

# The New England Research Institutes, Inc. (NERI) Nocturia Advisory Conference 2012: focus on outcomes of therapy

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## What's known on the subject? and What does the study add?

A consensus statement published in 2011 summarised current research, clinical approaches, and treatment options for nocturia. Since that time, new research has refined our understanding of nocturia in clinically important ways and new evidence has been presented on the efficacy and outcomes of several treatment methods for this underreported, infrequently recognised, and undertreated problem in adults. This paper provides updated guidance to clinicians in light of recent advances in the field.

## Keywords

nocturia, nocturnal polyuria, consensus, incontinence, polyuria, outcomes

## Introduction

Nocturia, awaking to void urine, is a common and sometimes bothersome symptom that may impose detrimental impacts on sleep-quality, mood, and overall health [1]. The multi-factorial aetiology of nocturia, coupled with the recent demonstration that this symptom is highly variable over time and often resolves spontaneously [2], makes nocturia a challenging clinical entity. Although nocturia may have little health impact for some, for others it can be a highly bothersome, debilitating condition. Multiple studies have shown an association between nocturia and disturbed sleep, reduced well-being, and increased morbidity [3–5].

A consensus statement published in 2011 provided guidance to clinicians who are confronted with the wide range of clinical presentations of nocturia [1]. That paper focused primarily on a description of nocturia, its

prevalence, its impact on health-related quality of life (QOL) and overall health, and an overview of available treatment options. The present paper extends and elaborates on the previous paper by examining the most recent research on diagnostic and treatment outcomes. Numerous papers have been published in the 2 years since the previous conference was organised, and the field, as a whole, has a large and dynamic research agenda. This paper summarises the findings resulting from a 2012 conference of key thought leaders in the field of nocturia who focused on updating outcome studies published since the previous conference was held.

## Methods

In June, 2012, 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

### In Brief: Key Conclusions of the 2012 Conference

- Questionnaires, e.g. such as the IPSS do not adequately estimate nocturia in most patients, hence frequency-volume charts (FVCs) should be a required part of any assessment of nocturia.
- Nocturia may have a positive association to mortality, although studies on this topic are contradictory.
- The observed detrimental effects of nocturia on QOL follow a dose-response pattern (i.e. the more frequent the nocturia, the more severe the impact on QOL).
- Voiding  $\geq 2$  times nightly appears to be the threshold value of nocturia at which nocturia has adverse effects on QOL and well-being.
- There is a causative relationship between sleep disordered breathing, primarily obstructive sleep apnoea, and nocturia.
- Nocturia is associated with an increased prevalence of depression, especially in younger men and women.
- The evidence base for determinations of the efficacy of various treatments for nocturia is weak.
- Multi-component behavioural interventions may be attractive for a multifactorial condition such as nocturia despite the limited evidence base currently available.
- Some primary benign prostatic enlargement (BPE) therapies, e.g. TURP, may reduce nocturia, especially where obstruction is its main pathophysiology. TURP is reasonably effective in this instance, while the benefit of  $\alpha$ -blockers is less compelling.
- Antimuscarinics as stand-alone therapy are rarely more effective than placebo for reducing nocturia, although they may be useful for treating overactive bladder (OAB), or as a component of multi-modality therapy where the urgency component is severe enough to be contributory.
- Antidiuretic therapy appears to be effective in patients with nocturnal polyuria (NP), but safety concerns about hyponatraemia suggest the need for careful monitoring.
- Women appear to have an increased sensitivity to desmopressin and a lower therapeutic dose may, therefore, achieve a clinical effect similar to that obtained with a higher dose in men and with a safer therapeutic index.

conference was to update and expand upon the conclusions of a consensus conference on nocturia held in May, 2010. The 2012 conference focused on aspects of nocturia that have changed since the previous conference, principally in details of the management of nocturia. The goal was to summarise outcome data on the assessment and treatment of nocturia and to publish the findings for the benefit of primary care providers, urologists, and other health professionals who may treat patients with nocturia.

In all, 11 panellists were selected based on their 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, primary care, and sleep physiology. Full attendance at the conference was required.

The 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 to 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 organisers 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. The panellists reviewed all key clinical studies relevant to each area. After the conference, a summary of findings from the conference was provided to all panel members for review and approval, and these findings provided the basis for this paper.

## Results

### Defining Nocturia and NP

The ICS in 2002 defined nocturia as 'waking at night to void' [6] ('Night' was defined as the period of time between going to bed with the intention of sleeping and waking with the intention of arising regardless of when this period of time occurs). The ICS definition did not include any measure or assessment of bother, nor did it differentiate between awakenings due to a sensation of the necessity to urinate from awakenings for other reasons.

Later authors have attempted to narrow the definition of nocturia to make the term more clinically meaningful. For example, evidence suggests that most people with <2 voids/night generally have only minimal bother from the condition, although some people may be bothered by lower levels of nocturia if they have difficulty falling back to sleep [7]. When  $\geq 2$  voids/night occur on a regular basis, nocturia is likely to be associated with more serious consequences for the patient [7]. In addition, as some panellists noted, the *cause* of waking is an important clinical distinction. Waking at night because of a perceived need to urinate is far more diagnostically relevant to urological interventions than urinating at night after awakening from some other cause, although it may be difficult to make this distinction.

Regardless of its frequency or cause, nocturia results from a production of nocturnal urine that exceeds the capacity of the urinary bladder to comfortably store it. As such, an important part of diagnosis is determining if a patient is experiencing NP, a greater-than-normal production of urine during sleep. However, the definition of NP and the estimates of 'normal' nocturnal urine production, do not rest on strong evidence. In the course of the NERI conference, Blanker presented the results of his research into the definitions of NP. A PubMed search yielded 58 studies including 16 different definitions of NP, with highly diverse methods of determining or justifying those definitions. Even the most widely-accepted definition of NP, from the 2002 ICS panel, was found to be lacking in scientific rigour. The ICS defined NP as 'production of an abnormally large volume of urine during sleep' with 'normal' urine production varying considerably from person to person and normally increasing with age [6]. NP was thus defined as an output of >20% of the daily total urine production in 'the young' and 33% of daily total urine production in 'the elderly' with the value for 'middle age' falling somewhere between these two extremes [6]. However, these estimates are based on very small sample sizes, 18 subjects in the study of 'young adult' NP [8] and 45 subjects in the study of 'elderly' NP [9]. Applying the ICS definition in the general population showed that the prevalence of NP was high, both in men with nocturia (92%) and those without nocturia (70%). This is consistent with the findings of Swithinbank et al. [10], showing that only a minority of women with NP have nocturia.

