diagnosed with BPH or OAB have comorbid NP. As previously noted, nocturia is resistant to treatment with α_1-blockers and/or anticholinergics. It is important, therefore, FVCs are used wherever possible and early in the diagnostic process to gain a full insight into the causes of nocturia in each patient. Appropriate treatment selection, designed to address each underlying factor at the outset, is then possible. It is also important that clinicians take time to verify whether patients who have been prescribed traditional BPH and OAB therapies for daytime LUTS have an improvement in their nocturia. If not, combined therapy using α_1-adrenergic blockers and/or anticholinergics in conjunction with desmopressin should be considered.

Combined therapy is an emerging standard in the field of urology, and is becoming recognised for its potential to improve patient outcomes. Clinical progression and IPSSs in patients with BPH are reported to be reduced in those receiving concomitant 5ARI and α_1-blocker therapy as compared with those receiving monotherapy [83,84]. Combined anticholinergic and α_1-blocker therapy has also been shown to be better than monotherapy in men with BPH and OAB [85]. The use of combined therapy to address multiple factors underlying LUTS as well as nocturia is therefore accepted as a rational treatment strategy.

Surgical options

Nocturia is the least specific symptom of BPH and is the least responsive symptom for therapies directed at alleviating prostatic obstructions [86]. Nonetheless, outlet procedures, including minimally invasive procedures for the prostate, TURP, and open prostatectomy, are offered to address this symptom of BPH. Unfortunately, the absence of double blind placebo-controlled trials to gauge the effects of prostatectomy has limited the ability to assess its efficacy in relieving nocturia [87].

It is also difficult to identify predictive metrics for TURP and other interventions because of the documented poor correlation between objective and subjective measures in patients with obstructing BPH [88]. Studies reviewing the effect of prostatectomy on IPSSs focus on question seven when evaluating nocturia: 'during the last month, how many times did

you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning'? Although this question helps quantify nocturia, it does not measure the effect of nocturia on a patient's HRQL. In addition, patient age has a positive correlation with the IPSSs after TURP, with respect to nocturia, although age does not correlate with other score symptoms [89].

TURP appears to confer a greater improvement in BPH symptoms than either transurethral microwave thermotherapy (TUMT) or oral α-blocker therapy [87]. Antunes *et al.* [90] reported a 1.3 decrease in mean nocturia episodes after TURP, while van Dijk *et al.* [87] reported that the outlet procedure reduced nocturia by a mean of 23%. Improvement in symptoms after TURP, including nocturia, has been attributed to a reduction in DO with relief of the prostatic obstruction in addition to the effect of removing the adenoma on the detrusor muscle [91]. Margel *et al.* [91] commented that postvoid residual urine reduction will lead to increased nocturnal bladder filling time and a reduction in nocturia. Yoshimura *et al.* [92] reported a 19.2% reduction in nocturia after TURP, with an average of 1 point reduction for nocturia in the IPSS. However, they noted that this was the lowest degree of improvement among the seven IPSS individual symptom scores measured.

Interestingly, Antunes *et al.* [90] reported that the positive effects of TURP on nocturia were not correlated with the amount of resected tissue. Resection of <30% of prostate tissue was enough to alleviate LUTs associated with BPH. van Dijk *et al.* [87] showed that TUMT in patients with obstruction reduced nocturia episodes by 32% at 6–12 months after treatment compared with before treatment episodes, and improved patients' HRQL. An older study by Schatzl *et al.* [93] also showed reductions in nocturia in men treated with transurethral needle ablation, transrectal high-intensity focused ultrasound, and transurethral electrosurgical vaporization, although patient numbers were small.

Despite the lack of absolute metrics, TURP and/or laser ablation of the prostate are reasonable treatment options for men with prostatic obstruction and nocturia, as both conditions typically improve in most properly selected patients.

CONCLUSIONS

Education of community-based physicians

The authors recognise that healthcare providers in multiple specialties may be called upon to evaluate and treat patients bothered by nocturia. The present article attempts to begin the process of broadening the understanding of the underpinnings and effective treatment strategies for nocturia, but they are only a start. Continuing medical education regarding nocturia should be promoted by teams of experts lecturing on the subject in primary through tertiary centres in the format of traditional grand rounds, as well as dissemination of online materials available on commercial websites, Wiki articles, and websites maintained by academic centres.

