

## University of Groningen

### Nocturia

Marshall, Stephen D.; Raskolnikov, Dima; Blanker, Marco ; Hashim, Hashim; Kupelian, Varant; Tikkinen, Kari A. O.; Yoshimura, Koji; Drake, Marcus J.; Weiss, Jeffrey P.

*Published in:*  
Urology

*DOI:*  
[10.1016/j.urology.2015.02.043](https://doi.org/10.1016/j.urology.2015.02.043)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Publication date:*  
2015

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Marshall, S. D., Raskolnikov, D., Blanker, M. H., Hashim, H., Kupelian, V., Tikkinen, K. A. O., ... Weiss, J. P. (2015). Nocturia: Current Levels of Evidence and Recommendations From the International Consultation on Male Lower Urinary Tract Symptoms. *Urology*, 85(6), 1291-1299. DOI: 10.1016/j.urology.2015.02.043

#### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

#### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

# Nocturia: Current Levels of Evidence and Recommendations From the International Consultation on Male Lower Urinary Tract Symptoms

Stephen D. Marshall, Dima Raskolnikov, Marco H. Blanker, Hashim Hashim, Varant Kupelian, Kari A. O. Tikkinen, Koji Yoshimura, Marcus J. Drake, and Jeffrey P. Weiss

<b>OBJECTIVE</b>	To evaluate published evidence on nocturia in men and derive expert recommendations.
<b>METHODS</b>	The International Consultations on Urological Diseases—Société Internationale d'Urologie convened a Consultation of experts on male lower urinary tract symptoms. The Consultation assigned standardized levels of evidence and grades of recommendation to various studies of nocturia epidemiology, pathophysiology, assessment, and treatment.
<b>RESULTS</b>	Evidence review and consensus recommendations were made in the areas of epidemiology, pathophysiology, assessment, and treatment.
<b>CONCLUSION</b>	The review presents a condensed summary of the International Consultations on Urological Diseases—Société Internationale d'Urologie evaluation of nocturia, which offers contemporaneous expert consensus on this topic, with an assessment algorithm emphasizing the potential contribution of systemic conditions to the symptom. UROLOGY ■: ■—■, 2015. © 2015 Elsevier Inc.

Nocturia, one of the storage-type lower urinary tract symptoms (LUTS), is defined by the International Continence Society as the complaint of waking at night to void.<sup>1</sup> Despite this simple definition, nocturia is idiosyncratic in a number of ways. For example, nocturia of equivalent frequency causes markedly different reductions in quality of life (QoL) for different people. Consequently, QoL improvements deriving from treatment responses may differ between study populations. In some patients, nocturia progresses slowly, whereas in others, it remains stable or regresses with time. Finally, nocturia is multifactorial in etiology, making both assessment and treatment a potential challenge. This

challenge is an especially important one, however, as nocturia may indicate serious underlying illness. Illnesses such as cardiovascular, renal, or endocrine disease can disrupt water and salt homeostasis, resulting in increased production of urine.<sup>2</sup> For this reason, even one nightly void may be considered a progression from no nocturia and thus an opportunity for secondary prevention. In such contexts, where the pathophysiology of nocturia is not in the lower urinary tract but reflecting systemic disease, alluding to it as LUTS are potentially misleading.

The body of literature describing the evaluation and management of nocturia has expanded at a rapid rate. For this reason, in 2012, the International Consultations on Urological Diseases (ICUD) partnered with the Société Internationale d'Urologie (SIU) to convene a Consultation on male LUTS. The goal of this Consultation was to use established criteria to assign objective levels of evidence (LOEs, 1 through 4) and grades of recommendation (GORs, A through D) to the most salient research in the field.<sup>3</sup> The purpose of this review is to present a condensed summary of the ICUD-SIU evaluation of nocturia, incorporating additional subsequent panel review of the evidence base, which offers contemporaneous expert consensus on this topic. LOEs and GORs are presented here as the verbatim conclusions of the ICUD-SIU panel, with more detailed descriptions published elsewhere.<sup>4</sup> Where published evidence was found to be sparse, but the committee considered a recommendation was required, the GOR is given without any LOE.

**Financial Disclosure:** Hashim Hashim is a consultant for Allergan, American Medical Systems, and Astellas; Marcus J. Drake is a consultant for Allergan, Astellas, and Ferring; and Jeffrey P. Weiss is a consultant for Ferring, Pfizer, Astellas, Allergan, Vantia, and Sympthelligence. The remaining authors declare that they have no relevant financial interests.

From the Department of Urology, SUNY Downstate Medical Center, Brooklyn, NY; the Department of General Practice, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands; the University of Bristol and Bristol Urological Institute, Southmead Hospital, Bristol, United Kingdom; the New England Research Institutes, Watertown, MA; the Department of Urology, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland; the Departments of Urology and Public Health, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; and the Department of Urology, Shizuoka General Hospital, Shizuoka, Japan

Address correspondence to: Marcus J. Drake, D.M., F.R.C.S.(Urol.), University of Bristol and Bristol Urological Institute, Southmead Hospital, Bristol BS10 5NB, United Kingdom. E-mail: [marcus.drake@bui.ac.uk](mailto:marcus.drake@bui.ac.uk)

Submitted: November 14, 2014, accepted (with revisions): February 17, 2015

## EPIDEMIOLOGY

### Prevalence

Studies of nocturia prevalence have demonstrated that it is relatively common in both genders and all age groups. For example, in the population-based Finnish National Nocturia and Overactive Bladder Study, 1 of 8 men and women 18-79 years old reported at least 2 voids per night.<sup>5</sup> Among young respondents, nocturia was more common in women than men, but this gender difference disappeared after middle age.