An alternative definition of NP was used in the Blanker et al. [11] of 1688 community-dwelling men: nocturnal urine production of  $\geq 90$  mL/h regardless of a patient's age or condition. Using this definition, Van Doorn et al. [2] estimated that 28% of the men with nocturia had NP, compared with 8% of those without nocturia. Based on these figures, Blanker estimated that the proportion of nocturia that is related to the exposure to NP (attributable

proportion) was  $\approx 54\%$ , and the proportion of nocturia in the population that might be attributable to NP (population attributable proportion) was 15%. The degree to which nocturia is related to NP, therefore, depends on which definition of NP is used.

After a robust discussion of these issues, panellists at the NERI conference concluded that the original, broad definition of nocturia by the ICS 2002 sub-committee retains utility. Based on the fact that nocturia, by definition, results when nocturnal urine production exceeds bladder capacity, reducing nocturnal urine production in some manner must be considered for effective therapy. One might conclude from this argument that a specific definition of 'abnormal' nocturnal urine production is not necessary. Considering the weaknesses noted in the evidence base used to define NP in the ICS 2002 guidelines, the NERI panellists agreed that more research is required to determine appropriate population-based norms for NP, as well as for the setting of thresholds for the number of night-time awakenings that could reliably guide decisions about which patients might benefit from lifestyle and/or medical interventions.

### Evaluation of Nocturia Outcome Instruments

There is currently no simple, validated self-report questionnaire or diary measure that allows a practitioner to determine all of the following important parameters of nocturia:

- Number of nocturnal voids
- How many nights per week nocturia occurs
- Whether nocturia frequency varies over time
- Why patients perceive that they awakened
- Why patients voided
- How much sleep occurred
- Whether patients fell back asleep
- The degree to which patients are bothered by symptoms
- Whether (and in what way) nocturia symptoms impact the patient's quality or quantity of sleep and QOL

Several available questionnaires capture some, but not all, of the outcomes of interest in the study of nocturia, and all questionnaires suffer from the potential limitation of recall bias or other difficulties (Table 1). For example, a frequently-reported outcome measure of nocturia symptoms is question 7 on IPSS: '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?'. This question is flawed as an outcome measure in several ways: it asks patients to mentally average nightly voids over the span of a month; the question is often misunderstood; and the question fails to exclude (or define) the first morning void.

**Table 1** Outcomes assessed by questionnaires pertaining to nocturia.

Questionnaire	Efficacy	Bother	QOL
AUA Symptom Index (AUASI/IPSS)	✓		✓
Nocturia, Nocturnal Enuresis and Sleep – interruption Questionnaire (NNES-Q)	✓	✓	
International Consultation on Incontinence Modular Questionnaire-Female LUTS (ICIQ-FLUTS)*	✓		✓
International Consultation on Incontinence Modular Questionnaire-Male LUTS (ICIQ-MLUTS)	✓		✓
ICS Male Questionnaire	✓	✓	✓
Danish Prostate Symptom Score (Dan – PSS – 1)	✓	✓	✓
Urgency, Weak Stream, Incomplete Emptying and Nocturia (UWIN)	✓	✓	
Urogenital Distress Inventory (UDI)	✓	✓	
Nocturia Quality of Life Questionnaire (N-QOL)			✓
International Consultation on Incontinence Modular Questionnaire –Nocturia Quality of Life (ICIQ – NQOL)		✓	✓
Leicester Impact Scale			✓
International Prostate Symptom Score Quality of Life Index (IPSS – QOL)			✓

\*Previously known as Bristol Female LUTS.

The FVC requires patients to record the volume and timing of daytime and night-time voids for periods ranging from 1 to 7 days using a calibrated measuring device and a paper 'diary'. Although valuable and recommended as a key component of nocturia assessment, FVCs are insufficient (at least as presently configured) to capture the level of detail and qualitative dimensions about nocturia that are needed for accurate differential diagnosis of this often complex condition. The panel concurred that bladder diaries, which can annotate an FVC, are more relevant for both research and clinical assessments.

Most short-term bladder diaries (as distinct from FVCs in which actual volumes are measured) have not been shown to produce reliable data on the number of nocturnal voids (Table 2) [12–16]. Seven-day bladder diaries have acceptable reliability for the number of nocturia episodes, but such diaries are relatively labour-intensive and, hence, often suffer from poor compliance on the part of patients [14]. In fact, variation in nocturia severity from night to night may simply reflect fluctuation of nocturnal frequency during the registration period rather than unreliability of the diary instrument. Nonetheless, bladder diaries can provide valuable data and may offer the potential advantages of helping to distinguish urgency from non-urgency voids, convenience voids from insomnia voids, and nocturia from other LUTS.

**Table 2** Reliability of bladder diaries.

Diary	1-day	2-day	3-day	4-day	7-day
Groutz et al.* [12]	<0.6	<0.6	0.69		NA
Brown et al. <sup>†</sup> [13]			0.7	0.79	0.81
Wyman et al. <sup>‡</sup> [14]					0.86
Nygaard et al. <sup>‡</sup> [15]			0.887 <sup>§</sup>	0.887 <sup>§</sup>	0.906
Bright et al. [16]	[Phase I study – no reliability data available]				

\*Study uses Concordance Correlation Coefficient (acceptable reliability is >0.7);  
<sup>†</sup>Study uses Intraclass Correlation Coefficient (acceptable reliability is >0.75);  
<sup>‡</sup>Study uses Pearson's correlation coefficient; <sup>§</sup>Indicates the correlation of the first 3 days of the 7-day diary to the last 4 days of the diary.

An ideal assessment tool (or set of tools) would capture the following outcomes:

1. Primary efficacy outcome
  - Number of night-time voids
2. Secondary efficacy outcomes
  - Proportion of nights affected
  - Nocturnal urine volume
  - Maximum nocturnal voided volume
  - Why the patient was awakened
  - Patient's perception of why he or she voided
  - Whether the patient fell back asleep
3. Bother
4. QOL issues

Panellists agreed on the need to create assessment measures that fulfil these demands, and that this will probably involve combining data from an FVC with data from a thorough and well-validated questionnaire and/or bladder diary. Preliminary work to create a validated 'urinary diary' was recently reported by Bright et al. [16]

### Outcomes of Epidemiology

Although nocturia has been thought to affect males predominantly (because of an assumed relation with prostate disorders), current evidence shows that nocturia affects many adults of both genders and in all age ranges [17]. The prevalence of nocturia (defined as  $\geq 2$  voids/night) clearly increases with age, although it also manifests in younger people. In a recent review, Bosch and Weiss (2010) [16] found the following prevalence ranges (data were not available for patients aged 40–70 years):

- 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%

Several studies have found a higher prevalence of nocturia in both male and female African-Americans [18,19]. This may be due to a higher prevalence among

African-Americans of conditions associated with nocturia (i.e. diabetes mellitus, hypertension, sleep apnoea, and cardiovascular disease), or the influence of sickle-cell trait (which may cause renal concentration deficits).