Nocturia symposia have been readily available at urological meetings worldwide, e.g. those of the AUA (and its section meetings), ICS, Society for Urodynamics and Female Urology, International Urogynecological Society, and European Association of Urology. These symposia may be made available online in the form of webcasts that need not be viewed live. In the case of uropharmaceuticals approved for nocturia (none currently have a specific nocturia indication in the USA), package inserts could be designed effectively for counselling both physicians and patients as to optimal use of these drugs, much as in the case for medications with complex applications (a fine example being intraurethral alprostadil for phosphodiesterase 5 refractory erectile dysfunction) as well as on the need for follow-up (e.g. package inserts accompanying sodium cellulose phosphate for patients with absorptive hypercalciuria).

Clinical recommendations

Participants in the interdisciplinary conference on nocturia agreed on the following recommendations for the evaluation and treatment of patients with nocturia:

1. Nocturia is a highly multi-factorial condition that can exert a range of deleterious effects on health and HRQL.
2. Rather than being viewed simply as a secondary symptom of other conditions, nocturia should be recognised as a condition in its own right with potentially profound consequences for health, well-being, longevity, and functioning.
3. FVCs are the most useful initial diagnostic tools for evaluating nocturia and should be used wherever possible, and early in the diagnostic process, to most accurately characterise the causes of nocturia in each patient.
4. Herbal supplements, such as saw palmetto berry extract, have not been well studied and, while potentially helpful in some individuals, cannot be recommended at this time.
5. Treatment of nocturia with α_1-blockers and/or anticholinergics is not generally effective. Although statistically significant improvements in symptoms have been reported, the clinical significance of the reported changes is debatable.
6. Timed diuretics given at mid-afternoon may be effective in patients with third spacing as an aetiology for nocturia.
7. Antidiuretic therapy (e.g. desmopressin) has proven well-tolerated and effective in several randomized, placebo-controlled trials and is recommended as a first-line treatment (either as monotherapy or in combination with other agents) for patients who have been appropriately evaluated and whose nocturia is related to NP whether or not accompanied by BPH or OAB.
8. Surgical options to remove or reduce prostatic or urethral obstructions may help alleviate nocturia symptoms. TURP and/or laser ablation of the prostate are reasonable treatment options for men with prostatic obstruction and nocturia.

Future research needs

Although there is a rising awareness of its existence, nocturia remains under-studied. Conference attendees identified the following areas in need of further research:

- Validation and clarification of the definition of nocturia in regards to the clinical relevance of the ICS definition as well as a clearer articulation of the reasons for any night-time awakenings [3].
- Basic research into age-related circadian rhythms, the effects of 'near nocturia' (nocturnal arousals owing to the sensation of needing to pass urine, followed by sleep without voiding) on sleep quality, and the relationship between nocturia and restorative stages of sleep (e.g. SWS) [94]