### Incidence

The incidence of nocturia is not well understood, as the required longitudinal studies are difficult to perform. In the community-based Krimpen study, for example, nocturia was assessed longitudinally with frequency-volume charts over a period of several years.<sup>6</sup> Overall incidence and remission rates for nocturia  $\geq 2$  voids per night after 2 years were 24% and 37%, respectively. Considerable fluctuation was noted at different study time points.

### Bother and Impact on Quality of Life

Sleep disturbance is an important cause of the increased morbidity that is associated with nocturia. However, one nightly void does not appear to be sufficiently disruptive to cause significant bother in most patients. In the Finnish National Nocturia and Overactive Bladder Study, for example, the majority of people reported having bother when the number of nocturia episodes was 2, and 2 voids per night was associated with an impaired Health Related Quality of Life. Two nocturia episodes impaired Health Related Quality of Life compared with those with no nocturia.<sup>7</sup>

### Impact of Nocturia: Falls, Fractures, Mortality, and Productivity

Much of the increased mortality associated with nocturia may be due to the risk of hip fracture in patients who frequently wake to void. Interestingly, in a study of men aged 40-80 years, nocturia  $\geq 2$  voids per night was an age-independent risk factor for hip fracture.<sup>8</sup>

### Conclusions

The ICUD committee considered that nocturia is a highly prevalent symptom, with similar overall prevalence in both genders. Prevalence increases more markedly with age in men. The literature on the incidence of nocturia remains relatively sparse. Incidence of nocturia increases with age, but significant short-term fluctuation in nocturia severity in individuals makes studies on incidence challenging. Two or more episodes of nocturia per night constitutes clinically meaningful nocturia severity in the general population, affecting QoL and perceived health, whereas a single episode usually does not. Nocturia has been suggested to increase risk of falls, fractures, death, and impaired productivity.<sup>4</sup>

## Recommendations

The ICUD committee considered that epidemiologic studies need to use strictly defined and clearly stated criteria of terminology and assessment. Approaches to identify intraindividual variation and other confounding influences need to be considered. Longitudinal studies using high-quality methodology remain a priority requirement. Nocturia of twice or more per night may be a threshold of clinical significance in the general population. However, this threshold is not irrefutably established and should not be extrapolated to subpopulations. Research into all grades of nocturia severity may yield information of clinical relevance.<sup>4</sup>

## PATHOPHYSIOLOGY

### Classification and Risk Factors

Nocturia may be divided into the following 5 causative categories:

- (1) Bladder storage problems,
- (2) Twenty-four-hour (global) polyuria ( $>40$  mL/kg urine output over a 24-hour period),
- (3) Nocturnal polyuria<sup>1</sup> (NP; nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people aged  $>65$  years),
- (4) Sleep disorders,
- (5) Mixed etiology.

Examples of bladder storage problems include overactive bladder (OAB) and urinary tract infection. Global polyuria is commonly caused by polydipsia and by conditions such as diabetes insipidus. NP is seen with peripheral edema and circadian defects in arginine vasopressin secretion, among many other conditions.<sup>2</sup> Sleep disorders may be primary or secondary. Nocturia of mixed etiology is caused by combinations of any of the aforementioned. A summary of the ICUD-SIU conclusions regarding common risk factors for nocturia is presented in [Table 1](#).

### Conclusions and Recommendations

The ICUD committee considered that the pathophysiology of nocturia can be divided into the following 5 categories and associated with several risk factors (LOE 2, GOR B): (1) bladder storage problems, (2) NP, (3) global polyuria, (4) sleep disorders, and (5) mixed mechanisms. Research into pathophysiology remains a priority. Mechanisms underlying nocturia are poorly understood. Establishing why some patients manifest nocturia and not others with apparently similar predisposing factors, basic research into age-related circadian rhythms, effects on sleep quality, and the relationship between nocturia and restorative stages of sleep are a priority.<sup>4</sup>

## ASSESSMENT

Components of clinical assessment of nocturia are presented in [Figure 1](#) and [Table 2](#).