Nocturia is associated with some significant comorbid conditions. Chief among these are insomnia and poor self-reported sleep quality [20]. In one study, nocturia was listed as a self-perceived cause of poor sleep four-times more frequently than the next most-cited cause: pain [21]. Poor sleep and daytime sleepiness have been associated with the number of nocturia episodes overall, and also with nocturia episodes after which a person has difficulty getting back to sleep [22]. It is worth noting that chronically impaired sleep is not just bothersome; it is, in fact, associated with increased mortality [23,24].

The fear of falling experienced by many older persons with nocturia is well-founded: most night-time falls are associated with toilet visits [25]. Nocturia increases the risk of an incident fall by 25% over 3 years [26]. 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 [21]. Significantly, nocturia is associated with injurious falls, and higher nocturia frequency is associated with greater risk. The OR for a hip fracture is 1.36 in older men having  $\geq 2$  voids/night, and 1.80 having  $\geq 3$  voids/night, compared with men without nocturia episodes [27]. In the latter group, the absolute risk of hip fracture was 1%.

### Outcomes of Evaluation

The multifactorial nature of nocturia has several implications for its evaluation and management. The usual practice of history-taking and clinical examination must be conducted with a consideration of the full range of potential psychological, socio-economic, and cultural dimensions of the condition. In addition to the many physical problems that may be related to nocturia (i.e. OAB, BPE, congestive heart failure [CHF], and many others), nocturia may also plausibly be affected by a range of factors, e.g. sleep disorders, arousal disorders, neurological conditions, psychiatric conditions, chronic pain disorders, the use of other medications (e.g. diuretics), use of herbal or alternative medicine therapies; use of alcohol, caffeine or other substances; or conditions in the home that interrupt sleep.

Various attempts have been made to capture in algorithm form this wide range of possible causes as well as the range of possible outcomes an evaluation for nocturia might produce. The participants in the NERI conference, after reviewing several existing algorithms, agreed that the management algorithm developed by Weiss [28], and modified to include some specific values arising from the

administration of an FVC (or bladder diary containing information for voided volumes throughout the day/night cycle), is the most clinically useful of the currently available algorithms (Fig. 1).

As discussed earlier, FVCs and bladder diaries are recommended because data obtained from subjective questionnaires, e.g. the IPSS, have been shown to overestimate nocturia in most patients [29–31]. The voiding patterns revealed by FVC and bladder diary data provide critical guidance for clinicians about the cause and treatment of nocturia, as can be seen in the four fundamental FVC outcomes shown in Fig. 1. Based upon analysis of the FVC/diary data, a patient presenting with nocturia may have [32]:

1. **Low global bladder capacity** (indicated by a maximum voided volume of  $\leq 200$  mL) or **low nocturnal bladder capacity** (indicated by a nocturnal bladder capacity of  $\leq 200$  mL or a nocturnal bladder capacity index of  $\geq 2$ ).
2. **NP** (indicated by a NP index of  $>33\%$ , adjusted for age).
3. **Polyuria** (indicated by a 24-h urine volume of  $>40$  mL/kg body weight, i.e. 2800 mL for a 70 kg male).
4. **Mixed aetiology** (any combination of 1, 2, or 3 above)

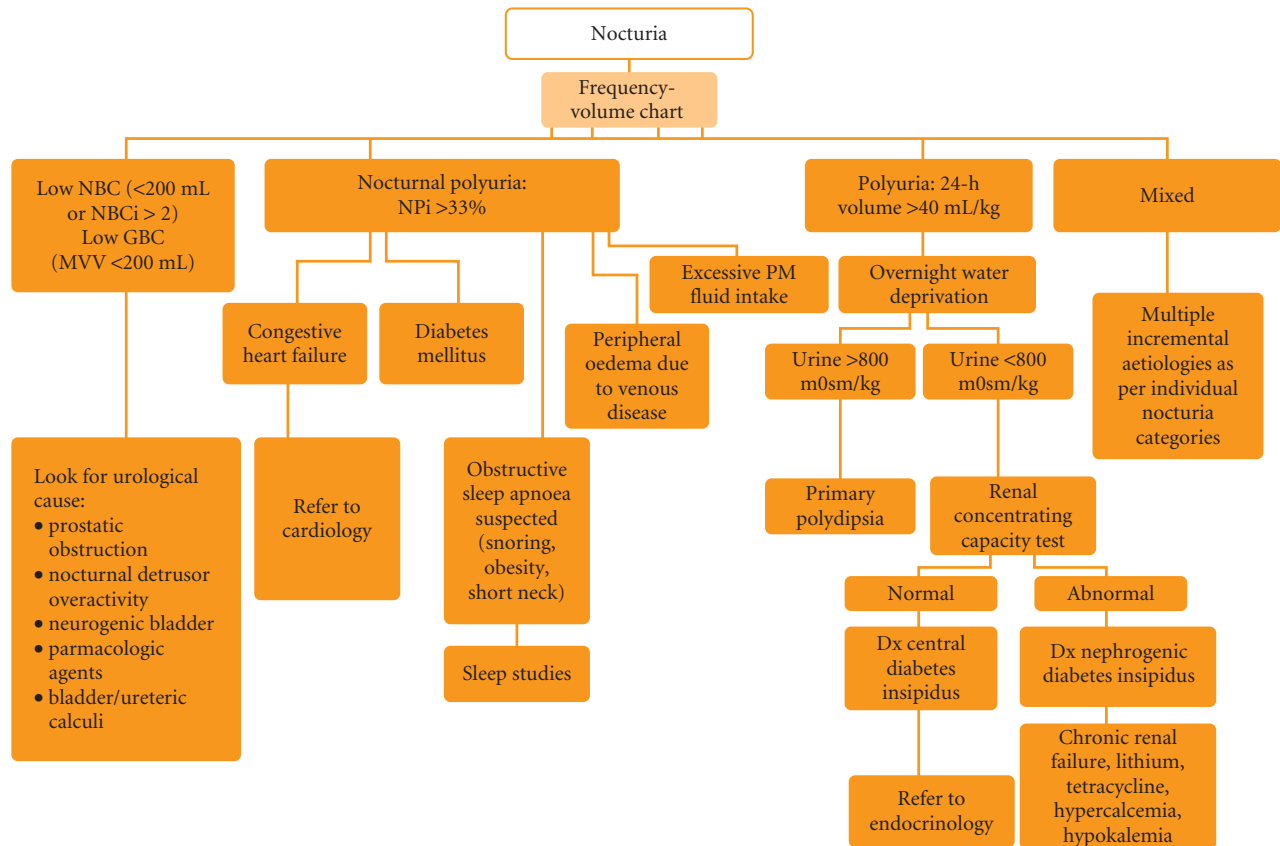
Each of these potential initial diagnoses will lead a clinician to further choices of diagnosis and treatment, as summarised in the algorithm. The critical point to consider is that the multifactorial nature of nocturia means that ‘mixed aetiology’ may account for the bulk of patient diagnoses, which suggests that, for many patients, treatment may involve multiple, incremental, therapeutic interventions on all levels of a patient’s life to obtain clinically meaningful improvements in nocturia symptoms [33].