- Research into the question of why patients awaken at night and whether, upon such awakenings, they void with little or no urge.
- Research to determine the extent to which nocturia interferes with objectively (polysomnographically) assessed sleep duration and sleep continuity, with particular emphasis on the duration of sleep before the first awakening of the night and the relative amount of SWS that occurs during that period.
- Epidemiological research into the following aspects of nocturia: effect on HRQL, and effect on mortality in different age categories, genders, and worldwide populations.
- Patient-reported outcomes research into the most relevant endpoints to consider in research (e.g., number of nocturia episodes, nocturia-related impairment in HRQL, nocturia-related impairment of sleep quality and cognitive function, morbidity, mortality)
- Health economics research into the true costs of nocturia to society and the individual, as well as the impact and cost-effectiveness of different therapeutic strategies at both patient and systems levels.
- Outcomes of therapy for nocturia (e.g. behavioural, timed diuretics, timed antidiuretics, antimuscarinics, continuous positive airway pressure for sleep apnoea, combined therapies).
- Research into whether antidiuretic therapy should be limited to patients with diary-confirmed NP and whether antimuscarinic therapy is effective in subpopulations of patients with significant nocturnal urgency.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Abrams P, Cardozo L, Khoury S, Wein A eds.** *Continence*. 4th ed, Paris: Health Publications Ltd, 2009
2 **Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E.** The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. *BJU Int* 2003; **92**: 948–54
3 **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**: 488–96
4 **Chen FY, Dai YT, Liu CK, Yu HJ, Liu CY, Chen TH.** Perception of nocturia and medical consulting behavior among community-dwelling women. *Int Urogynecol J Pelvic Floor Dysfunct* 2007; **18**: 431–6
5 **Asplund R.** Nocturia: consequences for sleep and daytime activities and associated risks. *Eur Urol Suppl* 2005; **3**: 24–32
6 **Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC.** Association of Nocturia and Mortality: results from the Third National Health and Nutrition Examination Survey. *J Urol* 2011; **185**: 571–7
7 **van Dijk L, Kooij DG, Schellevis FG, Kaptein AA, Boon TA, Wooning M.** Nocturia: impact on quality of life in a Dutch adult population. *BJU Int* 2004; **93**: 1001–4
8 **MacDiarmid S, Rosenberg M.** Overactive bladder in women: symptom impact and treatment expectations. *Curr Med Res Opin* 2005; **21**: 1413–21
9 **Bosch JL, Weiss JP.** The prevalence and causes of nocturia. *J Urol* 2010; **184**: 440–6
10 **Burgio KL, Johnson TM 2nd, Goode PS *et al.*** Prevalence and correlates of nocturia in community-dwelling older adults. *J Am Geriatr Soc* 2010; **58**: 861–6
11 **Choo MS, Ku JH, Park CH *et al.*** Prevalence of nocturia in a Korean population aged 40 to 89 years. *Neurourol Urodyn* 2008; **27**: 60–4
12 **Tikkinen KA, Tammela TL, Huhtala H, Auvinen A.** Is nocturia equally common among men and women? A population based study in Finland. *J Urol* 2006; **175**: 596–600
13 **Fitzgerald MP, Litman HJ, Link CL, McKinlay JB, BACH Survey Investigators.** The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. *J Urol* 2007; **177**: 1385–9
14 **Stember DS, Weiss JP, Lee CL, Blaivais JG.** Nocturia in men. *Int J Clin Pract Suppl* 2007; **155**: 17–22
15 **Robinson D.** Nocturia in women. *Int J Clin Pract Suppl* 2007; **155**: 23–31
16 **Tikkinen KA, Auvinen A, Johnson TM 2nd *et al.*** A systematic evaluation of factors associated with nocturia – the population-based FINNO study. *Am J Epidemiol* 2009; **170**: 361–8
17 **Klingler HC, Heidler H, Madersbacher H, Primus G.** Nocturia: an Austrian study on the multifactorial etiology of this symptom. *Neurourol Urodyn* 2009; **28**: 427–31
18 **Heidler S, Deveza C, Temml C *et al.*** The natural history of lower urinary tract symptoms in females: analysis of a health screening project. *Eur Urol* 2007; **52**: 1744–50
19 **Asplund R.** Obesity in elderly people with nocturia: cause or consequence? *Can J Urol* 2007; **14**: 3424–8
20 **Asplund R, Aberg H.** Diurnal variation in the levels of antidiuretic hormone in the elderly. *J Intern Med* 1991; **229**: 131–4
21 **Ikehara S, Iso H, Date C *et al.*** Association of sleep duration with mortality from cardiovascular disease and other causes for Japanese men and women: the JACC study. *Sleep* 2009; **32**: 295–301
22 **Gottlieb DJ, Punjabi NM, Newman AB *et al.*** Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med* 2005; **165**: 863–7
23 **Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK.** Nocturia and disturbed sleep in the elderly. *Sleep Med* 2009; **10**: 540–8
24 **Spiegel K, Leproult R, Van Cauter E.** Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; **354**: 1435–9
25 **Copinschi G.** Metabolic and endocrine effects of sleep deprivation. *Essent Psychopharmacol* 2005; **6**: 341–7
26 **Tasali E, Leproult R, Ehrmann DA, Van Cauter E.** Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci USA* 2008; **105**: 1044–9
27 **Endeshaw YW, Johnson TM, Kutner MH, Ouslander JG, Bliwise DL.** Sleep-disordered breathing and nocturia in older adults. *J Am Geriatr Soc* 2004; **52**: 957–60
28 **Margel D, Shochat T, Getzler O, Livne PM, Pillar G.** Continuous positive airway