**Table 1.** Representative studies demonstrating common risk factors for nocturia

	Risk Factor	Study	N	Conclusion
Medical conditions	Benign prostatic obstruction	Tikkinen et al <sup>42</sup>	3727	Half of the men with BPH reported nocturia of $\geq 2$ voids/night
	Depression	Asplund et al <sup>43</sup>	1375	Population-based study that demonstrated a significant association between major depression and nocturia
	HTN and CAD	Yoshimura et al <sup>44</sup>	1856	HTN and CAD were both associated with nocturia, though, with a modest effect size
	Neurologic disease	DasGupta and Fowler <sup>45</sup>	n/a	Review of evidence linking multiple sclerosis to bladder dysfunction, including nocturia
	Menopause and hormonal therapy	Tikkinen et al <sup>46</sup>	2002	Parity, postpartum, and postmenopausal periods were associated with nocturia
	NP	Torimoto et al <sup>47</sup>	1632	Demonstrated association between lower extremity edema and nocturnal urine volume, providing mechanistic basis for NP
	Obesity and diabetes	Fitzgerald et al <sup>48</sup>	5506	On multivariate regression, nocturia was associated with both type 2 diabetes and increased body mass index
	Overactive bladder and detrusor overactivity	Krystal et al <sup>49</sup>	24	Nocturnal cystometrogram evidence of temporal relationship between nocturnal detrusor overactivity and night-time voiding
	Pelvic surgery	Thakar et al <sup>50</sup>	279	Women reported fewer nightly voids after total or subtotal abdominal hysterectomy
		Alling et al <sup>51</sup>	1051	In a population-based study, history of hysterectomy was associated with nocturia
	PCa	Tikkinen et al <sup>42</sup>	3727	Over 70% of men with PCa reported at least 2 voids/night, although it is unclear if such men are simply being screened more carefully, or if the 2 conditions are causally related
Lifestyle	Coffee and alcohol	Tikkinen et al <sup>42</sup>	3727	No association between consumption of either substance and nocturia
	Smoking	Tikkinen et al <sup>42</sup>	3727	No association between smoking and nocturia
	Physical activity	Soda et al <sup>52</sup>	56	Prospective study demonstrating a decrease in nocturnal voids after multicomponent lifestyle modification, including "moderate daily exercise"
Misc.	Race/ethnicity and socioeconomic status	Fitzgerald et al <sup>48</sup>	5506	Higher odds of nocturia for black and Hispanic study participants vs whites

BPH, benign prostatic hyperplasia; CAD, coronary artery disease; HTN, hypertension; NP, nocturnal polyuria; PCa, prostate cancer.

### Conclusions and Recommendations

The ICUD committee considered that validated symptom questionnaires are recommended as tools for initial and treatment response evaluation in the clinical setting (grade C). Questionnaires are unsuitable for the estimation of nocturnal voiding frequency (LOE 4, grade C). Nocturia-specific QoL questionnaires can be used to determine the impact of nocturia on QoL (LOE 4, grade C). Urinary diaries are essential in the analysis of nocturia (LOE 4, grade C). The International Consultation on Incontinence Questionnaire (ICIQ) bladder diary has been developed according to methodological requirements for assessment tools and has proceeded through contextual validations (LOE 2, grade B).<sup>9</sup> Medication review is an important part of nocturia clinical assessment (grade A). Physical examination, flow rate testing, and urinalysis as relevant to assessment of LUTS help identify potential contributory mechanisms in some cases of nocturia (grade C). Postvoid residual measurement is directly relevant to nocturia (grade C). Routine use of invasive urodynamics, such as filling

cystometry and pressure flow study, is not recommended (grade D). Blood chemistry examination is optional (grade C~D). Radiologic examinations or cystoscopy should only be used where indicated by the medical context, such as suspected malignant disease (grade D).<sup>4</sup>

### TREATMENT

Selected studies that were assigned LOEs by the ICUD-SIU Consultation are briefly described. A particular issue in these studies is the extent to which any reduction in nocturia could be considered clinically beneficial. Small reductions in nocturia severity as compared against a control group could be statistically significant but may not be regarded as clinically significant. This is particularly the case if reduction compared with placebo is  $<0.5$  episode per night. Nonetheless, it should be remembered that statistical analysis is derived from the full population. A small overall change could reflect varied responses in the population, with some ("responders") seeing a clinically useful reduction and others seeing no change or only

marginal reduction. Furthermore, placebo responses can be comparatively large, which can obscure detection of therapeutic response. Thus, a small additional reduction in the overall study population does not preclude the possibility that some patients could get useful benefit from an intervention. Most published studies were not clear on whether the results could indicate the presence of a subgroup of responders, and this is an area in which future research publications should be explicit.

### Conservative Management

**Behavioral Modification With Biofeedback.** Burgio et al conducted a randomized controlled trial (RCT) of 143 men with bladder outlet obstruction (BOO) and OAB who had failed alpha-blocker therapy.<sup>10</sup> Patients were assigned to 8 weeks of behavioral therapy or oxybutynin. Behavioral therapy reduced nocturia by 0.7 voids per night, as compared with 0.32 voids per night for oxybutynin ( $P = .05$ ; LOE 3).

Song et al randomized 139 women with OAB and nocturia to 12 weeks of bladder training, tolterodine, or both.<sup>11</sup> Nocturia decreased by 56% in the bladder training group, 65% in the tolterodine group, and 66% for both ( $P < .05$ ; LOE 3).

**Conclusions.** The ICUD committee considered that lifestyle changes and behavioral modification are noninvasive conservative methods that can successfully reduce the number of nocturia episodes (LOE 3). Behavioral modification in conjunction with antimuscarinic pharmacotherapy is more effective at reducing nocturia episodes than either method alone (LOE 3).<sup>4</sup> However, larger studies may be necessary to support this latter finding.