### Medications Contributing to Nocturia/Polyuria

An important contributing factor to nocturia is the effect of concurrent medication use on urine production, bladder storage capacity, or both. In the USA,  $>40\%$  of men aged  $\geq 65$  years, and 57% of women aged  $\geq 65$  years reported taking five or more medications in a given week [34]. Such polypharmacy greatly complicates the diagnosis and treatment of nocturia and must be considered at every step in the continuum of patient care.

Renal homeostasis is complex, with reabsorption of water and the resulting concentration of urine controlled by arginine vasopressin (AVP, otherwise known as antidiuretic hormone), which is released by the posterior pituitary gland whenever water deprivation causes an increased plasma osmolality or whenever the cardiovascular system is challenged by hypovolaemia and/or hypotension. AVP increases the water permeability of the cell membrane in the distal nephron, thus permitting water to move passively

**Fig. 1** Algorithm for the evaluation of nocturia. NBC, nocturnal bladder capacity; NBCi, nocturnal bladder capacity index; NPi, nocturnal polyuria index; MVV, maximum voided volume; mOsm/kg, osmolality.



Abbreviations: NBC = nocturnal bladder capacity; NBCi = nocturnal bladder capacity index; NPi = nocturnal polyuria index; MVV = maximum voided volume; mOsm/kg = osmolality

down an osmotic gradient across the collecting duct into the extracellular compartment (e.g. circulation). Many classes of medications affect this system in ways that may manifest as polyuria, NP, or bladder storage dysfunctions (Tables 3 and 4).

Broadly speaking, medications can cause polyuria in the following ways:

- Increasing water or liquid intake (polydipsia; compensation for dry mouth)
- Interfering in renal ability to concentrate urine:
  - Diabetes insipidus (central or nephrogenic)
  - Solute diuresis impairment of sodium reabsorption
  - Carbonic anhydrase inhibition
  - Impaired generation of the interstitial osmotic gradient
- Causing peripheral oedema

Clearly, multiple medications or medication classes may contribute to nocturia, primarily by inducing polyuria.

**Table 3** Medications potentially associated with polyuria/nocturia.

Category	Medications
Polydipsia	Phenothiazines Anticholinergics
Central diabetes insipidus	Ethanol Phenytoin (e.g. Dilantin®) Low doses of morphine Glucocorticoids Fluphenazine (e.g. Prolixin®) Haloperidol (e.g. Haldol®) Atypical antipsychotics (e.g. risperidone) Promethazine (e.g. Sominex®) Oxilorphan Butorphanol
Nephrogenic diabetes insipidus	Lithium Demeclocycline (e.g. Declomycin®) Cisplatin (e.g. Platin®) Amphotericin B (e.g. Fungizone®) Foscarnet (e.g. Foscavir®) Ifosfamide (e.g. Ifex®) Clozapine (e.g. Clozaril®)

**Table 4** Medications known to exacerbate nocturia or polyuria and their mechanisms of action.

Medications	Mechanism of Action
Calcium channel blockers	Direct blocking of proximal tubular sodium reabsorption or increased atrial natriuretic peptide levels; promote peripheral oedema and/or pedal oedema
Conivaptan; tolvaptan	V <sub>2</sub> -receptor antagonism
Carbonic anhydrase inhibitors	Reduced sodium and bicarbonate reabsorption in proximal tubule
Excessive vitamins A and D; thiazides	Tubulointerstitial injury secondary to deposition of calcium in the medulla with subsequent renal concentrating defects
NSAIDs; thiazolidinedione anti-diabetic agents, GABAergic agents	Promote peripheral oedema and/or dependant oedema

Source: Weiss JP et al. 2012 [93].

Further research is needed to better characterise the effect sizes of these medications in relation to nocturia and to determine dosage levels that may allow such medications to be used effectively in patients bothered by nocturia.

### Outcomes Related to Nocturia and OAB

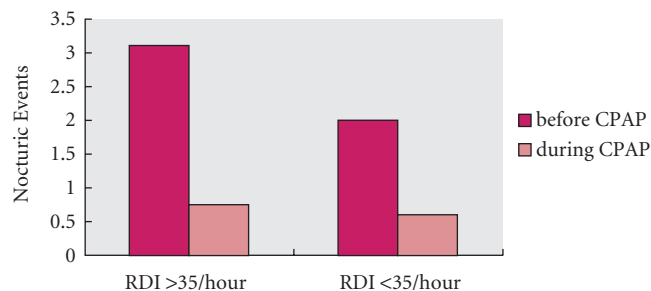
OAB and nocturia are clearly associated, although the relationship is not reciprocal: most patients with nocturia do not have OAB, while many patients with OAB *do* have nocturia [35]. In addition, OAB probably plays a relatively minor role in the genesis of nocturnal voids [36,37]. For these reasons, antimuscarinics, which reduce night-time voids due to urgency, do not appear to be efficacious for most cases of nocturia, although they may be effective for urgency-related nocturnal voids (fuller discussion later in this paper).

### Outcomes Related to Nocturia and Sleep Apnoea

The relationship between nocturia and sleep-disordered breathing, primarily obstructive sleep apnoea (OSA), has become increasingly apparent in recent years. The causal connections between these two conditions are compelling. Community-based elderly populations who have higher levels of sleep-disordered breathing (in excess of 25 breathing events/h) have nearly double the number of nocturia episodes as individuals with low rates of OSA [38]. In addition, nocturia confers an ≈30% increased risk for OSA, even after controlling for age, body mass index (BMI), diuretic use, diabetes, and use of  $\alpha$ -blockers [39].

Reduced total sleep time, in turn, correlates with a range of detrimental effects including increased daytime fatigue, decreased daytime alertness, increased risk for falls, depressed mood, cognitive impairment, and decreased QOL, outcomes that are particularly salient for older adults.

**Fig. 2** Comparison of outcomes of 50 patients with mild-moderate OSA (Respiratory Disturbance Index [RDI] < 35/h) and 47 patients with severe OSA (RDI > 35/h). Source: Margel et al. 2006 [45].



In addition, a 2012 study involving 6342 older subjects found a clear positive association between nocturia (and degree of OSA) and cardiovascular mortality, even after adjustment for known confounders such as age, BMI, diuretic use, diabetes mellitus, and  $\alpha$ -blocker use [39]. Myriad mechanisms may underlie the relationship between OSA and cardiovascular risk.