pressure reduces nocturia in patients with obstructive sleep apnea. *Urology* 2006; **67**: 974–7
29 **Dubeau CE, Simon SE, Morris JN.** The effect of urinary incontinence on quality of life in older nursing home residents. *J Am Geriatr Soc* 2006; **54**: 1325–33
30 **Booth JM, Lawrence M, O'Neill K, McMillan L.** Exploring older peoples' experiences of nocturia: a poorly recognised urinary condition that limits participation. *Disabil Rehabil* 2010; **32**: 765–74
31 **Hake AM.** The treatment of Alzheimer's disease: the approach from a clinical specialist in the trenches. *Semin Neurol* 2002; **22**: 71–4
32 **Endeshaw Y.** Correlates of self-reported nocturia among community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2009; **64**: 142–8
33 **Stewart RB, Moore MT, May FE, Marks RG, Hale WE.** Nocturia: a risk factor for falls in the elderly. *J Am Geriatr Soc* 1992; **40**: 1217–20
34 **Temml C, Ponholzer A, Gutjahr G, Berger I, Marszalek M, Madersbacher S.** Nocturia is an age-independent risk factor for hip-fractures in men. *Neurourol Urodyn* 2009; **28**: 949–52
35 **Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA.** Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 2002; **287**: 337–44
36 **Nakagawa H, Niu K, Kaiho Y, Ikeda Y, Arai Y.** Mortality in the elderly correlates with the frequency of nighttime voiding: results of a 5 year prospective cohort study in Japan. *J Urol* 2010; **183** (Suppl.): e1–2
37 **Asplund R, Aberg H.** Nocturnal micturition, sleep and well-being in women of ages 40–64 years. *Maturitas* 1996; **24**: 73–81
38 **Holm-Larsen T, Weiss JP, Langkilde LK.** Economic burden of nocturia in the US adult population. *J Urol* 2010; **183** (Suppl.): e1
39 **Sintonen H.** The 15D instrument of health-related quality of life: properties and applications. *Ann Med* 2001; **33**: 328–36
40 **Partinen M, Gislason T.** Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *J Sleep Res* 1995; **4**: 150–5
41 **Koseoglu H, Aslan G, Ozdemir I, Esen A.** Nocturnal polyuria in patients with lower urinary tract symptoms and response to alpha-blocker therapy. *Urology* 2006; **67**: 1188–92
42 **Lee CL, Weiss JP, Blaivas JG.** Nocturia: diagnosis and management. In Staskin DS ed. *Atlas of Bladder Disease*, Philadelphia: Current Medicine Group, 2009: 23–34
43 **Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL.** Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. *J Urol* 2000; **164**: 1201–5
44 **Tikkinen KO.** Epidemiology of nocturia. Academic dissertation. University of Tampere, 2010
45 **Rembratt A, Norgaard JP, Andersson KE.** Nocturia and associated morbidity in a community-dwelling elderly population. *BJU Int* 2003; **92**: 726–30
46 **Schatzl G, Temml C, Schmidbauer J, Dolezal B, Haidinger G, Madersbacher S.** Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project. *Urology* 2000; **56**: 71–5
47 **Weiss JP, Blaivas JG, Jones M, Wang JT, Guan Z, 037 Study Group.** Age related pathogenesis of nocturia in patients with overactive bladder. *J Urol* 2007; **178**: 548–51
48 **Matharu G, Donaldson MM, McGrother CW, Matthews RJ.** Relationship between urinary symptoms reported in a postal questionnaire and urodynamic diagnosis. *Neurourol Urodyn* 2005; **24**: 100–5
49 **Brubaker L, Fitzgerald MP.** Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. *Int Urogynecol J Pelvic Floor Dysfunct* 2007; **18**: 737–41
50 **Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z.** Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. *Urology* 2006; **67**: 731–6
51 **Abrams P, Cardozo L, Fall M *et al.*** The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; **21**: 167–78
52 **Blaivas JG, Panagopoulos G, Weiss JP, Somaroo C.** Two types of urgency. *Neurourol Urodyn* 2009; **28**: 188–90
53 **Blaivas JG, Panagopoulos G, Weiss JP, Somaroo C, Chaikin DC.** The urgency perception score: validation and test-retest. *J Urol* 2007; **177**: 199–202
54 **Nixon A, Colman S, Sabounjian L *et al.*** A validated patient reported measure of urinary urgency severity in overactive bladder for use in clinical trials. *J Urol* 2005; **174**: 604–7
55 **Zinner N, Harnett M, Sabounjian L, Sandage B Jr, Dmochowski R, Staskin D.** The overactive bladder-symptom composite score: a composite symptom score of toilet voids, urgency severity and urge urinary incontinence in patients with overactive bladder. *J Urol* 2005; **173**: 1639–43
56 **Blaivas JG, Marks BK, Weiss JP, Panagopoulos G, Somaroo C.** Differential diagnosis of overactive bladder in men. *J Urol* 2009; **182**: 2814–7
57 **Lowe FC, Ku JC.** Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. *Urology* 1996; **48**: 12–20
58 **Feifer AH, Fleshner NE, Klotz L.** Analytical accuracy and reliability of commonly used nutritional supplements in prostate disease. *J Urol* 2002; **168**: 150–4
59 **Dreikorn K, Lowe F, Borkowski A *et al.*** Other medical therapies. In Chatelain C, Denis L, Foo KT, Khoury S, McConnell J eds. *Proceedings of the 5th International Consultation on Benign Prostatic Hyperplasia*, Plymouth: UK Plymbride Distributors, 2001: 479–511
60 **Boyle P, Robertson C, Lowe F, Roehrborn C.** Meta-analysis of clinical trials of permixon in the treatment of symptomatic benign prostatic hyperplasia. *Urology* 2000; **55**: 533–9
61 **Boyle P, Robertson C, Lowe F, Roehrborn C.** Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. *BJU Int* 2004; **93**: 751–6
62 **Bent S, Kane C, Shinohara K *et al.*** Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006; **354**: 557–66
63 **Speakman M.** Efficacy and safety of Tamsulosin OCAS. *BJU Int* 2006; **98** (Suppl. 2): 13–7
64 **Johnson TM 2nd, Jones K, Williford WO, Kutner MH, Issa MM, Lepor H.** Changes in nocturia from medical treatment of benign prostatic

hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial. *J Urol* 2003; **170**: 145–8

65 **Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R.** Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 2006; **67**: 275–80

66 **Zinner N, Gittelman M, Harris R, Susset J, Kanelos A, Auerbach S.** Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol* 2004; **171**: 2311–5

67 **Chapple CR, Martinez-Garcia R, Selvaggi L, Toozs-Hobson P, Warnack W, Drogendiji T, Wright DM, Bolodeoku J.** A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005; **48**: 464–70

68 **Nitti VW, Dmochowski R, Sand PK, Forst H-T, Haag-Molkenteller C, Massow U, Wang J, Brodsky M, Bavendam T.** Efficacy and tolerability of fesoterodine for overactive bladder syndrome. *J Urol* 2007; **178**: 2488–94

69 **Herschorn S, Swift S, Guan Z, Carlsson M, Morrow JD, Brodsky M, Gong J.** Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: A head-to-head placebo controlled trial. *BJU Int* 2010; **105**: 58–66

70 **Dmochowski RR, Peters KM, Morrow JD, Guan Z, Gong J, Sun F, Siami P, Staskin DR.** Randomized, double-blind, placebo controlled trial of flexible-dose fesoterodine in subjects with overactive bladder. *Urology* 2010; **75**: 62–8

71 **Nitti VW, Dmochowski R, Appell RA, Wang JT, Bavendam T, Guan Z.** Efficacy and tolerability of tolterodine extended-release in continent patients with overactive bladder and nocturia. *BJU Int* 2006; **97**: 1262–6

72 **Pedersen PA, Johansen PB.** Prophylactic treatment of adult nocturia with bumetanide. *Br J Urol* 1988; **62**: 145–7

73 **Reynard JM, Cannon A, Yang Q, Abrams P.** A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. *Br J Urol* 1998; **81**: 215–8

74 **The Committee for Establishment of the Clinical Guidelines for Nocturia of the Neurogenic Bladder Society.** Clinical guidelines for nocturia. *Int J Urol* 2010; **17**: 397–409

75 **Abrams P, Mattiasson A, Van Kerrebroeck P, Robertson G.** Nocturnal polyuria is a key factor in nocturia. *Neurourol Urodyn* 2004; **23**: 466–7

76 **van Kerrebroeck P, Rezapour M, Cortesse A, Thuroff J, Riis A, Norgaard JP.** Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. *Eur Urol* 2007; **52**: 221–9