**Recommendations.** The ICUD committee considered that lifestyle changes, such as reducing intake of caffeine and alcohol, limiting night-time fluid intake, and improving sleep hygiene, are effective methods that help reduce nocturnal urine volume and episodes of nocturia (GOR C). Consider using bladder training in conjunction with antimuscarinic medication (GOR C).<sup>4</sup>

### Pharmacotherapy

**5-Alpha Reductase Inhibitors.** A recent systematic review summarized the evidence of 23 RCTs encompassing 21,945 men to assess the efficacy and risks of finasteride vs placebo for LUTS associated with benign prostatic enlargement (BPE).<sup>4</sup> Although finasteride did significantly improve some LUTS, no significant effect was seen on nocturia in either short- or long-term use for the overall cohort. Men aged  $>70$  years did apparently see a reduction in nocturia in 1 study, but the modest reduction compared with placebo ( $-0.29$  vs  $-0.11$ , respectively) means the clinical benefit was marginal.<sup>4</sup>

**Conclusions.** The ICUD committee considered that finasteride does not reduce nocturia episodes in men.

Finasteride may improve nocturia in men with LUTS aged  $\geq 70$  years (GOR C).<sup>4</sup>

**Selective Alpha-1 Adrenergic Antagonists.** Roehrborn et al pooled the results of 3 RCTs of patients with BPE who were randomized to receive alfuzosin or placebo.<sup>12</sup> The treatment and placebo groups experienced reductions of 1.1 and 0.8 voids per night, respectively ( $P < .05$ ; LOE 1).

Johnson et al performed an RCT of 3047 men with LUTS suggestive of BPE who were assigned to receive doxazosin alone, finasteride alone, combination therapy, or placebo.<sup>13</sup> At 4-year follow-up, rates of self-reported nightly nocturia episodes were reduced in the doxazosin and combination groups as compared with those of placebo ( $P < .05$ ; LOE 1). In a separate study, Johnson et al performed a secondary analysis of data from the VA Cooperative Study Program Trial.<sup>14</sup> In that trial, 1229 men with benign prostatic hyperplasia aged 45-80 years were assigned to treatment with terazosin, finasteride, a combination, or placebo. Terazosin and combination therapy were the most effective, although the advantage of terazosin over placebo was only 0.3 voids per night (LOE 1).

Chapple et al randomized 955 men with LUTS to receive silodosin, tamsulosin, or placebo for 12 weeks.<sup>15</sup> Only silodosin significantly reduced nocturia vs placebo, but the absolute value of the difference in the study population was modest ( $-0.9$  vs  $-0.7$  voids per night;  $P = .0013$ ; LOE 1).

**Conclusions.** The ICUD committee considered that the majority of studies were undertaken in the context of men with LUTS and presumed BPE, and assessment used the IPSS, which has limitations in respect of evaluation of nocturia. Evaluation of secondary outcome measures could introduce type I errors (false-positive relationships). Alfuzosin, doxazosin, naftopidil, silodosin, tamsulosin, and terazosin are more effective than placebo at reducing number of nocturia episodes in patients with BPE (LOE 1), but the extent of reduction was small in the overall study populations. Administering an alternative alpha-adrenergic antagonist may achieve improvement if nocturia fails to improve sufficiently with the first drug tried (LOE 3). Studies comparing efficacy between agents need to take into account dose equivalence and population studied. Improving nocturia is an important factor for improving overall QoL.<sup>4</sup>

**Recommendations.** The ICUD committee considered that alpha-adrenergic antagonists may be offered to men with nocturia in association with LUTS and BPE (GOR A). In the event of insufficient response to an alpha-adrenergic antagonist, another may be offered (GOR C).<sup>4</sup>

**Combination Therapy.** *5-Alpha Reductase Inhibitor + Selective Alpha-1 Adrenergic Antagonist.* Johnson et al performed an RCT of 3047 men with LUTS suggestive of BPE who were randomly assigned to receive doxazosin,



Category	LUT dysfunction	Problem of fluid or salt balance	Sleep disturbance
Examples	OAB syndrome Bladder pain syndrome Neuro-urological	Cardiac Endocrine Neurological Pulmonary	Anxiety, depression Poor sleep habits Parasomnias Restless legs syndrome
History	LUTS, pain Pelvic disease/ cancer/ surgery.	Known medical history Ankle swelling, shortness of breath Snoring/ breathing interruptions.	Behavioural, Enuresis, Daytime sleepiness, Sleepwalking, Nightmares.
Medication	Drugs affecting LUT	Drugs affecting diuresis	Drugs affecting CNS/ sleep
Examination	Genital/ Pelvic Neuro-urological	Peripheral edema Screening for medical conditions	
Diary	Abnormal day and night	Global or nocturnal polyuria	Normal daytime pattern
Other tests	Urinalysis Free flow rate/ residual <b>Specific tests for suspected condition</b>	Renal/ liver function tests <b>Specific tests for suspected condition; Specialist advice</b>	<b>Polysomnography; Specialist advice</b>

**Figure 1.** Summary diagram for assessment of male nocturia patients based on potential mechanisms. CNS, central nervous system; LUT, lower urinary tract; LUTS, lower urinary tract symptoms; OAB, overactive bladder. (Color version available online.)

finasteride, combination therapy, or placebo.<sup>13</sup> At 4-year follow-up, rates of self-reported nightly nocturia episodes were reduced in the doxazosin and combination groups as compared with those of placebo ( $P < .05$ ), as described previously (LOE 1).

**Antimuscarinic + Alpha-1 Adrenergic Antagonist.** Kaplan et al studied the efficacy of tolterodine extended release (ER), tamsulosin, or both, as compared with that of placebo for the treatment of men with both BPE and OAB.<sup>16</sup> For the 879 men enrolled in this randomized study, only those who received combination therapy experienced a significant reduction in voids per night ( $-0.59$  vs  $-0.39$  episodes per night;  $P = .02$ ; LOE 1b).