In patients with nocturia, OSA should be considered if there is NP, report of sleep disturbance, snoring or apnoea (including report by bed partner), daytime somnolence, hypertension, or morning headache. If apnoea is suspected, it should become the priority for diagnosis and treatment. Diagnosis of OSA cannot be made solely based on reported snoring or fatigue. The American Academy of Sleep Medicine guidelines recommend that the diagnosis of OSA be based on clinical signs and symptoms determined during a comprehensive sleep evaluation, which includes a sleep-oriented history and physical examination, and findings identified by sleep testing [40].

Nocturia episodes in individuals with OSA may be at least partially ameliorated by use of one of three primary treatment options:

- Positive airway pressure (PAP)
- Oral appliance therapy
- Surgery

Of these options, continuous PAP (CPAP) is widely accepted to be the most effective [40]. Several intervention studies have found that treatment with CPAP decreases nocturia [41–43]. A 2012 study of 98 men with moderate to severe OSA found that treatment with CPAP reduced the percentage of men reporting nocturia from 38% to 24% after 6 months [44]. These results support earlier work by Margel et al. [45], the results of which are summarised in Fig. 2. Treatment of other primary sleep disorders (e.g. restless legs syndrome) might also be expected to ameliorate nocturia episodes if the disorder is the primary cause of awakening, but this remains untested to date.

## Response to Nocturia Therapy: Outcomes Related to QOL

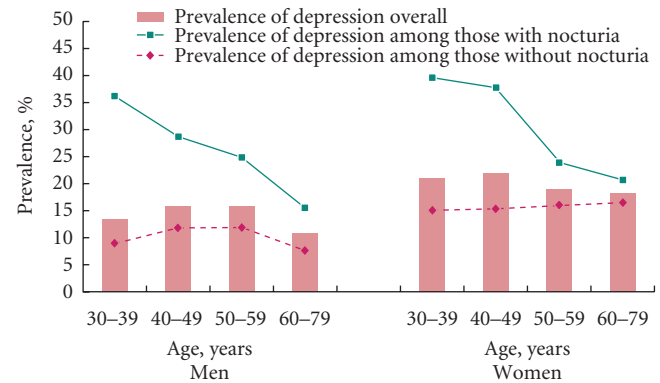
Although infrequent episodes of nocturia may not be bothersome for some people, studies to date have shown that more frequent nocturia can be associated with distress, discomfort, loss of sleep and significant functional impairment, all of which may erode one's overall QOL. Among men who complain of urinary tract symptoms, nocturia is reported to be the 'most bothersome' of such symptoms [46]. Affected persons describe their nocturia as 'debilitating, frustrating, distressing, and puzzling,' particularly in its perceived unpredictability [7]. Older persons experience a diminished self-image, feel prematurely 'old', and worry about nocturia causing night-time falls [47]. However, significantly some studies show that the impact on QOL from nocturia-related sleep fragmentation is more pronounced in younger compared with older patients, perhaps due to the effects of impaired productivity in younger persons [48,49].

Studies of the relationship between nocturia and various aspects of QOL have benefited from the existence of a validated instrument, the Nocturia Quality of Life questionnaire (N-QOL), which has been shown to provide good sensitivity in its ability to discriminate between subjects with different degrees of nocturia severity [50]. However, until recently data have been inconsistent about the frequency of nocturnal voiding as it affects QOL and bother. Studies have reported adverse effects from voiding frequencies of 1, 2, or >2 voids /night (although, as previously noted, mild nocturia may not be bothersome at all for many patients) [7,51].

The Boston Area Community Health survey (BACH) of a random sample of 5503 Boston-area residents has now shed valuable light on several key aspects of nocturia and QOL, specifically, the association between nocturia on QOL and symptom bother, the association of nocturia with depression, and whether the association of number of nightly voids with QOL and depression follows a severity-response pattern [52]. BACH confirmed the previously observed association between nocturia and significant decreases in health-related QOL in both sexes [52]. But BACH has also extended existing knowledge in several directions. It showed that nocturia is associated with increased symptom bother and an increased prevalence of depression, especially in younger men and women (Fig. 3) [52].

Most significantly from a clinical standpoint, the BACH results showed that the observed detrimental effects of nocturia on QOL followed a severity-response pattern (i.e. the more severe the nocturia, the more pronounced the impact on QOL) and that voiding  $\geq 2$  voids/night was the threshold value of nocturia beyond with the disorder had

**Fig. 3.** Nocturia and increased risk for depression. Source: Kupelian et al. 2012 [52].



adverse effects on QOL and well-being [52]. Although causality cannot be drawn from cross-sectional data such as these, the consistency and magnitude of the observed associations warrant clinical attention.

Complementing these findings are results from Weiss et al. (2012) [53] showing improvements in QOL scores related to bother, quality of sleep, and energy levels among patients whose nocturia was treated pharmacologically. In this study of 757 patients with nocturia, one less nocturnal void per night was associated with an increase of 4.68 in the total N-QOL score (raw QOL scores ranged from 0 to 4 and were then transformed into a standardised score out of 100). Similarly, a 1-h increase in the first period of undisturbed sleep was associated with an increase of 3.68 in total N-QOL score for bother/concern, and an increase of 3.27 for sleep/energy. These changes, combined with the data previously described, lend support to the conclusion that reducing nocturia may increase a patient's overall QOL.

## Outcomes Associated with Management and Treatment

### Behavioural Interventions

Patients typically respond to nocturia by engaging in one or more of the following lifestyle or behavioural modifications, motivated perhaps by suggestions in the lay press, internet, physicians' offices, or conversation with friends [1]:

- Pre-emptive voiding.
- Dietary and fluid changes (avoidance of caffeinated beverages, alcohol, etc., especially in the evening).
- Medication timing (diuretics in the mid-afternoon).
- Evening leg elevation to mobilise fluids.
- Use of sleep medications.
- Use of protective undergarments.



Some men may also try herbal supplements, e.g. Saw Palmetto berry extract, in the belief that nocturia is due to prostate enlargement. In the USA, for example, between 50% and 90% of men have tried supplements before seeking medical treatment for their LUTS/BPE [54]. The studies conducted to date on such supplements; however, have either been methodologically flawed or have found no statistical or clinically significant benefits [55–58].

In recent years, efforts have been made to evaluate the efficacy of focused, multi-component behavioural or lifestyle interventions, either alone or combined with medical therapies. However, there have been surprisingly few such studies and those that have been conducted have been uncontrolled, impairing the ability to draw firm conclusions about treatment effects. A behavioural study of 24 patients with OAB, for example, found that reducing fluid intake by 25% resulted in a statistically, but not clinically, significant reduction in nocturia 'episodes' from a mean of 1.4 voids/night to 1.3 voids/night [59]. An attempt to get patients in this study to reduce their fluid intake by 50% did not meet its goal, patients were only able to reduce intake by a mean of 32%, which reduced nocturia episodes from 2.3 to 1.8 voids/night after 4 days.