77 **Andersson K, Chapple C, Cardozo L, Cruz F, Hashim H, Michel M.** Pharmacological treatment of urinary incontinence. *Continence*, Paris: Health Publications Ltd, 2009: 631–99

78 **Rittig S, Jensen AR, Jensen KT, Pedersen EB.** Effect of food intake on the pharmacokinetics and antidiuretic activity of oral desmopressin (DDAVP) in hydrated normal subjects. *Clin Endocrinol (Oxf)* 1998; **48**: 235–41

79 **Vande Walle JG, Bogaert GA, Mattsson S *et al.*** A new fast-melting oral formulation of desmopressin: a pharmacodynamic study in children with primary nocturnal enuresis. *BJU Int* 2006; **97**: 603–9

80 **Mattiasson A, Abrams P, Van Kerrebroeck P, Walter S, Weiss J.** Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int* 2002; **89**: 855–62

81 **Lose G, Lalos O, Freeman RM, van Kerrebroeck P, Nocturia Study Group .** Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am J Obstet Gynecol* 2003; **189**: 1106–13

82 **Lose G, Mattiasson A, Walter S *et al.*** Clinical experiences with desmopressin for long-term treatment of nocturia. *J Urol* 2004; **172**: 1021–5

83 **McConnell JD, Roehrborn CG, Bautista OM *et al.*** The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; **349**: 2387–98

84 **Roehrborn CG, Siami P, Barkin J *et al.*** The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol* 2008; **179**: 616–21

85 **Kaplan SA, Roehrborn CG, Dmochowski R, Rovner ES, Wang JT, Guan Z.** Tolterodine extended release improves overactive bladder symptoms in men with overactive bladder and nocturia. *Urology* 2006; **68**: 328–32

86 **Homma Y, Yamaguchi T, Kondo Y, Horie S, Takahashi S, Kitamura T.** Significance of nocturia in the International Prostate Symptom Score for benign prostatic hyperplasia. *J Urol* 2002; **167**: 172–6

87 **van Dijk MM, Wijkstra H, Debruyne FM, de la Rosette JJ, Michel MC.** The role of nocturia in the quality of life of men with lower urinary tract symptoms. *BJU Int* 2010; **105**: 1141–6

88 **Seki N, Yunoki T, Tomoda T, Takei M, Yamaguchi A, Naito S.** Association among the symptoms, quality of life and urodynamic parameters in patients with improved lower urinary tract symptoms following a transurethral resection of the prostate. *Neurourol Urodyn* 2008; **27**: 222–5

89 **Seki N, Yuki K, Takei M, Yamaguchi A, Naito S.** Analysis of the prognostic factors for overactive bladder symptoms following surgical treatment in patients with benign prostatic obstruction. *Neurourol Urodyn* 2009; **28**: 197–201

90 **Antunes AA, Srougi M, Coelho RF, Leite KR, Freire Gde C.** Transurethral resection of the prostate for the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia: how much should be resected? *Int Braz J Urol* 2009; **35**: 683–91

91 **Margel D, Lifshitz D, Brown N, Lask D, Livne PM, Tal R.** Predictors of nocturia quality of life before and shortly after prostatectomy. *Urology* 2007; **70**: 493–7

92 **Yoshimura K, Ohara H, Ichioka K *et al.*** Nocturia and benign prostatic hyperplasia. *Urology* 2003; **61**: 786–90

93 **Schatzl G, Madersbacher S, Lang T, Marberger M.** The early postoperative morbidity of transurethral resection of the prostate and of 4 minimally invasive treatment alternatives. *J Urol* 1997; **158**: 105–11

94 **Stanley N.** The physiology of sleep and the impact of ageing. *Eur Urol Suppl* 2005; **3**: 17–23

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Abbreviations: **HRQL**, health-related quality of life; **NERI**, the New England Research Institutes; **BU CME**, Boston University School of Medicine Department of Continuing Medical Education; **BACH**, Boston Area Community Health (study); **AVP**, arginine vasopressin; **OR**, odds ratio; **NP**, nocturnal polyuria; **OAB**, overactive bladder; **BPO**, benign prostatic obstruction; **FVC**, frequency-volume chart; **DO**, detrusor overactivity; **Q_{max}**, maximum urinary flow rates; **OCAS**, oral-controlled absorption system; **5ARI**, 5α-reductase inhibitor; **SWS**, slow-wave sleep; **TUMT**, transurethral microwave thermotherapy.