**Alpha-1 Adrenergic Antagonist + PDE5 Inhibitor.** Kaplan et al conducted an RCT of 62 men with LUTS suggestive of BPE who also had erectile dysfunction.<sup>17</sup> Patients were randomized to receive alfuzosin, sildenafil, or both for 12 weeks. Patients treated with the combination experienced the greatest improvement in IPSS score ( $-24\%$ ), compared with  $-16\%$  for alfuzosin alone and  $-12\%$  for sildenafil alone. Nocturia as measured by voiding diary was significantly improved by both the combination and alfuzosin alone (LOE 3).

**Conclusions.** The ICUD committee considered that alpha-adrenergic antagonists can be used in conjunction with 5-alpha reductase inhibitors (5-ARIs). Combination therapy may be more effective than either drug used separately (LOE 1). A combination of an antimuscarinic and an alpha-1 adrenergic blocker significantly reduces the number of nocturnal micturitions over placebo (LOE 1). A combination of an antimuscarinic and an alpha-1 adrenergic blocker can improve urgency, frequency, and nocturia severity compared with alpha-1 adrenergic blockade alone (LOE 3). Alpha-1 adrenergic blockers may be more effective at improving nocturia when given with a PDE5 inhibitor (LOE 3).<sup>4</sup> However, many of these

studies were not originally designed with nocturia improvement as a primary endpoint. Because these results thus represent secondary analysis, the resulting conclusions are somewhat weakened.

**Recommendations.** The ICUD committee considered that alpha-adrenergic antagonists in conjunction with 5-ARIs may be offered to men with nocturia in association with LUTS and BPE (GOR A). Alpha-adrenergic antagonists in conjunction with antimuscarinic drugs may be offered to men with nocturia in association with storage LUTS (GOR A). Alpha-adrenergic antagonists in conjunction with PDE5 inhibitors may be offered to men with nocturia (GOR C).<sup>4</sup>

**Anticholinergic or Antimuscarinic.** Wyndaele et al<sup>18</sup> studied the effects of flexible-dose fesoterodine (no placebo control) in 516 men with OAB. By the end of the 12-week study period, patients experienced a 31% decrease in nightly voids from 2.6 to 1.8 voids per night (LOE 3). Rackley et al<sup>19</sup> conducted an RCT of 850 patients assigned to receive tolterodine ER or placebo 4 hours before bed. Although tolterodine ER was effective in reducing OAB-related and severe OAB-related nocturnal micturitions (30% and 59% reduction, respectively) vs placebo (22% and 43%, respectively), it was not effective for non-OAB micturitions. Chapple et al<sup>20</sup> studied the effects of treatment with fesoterodine, tolterodine, or placebo in 1135 patients with OAB. After 12 weeks of treatment, the median decrease in nocturnal micturitions was 23%-29%, with no difference between treatment groups and placebo (LOE 1).

Zinner et al<sup>21</sup> reported the results of a 12-week multicenter study, in which 523 patients with OAB were randomized to receive trosipium chloride or placebo. After 12 weeks of treatment, patients in the treatment group reported a reduction of 0.47 voids per night vs 0.29 voids per night for placebo ( $P < .05$ ; LOE 1).

**Table 2.** ICUD-SIU recommendations regarding the clinical assessment of nocturia

	Assessment Tool	ICUD Committee Notes
Questionnaires and diaries	Generic (eg, IPSS)	IPSS is a generic LUTS-related questionnaire which includes a question regarding nocturia that has not been specifically validated. Subject to recall bias.
	Disease specific (eg, ICIQ N-QoL)	ICIQ N-QoL questionnaire has been validated as a symptom-specific QoL measure.
	FVC	Chart that is based on patient-recorded volumes and times of micturition over a minimum of 24 h. Essential to explore underlying conditions.
	Bladder diary	Combines FVC data with additional relevant information, such as pad usage or degree of urgency.
History and physical	Medical history	Should thoroughly describe nocturia, as well as other LUTS. Must rule out urologic causes of decreased bladder capacity and underlying medical conditions, as many of these are treatable.
	Physical examination	Neurologic, cardiac, and abdominal examinations are all critical.
Investigations	Urinalysis	Not specific to nocturia but allows for the evaluation of possible causative conditions such as urinary tract infection, malignancy, or diabetes.
	PVR	Incomplete bladder emptying reduces functional capacity and may lead to nocturia. Treatment should aim at underlying etiology, although no studies specifically support routine measurement of PVR in patients with nocturia.
	Uroflowmetry	Not specific to nocturia but may aid LUTS assessment.
	Transabdominal ultrasonography	Noninvasive option for the assessment of the prostate.
	Urodynamics	Cystometry not routinely recommended.
	Blood chemistry examination	Useful for specific conditions such as chronic kidney disease (serum creatinine) and diabetes (glucose and hemoglobin A1c).
	Radiologic examination Cystoscopy	Not routinely recommended. Not routinely recommended.

FVC, frequency-volume chart; ICIQ, International Consultation on Incontinence Questionnaire; ICUD, International Consultations on Urological Diseases; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; N-QoL, nocturia-quality of life; PVR, postvoid residual; QoL, quality of life; SIU, Société Internationale d'Urologie.