A Japanese trial of a multi-component lifestyle modification regimen that included restriction of fluid intake, refraining from excess hours in bed, moderate daily exercise, and keeping warm in bed showed a reduction in mean nocturnal voids from 3.6 to 2.7 and a decrease in mean nocturnal urine volume from 923 to 768 mL after 4 weeks [60]. Of the 56 patients in the study, 53% showed an improvement of >1 void/night, with the intervention being more effective in patients with greater polyuria at baseline.

A more recent study of a multi-component lifestyle intervention for 82 patients with NP involved a 30-min patient education/behaviour modification programme, regulation of fluid intake, and regular meetings/discussions with a nurse-practitioner [61]. The authors reported that mean nocturnal voids decreased from 2.6 at baseline to 1.1 voids/night over the course of the study, interestingly with no statistically significant change in measures of nocturnal urine volume.

A 4-week uncontrolled study combining a multi-component behavioural intervention with targeted use of terazosin (an  $\alpha$ -adrenergic antagonist used for treatment of voiding LUTS) and the sedative/hypnotic zaleplon found that mean diary-recorded nocturia decreased from 2.6 to 1.9 and the bother score reduced from 3.1 to 1.1 voids/night [62]. The study authors deemed these results 'promising', although with the caveat that the study should be repeated with a randomised, controlled trial.

Burgio et al. [63] conducted a randomised controlled equivalence trial of 143 men with LUTS who had persistent urgency and >8 daily voids (despite a 4-week run-in period using an  $\alpha$ -adrenergic antagonist). Men were randomised to receive either 8 weeks of behavioural treatment (consisting of pelvic floor muscle exercises, urge suppression techniques, and delayed voiding) or treatment with an individually titrated extended-release antimuscarinic (oxybutynin, 5–30 mg/day). There were no statistically significant between-group differences in mean voids per day or self-reports of satisfaction or improvements in symptoms. The behavioural group had a mean reduction in nocturnal episodes of 0.70, which was statistically significantly greater than the mean reduction of 0.32 for those in the drug therapy group ( $P = 0.05$ ). The drug therapy group showed greater reductions in maximum urgency scores (mean reduction of 0.44 vs 0.12,  $P = 0.02$ ) as measured by the AUA Symptom Index.

Panellists concluded that multi-component interventions are an attractive approach to a multifactorial condition such as nocturia, despite the relative paucity of supporting data.

### Diuretic Treatment of Nocturia

Paradoxically, diuretics are associated with a greater risk of nocturia [64] even though they are sometimes used as pharmacotherapy for nocturia. At least part of the explanation lies in the fact that the indications for diuretic treatment (e.g. oedema, CHF, OSA) are independently associated with nocturia. In addition, diuretics are often prescribed for peripheral oedema with no particular attention to the time of day at which they would be most effective. This may cause or exacerbate nocturia in patients with NP owing to reabsorption of lower extremity fluid during recumbency. In such patients, diuretics should be administered during the mid-afternoon to address fluid accumulated over the course of the day, but not so late as to exacerbate NP [65,66].

After reviewing the few studies of diuretics as a treatment for nocturia, either alone or combined with other medications, panellists concluded that loop and thiazide diuretics may decrease nocturia episodes, with relatively greater decreases in NP. But the quality of existing studies is generally poor to moderate, the trials have been small and short term, many have not been 'blinded', and the effects of diuretic therapy for nocturia on renal function and electrolytes has not been assessed.

In addition, there is insufficient evidence on which to decide which patients might benefit most from diuretic therapy (although panellists acknowledged that this difficulty applies more broadly because of a lack, to date, of methods to sub-categorise patients with nocturia). Of

course, decreasing night-time urine volume will not likely have any effect for patients whose night-time voiding is out of convenience when awakened by something other than the need to void. These conclusions are consistent with the recommendations of the Committee for Establishment of the Clinical Guidelines for Nocturia of the Neurogenic Bladder Society, which ranked the evidence from existing nocturia studies involving azosemide, bumetanide, and furosemide (frusemide) as Level 2 with a Grade C recommendation [67].

### BPE Therapy and Nocturia

Because BPE is highly associated with nocturia, much attention has been devoted to exploring whether treatments for BPE may improve symptoms of nocturia. A range of treatments has been investigated in this regard, including:

- $\alpha$ -adrenergic antagonists.
- 5 $\alpha$ -reductase inhibitors (5ARIs).
- Combined  $\alpha$ -adrenergic antagonist and 5ARI therapy.
- Botulinum toxin.
- NSAIDs.
- Surgery.

The results from the most recent studies of each of these agents, in relation to nocturia, are summarised in Table 4.

Although much of the evidence reviewed above is limited by the use of nonspecific outcome measures for evaluating nocturia symptoms (e.g. IPSS or AUA-7), and methodological weaknesses (i.e. not 'blinded', uncontrolled), it does suggest that specific nocturia outcomes might be positively affected by some primary BPE therapies, primarily 5ARIs, botulinum toxin-A, and TURP. In contrast, and as summarised in Table 5 [68–79], available evidence suggests only modest efficacy for  $\alpha$ -adrenergic antagonists and NSAIDs. Continuing research in these areas will be improved only if more specific and validated nocturia outcome measures are incorporated into study methodologies.

### Antimuscarinics for Nocturia

As reviewed in detail in the 2011 consensus paper [1], antimuscarinic therapy has been repeatedly explored as a treatment approach for nocturia. As antimuscarinics exert no effect on NP, these agents may reduce nocturia symptoms by increasing bladder capacity, which may benefit patients whose awakenings are associated with urgency. The data summarised in the previous consensus paper support this expectation, with the significant caveat that even studies showing statistically significant improvements with an antimuscarinic in the sub-group of nocturia patients with OAB, may not, in fact, be demonstrating any *clinically* significant differences [80–84].

Results of recent studies do not support any change in these conclusions. Ginsberg et al. [85], for example, studied once-daily administration of trospium chloride (extended release, XR) against placebo for nocturnal and diurnal symptoms of OAB in two phase III trials. After 12 weeks, the group on trospium XR was found to have a statistically significantly greater mean reduction from baseline in nocturnal voids (–0.8 vs –0.6;  $P = 0.006$ ) and diurnal voids (–1.9 vs –1.4;  $P < 0.001$ ). Although this result was deemed enough to justify a conclusion that trospium XR 'significantly improved both nocturnal and diurnal OAB symptoms', the consensus panellists doubted that the reported reduction of 0.2 voids/night with the medication held any real clinical value.

The conclusion of the panel was that antimuscarinics as stand-alone therapy are minimally more effective than placebo for reducing nocturia, although they may be useful for treating OAB, or as a component of multi-modality therapy where the LUT problem is severe enough to be contributory, as in cases involving severe nocturnal OAB episodes.

### Antidiuretic Therapy for Nocturia

At present, the only antidiuretic therapy indicated specifically for nocturia is the synthetic analogue of AVP, desmopressin. 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 [86]. 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, thereby concentrating urine, decreasing urine production, and postponing the need to void.

Several randomised placebo-controlled trials have shown the efficacy of oral desmopressin in the treatment of adults with nocturia [86–88]. A series of 3-week, randomised, 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  $\geq 18$  years with nocturia. In these studies, clinical response was defined as  $\geq 50\%$  reduction in nocturnal voids from baseline. Regarding safety, hyponatraemia is a potentially serious adverse event associated with desmopressin use. In one study of 632 patients receiving desmopressin for nocturia, 31 (4.9%) had significant hyponatraemia, with risk rising with age and the presence of low serum sodium at baseline [89]. Initiation of desmopressin is therefore currently not indicated for patients aged  $\geq 65$  years. The mechanisms behind desmopressin-induced hyponatraemia have been extensively studied, and panellists concluded that serum sodium monitoring at baseline and early in treatment

**Table 5** Recent study results of selected BPE therapies related to nocturia.

Class	Study	Study design	N	Nocturia results
α blockers	Zhang et al. 2011 [68]	Prospective, randomised, open comparison of doxazosin gastrointestinal therapeutic system (GITS) 4 mg and tamsulosin 0.2 mg	189	Mean nocturia reduction doxazosin-GITS vs tamsulosin on FVC (1.7 vs 1.3 voids/night at week 4; 2.1 vs 1.7 voids/night at week 8, both $P = 0.001$ ), IPSS-question 7 (1.5 vs 1.1 at 4 weeks, $P = 0.001$ ; 2.0 vs 1.6 at 8 weeks, $P < 0.001$ ).
	Lojanapiwat et al, 2011 [69]	8-week, open-label study of oral tamsulosin for LUTS	51	Total IPSS significantly decreased from 19.52 to 6.08 ( $P < 0.001$ ). IPSS-QOL and N-QOL scores significantly improved at visit 3 through to the end of study. Significant nocturia and hours of undisturbed sleep improvement at last clinic visit.
	Yoshida et al. 2010 [70]	8-week study of tamsulosin in patients with nocturia associated with LUTS/BPE	160	97 patients 'responders' based on FVC data. In this group, nocturnal voiding frequency decreased from 3.1 to 1.7 voids/night ( $P < 0.001$ ); nocturnal urine volume decreased from 712.5 to 533.3 mL ( $P < 0.001$ ); and hours of undisturbed sleep increased from 2.1 to 3.5 h ( $P < 0.001$ ).
	Curran, 2011 [71]	Analysis of three 12-week randomised, double-blind trials of silodosin vs placebo (2 trials) or tamsulosin (1 trial)	1878 (sum of 3 trials)	Silodosin significantly more effective than placebo or tamsulosin in simultaneously improving nocturia, frequency and incomplete emptying.
5ARIs	Vallancien et al. 2008 [72]	3-year open-label efficacy and safety study of alfuzosin 10 mg/day in men with LUTS	689	Significant ( $P < 0.001$ ) improvements from baseline in nocturia (−0.8, −25.5%) and bother score (−1.7, −40.7%).
	Tacklind et al. 2010 [73]	Cochrane systematic review	NA	Doxazosin and terazosin significantly more likely than finasteride to improve peak urine flow and nocturia. No significant difference with tamsulosin.
Combined therapy	Yang et al. 2007 [74]	6-week randomised comparison study of terazosin 2 mg/day vs terazosin 2 mg/day and tolterodine 2 mg/twice daily	191	IPSS scores for urgency, frequency and nocturia significantly improved in both groups, although score reduction in the combined therapy group was significantly greater ( $P < 0.01$ ). Differences in peak urinary flow rate and residual urine from the baseline not significant between the two groups. Incidence of adverse effects higher in the combined therapy group.
	Kaplan et al. 2007 [75]	12-week pilot study of alfuzosin 10 mg/day, sildenafil 25 mg/day, or combination of both on LUTS and erectile dysfunction	62	IPSS score improvement significant in all three arms, greatest with combination (−24.1%) compared with alfuzosin (−15.6%) and sildenafil (−11.8%). Frequency of nocturia, post-void residual urine volume, and maximum urinary flow rate significantly improved with alfuzosin only and the combination.
Botulinum toxin-A injection	Madani et al. 2012 [76]	Open-label pilot study	10	Mean (SD) nocturia events decreased from 4.1 (0.87) to 2.4 (0.84) voids/night ( $P < 0.001$ ) after mean duration of follow-up of 7.5 months.
NSAIDs	Shin et al. 2011 [77]	12-month comparison of nocturia patients. Group 1 received α-blocker, 5ARI and loxoprofen 60 mg/day. Group 2 received α-blocker and 5ARI only.	78	At 6 and 12 months, nocturia episodes decreased significantly compared with baseline in both group I and group II ( $P < 0.05$ ), but the degree of decrease was not significantly different between the groups ( $P > 0.05$ ). Long-term use of loxoprofen not recommended because of side-effects (gastric discomfort/leg oedema).
	Falahatkar et al. 2008 [78]	1-month randomised, double-blind study of men with LUTS/BPH comparing celecoxib 100 mg/day vs placebo	80	Nocturnal voiding frequency decreased from 5.17 to 2.5 voids/night in celecoxib group, vs 5.3 to 5.12 voids/night in placebo group ( $P < 0.001$ ). IPSS scores decreased from 18.2 to 15.5 in celecoxib group, vs 18.4 to 18 in placebo group. Celecoxib effective in treatment of patients with BPH complaining of refractory nocturia.
Surgery	Simaioforidis et al. 2011 [79]	Randomised comparison of tamsulosin 0.4 mg/day or TURP in men with LUTS/BPH	66	At the 3-month and 1-year follow-ups both tamsulosin and TURP improved all examined parameters. TURP was associated with a statistically significant improvement in the number of nocturnal awakenings and in the IPSS, ICIQ-N and ICIQ-NQOL scores compared with tamsulosin. Hours of undisturbed sleep increased in both groups without any statistically significant difference.

(within 1 week of dose initiation) in older patients can substantially reduce their risk of developing hyponatraemia. An exact scheme for sodium monitoring, particularly in frail elderly patients, has yet to be determined.

Several recent studies have produced evidence for a gender difference in sensitivity to desmopressin. Animal studies have suggested genetic differences related to expression of the  $V_2$  receptor [90], and clinical trials have shown that women appear to have an increased sensitivity to

desmopressin [91,92]. It is likely, therefore, that a lower therapeutic dose for women may provide the same degree of clinical effect as a higher dose in men [93].