**Conclusions.** The ICUD committee considered that antimuscarinic drugs can significantly reduce the number of nocturnal micturitions vs placebo (LOE 1). Antimuscarinic drugs are more effective than placebo at reducing OAB-related micturitions but not non-OAB nocturnal micturitions (LOE 1). Antimuscarinic drugs are not effective for reducing nocturia in NP (LOE 1).<sup>4</sup>

**Recommendations.** The ICUD committee considered that antimuscarinic drugs can be offered to men with OAB-related and severe OAB-related nocturnal micturitions with suitable counseling in regard to potential adverse effects (GOR A). Antimuscarinic drugs should not be offered to men with NP and no urinary urgency symptoms (GOR B).<sup>4</sup>

**Antidiuretic Pharmacotherapy.** In a systematic review of 13 trials of desmopressin for the treatment of nocturia, Zong et al<sup>22</sup> reported that desmopressin effectively

extends the duration of the first sleep period. Sleep quality improved and nocturnal voids also decreased (LOE 1).

Van Kerrebroeck<sup>23</sup> reported the results of the Noctopus trials, a set of 3 short-term RCTs of desmopressin for the treatment of nocturia. At 12-month follow-up, among >1000 patients, 67% experienced a significant reduction in nocturnal voids vs placebo (LOE 1).

Weiss et al conducted a 4-week RCT of 757 patients with nocturia who were randomized to receive various doses of desmopressin oral disintegrating tablet or placebo.<sup>24</sup> Significant reductions in nocturnal voids were seen with the 50- and 100- $\mu$ g doses ( $P < .05$ ). Transient clinically significant hyponatremia ( $\text{Na} < 125$  mmol/L) occurred in 7 patients over the age of 65 years (LOE 1).

**Conclusions and Recommendations.** The ICUD committee considered that desmopressin can decrease the frequency of nocturnal voids and decrease nocturnal diuresis (LOE

1). However, many of the evaluated studies used a dose titration phase, which may represent a source of bias.<sup>25</sup> Clinically significant hyponatremia (serum Na <125 mmol/L) is a rare but serious event; patients over the age of 65 years are at greater risk (LOE 1). Desmopressin can be prescribed to decrease nocturnal diuresis and night-time frequency in men (GOR A). Owing to the risk of hyponatremia, serum sodium testing is essential when starting desmopressin to exclude low sodium levels, particularly in patients over the age of 65 years (GOR A).<sup>4</sup>

**Diuretic Pharmacotherapy.** Reynard et al<sup>26</sup> conducted an RCT of 49 men with NP who were randomized to receive furosemide or placebo 6 hours before sleep. Patients in the treatment group experienced a decrease of 0.5 voids per night vs 0 voids per night for placebo, suggesting that men with NP may benefit from timed diuretic therapy (LOE 2).

Pederson and Johansen reported the results of an RCT of 28 patients with nocturia  $\geq 2$  voids per night who received late-afternoon bumetanide or placebo.<sup>27</sup> A decrease of 4 nightly voids per week was seen in the treatment group only after excluding the 10 patients with benign prostatic hyperplasia (LOE 3).

**Conclusions.** The ICUD committee considered that men with NP may benefit from diuretic therapy with furosemide 6 hours before sleep (LOE 2; GOR B). Bumetanide may reduce number of nocturnal micturitions but is not beneficial in men with BPE (LOE 3; GOR C).<sup>4</sup>

**Botulinum Toxin.** In a study by Chapple et al,<sup>28</sup> intravesical injection of onabotulinum-A achieved a reduction in nocturia (LOE 2); the study population was predominantly women, and data were not given separately for men. In a pilot study of 10 patients, Hamidi Madani et al<sup>29</sup> used intraprostatic botulinum toxin in men with LUTS suggestive of BPE who had failed medical therapy and were poor surgical candidates. Nocturia decreased from 4.1 voids per night before injection to 2.4 voids per night after injection ( $P < .001$ ; LOE 3).

**Conclusions and Recommendations.** The ICUD committee considered that botulinum toxin can reduce the number of nocturnal micturitions in patients who fail oral medical therapy and who are not surgical candidates (LOE 3) and therefore can be offered as a treatment option in this group of patients. Owing to counseling related to unlicensed use, very limited evidence base and potential need for self-catheterization is mandatory (GOR C).<sup>4</sup> More evidence is needed before botulinum toxin for therapy of nocturia can be recommended in other contexts (GOR C).

**Nonsteroidal Anti-inflammatory Agents.** Shin et al sought to evaluate the effect of nonsteroidal anti-inflammatory agents (NSAIDs) on nocturia by assigning 40 patients to therapy with either loxoprofen + alpha-blocker + 5-ARI vs alpha blocker + 5-ARI.<sup>30</sup> At

3-month follow-up, the treatment group which received additional NSAID experienced a greater reduction in nocturia ( $-1.5 \pm 0.9$  vs  $-1.1 \pm 0.9$ ;  $P = .034$ ). However, at 6- and 12-month follow-up, that group also reported an increased incidence of gastrointestinal side effects (LOE 3).