Several research groups are exploring a range of novel  $V_2$  receptor agonists for their antidiuretic activity with *in vitro* tests, animal models, and human trials [94]. A representative example is the oral non-peptide compound VA106483. A double-blind placebo trial in 27 men aged > 65 years with nocturia showed that mean diuresis decreased in those receiving VA106483, and that the duration of

antidiuretic action increased in a dose-dependent manner [95].

### Surgical Management of Nocturia

Current evidence does not support nocturia as a primary indication for the use of outlet obstruction-relieving surgery, because nocturia is the least specific symptom of BPE and is the least responsive LUTS for therapies directed at alleviating prostatic obstruction [96]. The fact that nocturia may improve after surgery for BPO, does not signify that BPO surgery is mandated for men presenting with nocturia. The absence of randomised trials of outlet surgery on nocturia outcomes makes assessment of efficacy difficult [97]. In addition, the most-frequently-reported outcome measure of nocturia symptoms in studies involving surgical interventions is question seven on the IPSS, which, as previously mentioned, is flawed in ways that make it difficult to draw firm conclusions about efficacy.

Also unclear is what mechanism/mechanisms, explain some of the studies showing a benefit for patients with nocturia of various types of surgery. For example, Anetunes et al. [98] reported that the positive effects of TURP on nocturia were not correlated with the amount of resected tissue.

Proposed mechanisms for benefits of surgical outlet reduction include:

- Resolution of detrusor overactivity with reinnervation of the bladder after removal of an obstruction [99].
- Destruction of prostatic/bladder neck urothelium leading to a 'deafferentation' of neurones that initiate involuntary detrusor contractions [100].
- Lower post-void residual urine volume, allowing increased time for bladder filling [101].

However, at present, insufficient data exist to support any of these theorised mechanisms.

A conclusion of the 2011 consensus paper that TURP appears to confer a greater improvement in LUTS due to BPE than either transurethral microwave treatment or oral  $\alpha$ -adrenergic blocker therapy has been reinforced by a recent trial by Simaioforidis et al. [79]. Men with untreated LUTS were randomised to the  $\alpha$ -blocker tamsulosin 0.4 mg ( $n = 33$ ) or TURP ( $n = 33$ ). TURP conferred significant benefits in number of nocturnal awakenings, IPSS, International Consultation on Incontinence Questionnaire Nocturia (ICIQ-N), and ICIQ-Nocturia Quality of Life (NQOL) scores vs tamsulosin. The authors concluded that TURP is superior to tamsulosin for the management of BPE-related nocturia. These results are consistent with previously-reported studies suggesting superiority for TURP for nocturia symptoms [98,101–103]. Improvements

**Table 6** Nocturia outcomes after RALP.

Preoperative	Postoperative, %		
	0–1 nocturnal voids	2 nocturnal voids	≥3 nocturnal voids
0–1 nocturnal voids ( $n = 63$ )	78	21	2
2 nocturnal voids ( $n = 29$ )	52	34	14
≥3 nocturnal voids ( $n = 24$ )	29	38	33

Source: Hutchinson et al. 2012 [106].

in nocturia symptoms have also been reported with laser or microwave ablation techniques [100,104,105].

A recent study by Hutchinson et al. [106] highlights the variability in nocturia outcomes that may be expected from radical prostatectomy. This study of 116 men with clinically localised prostate cancer tracked nocturia symptoms for 1 year after robot-assisted laparoscopic prostatectomy (RALP). RALP was associated with improved symptoms in patients who had more severe pre-intervention nocturia; interestingly, some patients with minimal preoperative nocturia had a worsening of their nocturia postoperatively (Table 6) [106].

### Conclusions and Future Directions

The awareness of and degree of clinical attention paid to nocturia has expanded significantly in the past decade. In 2000, nocturia was not recognised as a distinct condition, but was, rather, seen as part of an array of symptoms associated with other diseases such as OAB or BPE. It had often been considered to be a normal component of ageing that primarily affected men. Further, there was no standardised definition or terminology to describe nocturia. Nocturia is now viewed as a distinct medical condition in its own right, with NP being recognised as a frequent finding in patients with nocturia (although NP may also be present in patients without nocturia).

Nocturia is now understood to affect men and women equally. Although clearly associated with ageing, nocturia may, in fact, be significantly burdensome for younger patients. As summarised in this paper, there is also now a better appreciation for the relative ineffectiveness of many therapies directed at the LUT.

The treatment of nocturia continues to evolve, and the multifactorial nature of nocturia suggests an approach involving incremental treatments targeting individual pathophysiological states such as antidiuretic therapy for NP, antimuscarinics for nocturnal urgency, and medical/surgical therapy of the bladder outlet in cases of nocturia related to infravesical obstruction.

Panellists noted that the field of nocturia remains relatively under-researched and, in addition to previously articulated needs for more research, the following nocturia-related issues require investigation in the future:

- Clarification and validation of the definitions of both nocturia and NP and of methods to distinguish volume-related, bladder-related, and convenience voids.
- The relationship between nocturia and obesity, fluid and sodium intake, cardiovascular disease, and kidney disease.
- Evaluation of outcomes of multi-modal therapy of nocturia.
- Improved strategies for diagnosis and treatment of low bladder capacity as a cause of nocturia.
- Better definition and criteria for measurement of nocturnal urgency.
- Whether antidiuretic therapy should be limited to patients with diary-confirmed NP.
- The need for clinical trials of nocturia treatments on objective measures of sleep.
- Age-related changes in circadian rhythms.
- Whether there are any unfavourable outcomes of nocturia therapy such as falls, fractures, mortality, and costs to society, and whether there are correlations between improvements in nocturia and decreased risk of adverse effects secondary to interrupted sleep.
- Better characterisation of nocturia symptoms that are significant or meaningful from the patient's perspective

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## Conflict of Interest

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**Abbreviations:** AVP, arginine vasopressin; 5ARI, 5 $\alpha$ -reductase inhibitor; BACH, Boston Area Community Health survey; BMI, body mass index; BPE, benign prostatic enlargement; BPO, benign prostatic obstruction; (BU) CME, (Boston University School of Medicine Department of) Continuing Medical Education; CHF, congestive heart failure; DO, detrusor overactivity; FVC, frequency-volume chart; ICIQ(-N)(-NQOL), International Consultation on Incontinence Questionnaire (Nocturia) (Nocturia Quality of Life); NERI, The New England Research Institutes, Inc.; NP, nocturnal polyuria; N-QOL, Nocturia Quality of Life questionnaire; OAB, overactive bladder; OR, odds ratio; OSA, obstructive sleep apnoea; (C)PAP, (continuous) positive airway pressure; QOL, quality of life.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Video.**