Falahatkar et al<sup>31</sup> performed an RCT of 80 men with nocturia with BPE who were assigned to treatment with celecoxib or placebo. At 1-month follow-up, men in the celecoxib group reported a decrease in nocturnal frequency from 5.17 to 2.5 voids per night ( $P < .001$ ) as compared with no statistically significant decrease in the placebo group (LOE 3).

**Conclusions and Recommendations.** The ICUD committee considered that loxoprofen sodium may reduce nocturia for up to 3 months but should not be continued long term because of potential adverse effects (LOE 3). Celecoxib may reduce nocturia in men with BPE (LOE 3). More evidence is needed before NSAID therapy can be recommended for therapy of nocturia (GOR C).<sup>4</sup>

### Surgical Interventions for Benign Prostatic Enlargement

Van Dijk et al<sup>32</sup> retrospectively analyzed 1258 men who had undergone various treatments for LUTS suggestive of BPE, including watchful waiting, alpha-blockers, transurethral resection of prostate (TURP), and transurethral needle ablation. After 6-12 months of follow-up, the various modalities improved nocturia by 7%, 17%, 75%, and 32%, respectively (LOE 3).

Schatzl et al<sup>33</sup> prospectively studied a cohort of 95 men with BPE who were nonrandomized to treatment with TURP, transurethral needle ablation, high-intensity focused ultrasound, visual laser ablation, or transurethral electro-surgical vaporization. All modalities other than visual laser ablation resulted in significant reductions in nocturia frequency (LOE 3).

Simaioridis et al<sup>34</sup> randomized 66 men with LUTS suggestive of BPE to receive TURP or tamsulosin. At 3-month and 1-year follow-up, TURP was more effective than tamsulosin in reducing the number of nocturnal awakenings, IPSS, ICIQ-Nocturia, and ICIQ-Nocturia-QoL scores (LOE 2).

**Conclusions.** The ICUD committee considered that BOO-reducing procedures using various modalities of intervention can reduce the number of nocturnal micturitions (LOE 3). TURP is more effective than tamsulosin for treatment of BPE-related nocturia (LOE 3).<sup>4</sup>

**Recommendations.** The ICUD committee considered that BOO-reducing procedures may improve nocturia in some patients with voiding LUTS and BOO who fail medical therapy and who are good surgical candidates (GOR C). Surgery for relief of BOO is not indicated for management of patients whose primary complaint is nocturia (GOR C). Comprehensive evaluation of the cause(s) of nocturia



is essential before contemplating a surgical approach (GOR C). Patients must be warned of potential nonresponse of nocturia and of risks associated with surgery (GOR C).<sup>4</sup>

### Phytotherapy

In a Cochrane review of 30 RCTs of saw palmetto extract for the treatment of nocturia; Tacklind et al<sup>35</sup> found no significant difference between saw palmetto and placebo (LOE 1). Barry et al<sup>36</sup> conducted an RCT of 369 men with nocturia who were treated with saw palmetto or placebo. No difference in nocturia outcomes was seen at 24- or 48-week follow-up (LOE 2).

Wilt et al<sup>37</sup> reported the results of a Cochrane review of 18 RCTs of *Pygeum africanum* for the treatment of men with nocturia. Although *P africanum* was not directly compared with drug therapy, it did appear to reduce nocturia vs placebo by 19% (LOE 1). Wilt et al<sup>38</sup> also reviewed the literature on Cernilton, a rye-grass pollen derivative, which has been used to treat nocturia. Treatment with Cernilton appeared to relieve nocturia more effectively than did placebo and other phytotherapy-based active controls (LOE 1).

**Conclusions and Recommendations.** The ICUD committee considered that *Serenoa repens* (saw palmetto) does not reduce the number of nocturnal micturitions compared with that of placebo (LOE 1). *P africanum* (African plum tree) and Cernilton (rye pollen) reduce the number of nocturnal micturitions when compared with that of placebo (LOE 1). *S repens* should not be prescribed for treatment of nocturia (GOR A). *P africanum* and Cernilton can be offered as an option for treating nocturia (GOR A).<sup>4</sup>

### Agents to Promote Sleep

Kaye<sup>39</sup> described personal experience with oxazepam for the self-treatment of nocturia. Nocturia severity was reduced by 63%, but nocturnal urine volume was unchanged (LOE 3). Takami et al conducted a cross-sectional study of 123 patients assigned to triazolam, nitrazepam, or control groups for the treatment of nocturia.<sup>40</sup> The primary influence of therapy appeared to entail improving return to sleep after each episode, for which nitrazepam was most effective (LOE 3).

Drake et al<sup>41</sup> reported the results of an RCT of 20 men with BOO and nocturia who were assigned to treatment with bedtime melatonin or placebo. Melatonin and placebo caused a decrease in nocturia of 0.32 and 0.05 episodes per night, respectively ( $P = .07$ ). In this study, the presence of a subgroup of “responder” patients was identified.

**Conclusions and Recommendations.** The ICUD committee considered that hypnotics do not appear to influence nocturia directly but may be used to aid return to sleep (LOE 3, GOR C). Potential adverse effects of hypnotics should be considered. Melatonin may reduce number of nocturnal voids (LOE 2, GOR C).<sup>4</sup>

## CONCLUSION

The complex nature of nocturia has led to a significant proliferation in clinical studies that explore its epidemiology, pathophysiology, assessment, and treatment. In an attempt to grade these studies in a standardized way, the ICUD-SIU Consultation on LUTS recently assigned LOEs and GORs to the most influential research in this field. This Consultation’s recommendations provide contemporaneous expert consensus on this topic and offer practical recommendations for urologists who are faced with nocturia in everyday practice.

## References

1. van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the Standardisation Subcommittee of the International Continence Society. *NeuroUrol Urodyn.* 2002;21:179-183.
2. Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. *BJU Int.* 2011;107:702-713.
3. Abrams P, Khoury S. International consultation on urological diseases: evidence-based medicine overview of the main steps for developing and grading guideline recommendations. *NeuroUrol Urodyn.* 2010;29:116-118.
4. Drake MJ, Weiss JP, Blanker MH, et al. Nocturia. In: Chapple C, Abrams P, eds. *Male Lower Urinary Tract Symptoms*. Paris, France: Société Internationale d’Urologie; 2013:135-190.
5. Tikkinen KA, Tammela TL, Huhtala H, et al. Is nocturia equally common among men and women? A population based study in Finland. *J Urol.* 2006;175:596-600.
6. Van Doorn B, Blanker MH, Kok ET, et al. Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: the Krimpen study. *J Urol.* 2011;186:1956-1961.
7. Tikkinen KA, Johnson TM, Tammela TLJ, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol.* 2010;57:488-496.
8. Temml C, Ponholzer A, Gutjahr G, et al. Nocturia is an age-independent risk factor for hip-fractures in men. *NeuroUrol Urodyn.* 2009;28:949-952.
9. Bright E, Cotterill N, Drake M, et al. Developing and validating the International Consultation on Incontinence Questionnaire bladder diary. *Eur Urol.* 2014;66:294-300.
10. Burgio KL, Goode PS, Johnson TM, et al. Behavioral versus drug treatment for overactive bladder in men: the Male Overactive Bladder Treatment in Veterans (MOTIVE) trial. *J Am Geriatr Soc.* 2011;59:2209-2216.
11. Song C, Park JT, Heo KO, et al. Effects of bladder training and/or tolterodine in female patients with overactive bladder syndrome: a prospective, randomized study. *J Korean Med Sci.* 2006;21:1060-1063.
12. Roehrborn CG, Van Kerrebroeck P, Nordling J. Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. *BJU Int.* 2003;92:257-261.
13. Johnson TM, Burrows PK, Kusek JW, et al. The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. *J Urol.* 2007;178:2045-2050.
14. Johnson TM, Jones K, Williford WO, et al. Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial. *J Urol.* 2003;170:145-148.
15. Chapple CR, Montorsi F, Tammela TL, et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. *Eur Urol.* 2011;59:342-352.

16. Kaplan SA, Roehrborn CG, Rovner ES, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA*. 2006;296:2319-2328.
17. Kaplan SA, Gonzalez RR, Te AE. Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. *Eur Urol*. 2007;51:1717-1723.
18. Wyndaele JJ, Goldfischer ER, Morrow JD, et al. Effects of flexible-dose fesoterodine on overactive bladder symptoms and treatment satisfaction: an open-label study. *Int J Clin Pract*. 2009;63:560-567.
19. Rackley R, Weiss JP, Rovner ES, et al. Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. *Urology*. 2006;67:731-736.
20. Chapple C, Van Kerrebroeck P, Tubaro A, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. *Eur Urol*. 2007;52:1204-1212.
21. Zinner N, Gittelman M, Harris R, et al. Trosipium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol*. 2004;171:2311-2315.
22. Zong H, Yang C, Peng X, et al. Efficacy and safety of desmopressin for treatment of nocturia: a systematic review and meta-analysis of double-blinded trials. *Int Urol Nephrol*. 2012;44:377-384.
23. Van Kerrebroeck P. Nocturia Antidiuretic Pharmacotherapy. In: Weiss J, Blavias J, Van Kerrebroeck P, et al., eds. *Nocturia: Causes, Consequences and Clinical Approaches*. New York, NY: Springer; 2012:135-144.
24. Weiss JP, Zinner NR, Klein BM, et al. Desmopressin orally disintegrating tablet effectively reduces nocturia: results of a randomized, double-blind, placebo-controlled trial. *NeuroUrol Urodyn*. 2012;31:441-447.
25. Ebell MH, Radke T, Gardner J. A systematic review of the efficacy and safety of desmopressin for nocturia in adults. *J Urol*. 2014;192:829-835.
26. Reynard J, 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;81:215-218.
27. Pedersen P, Johansen PB. Prophylactic treatment of adult nocturia with bumetanide. *Br J Urol*. 1988;62:145-147.
28. Chapple C, Sievert KD, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2013;64:249-256.
29. Hamidi Madani A, Enshaei A, Heidarzadeh A, et al. Transurethral intraprostatic botulinum toxin-A injection: a novel treatment for BPH refractory to current medical therapy in poor surgical candidates. *World J Urol*. 2013;31:235-239.
30. Shin HI, Kim BH, Chang HS, et al. Long-term effect of loxoprofen sodium on nocturia in patients with benign prostatic hyperplasia. *Korean J Urol*. 2011;52:265-268.
31. Falahatkar S, Mokhtari G, Pourreza F, et al. Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study. *Urology*. 2008;72:813-816.
32. Van Dijk MM, Wijkstra H, Debruyne FM, et al. The role of nocturia in the quality of life of men with lower urinary tract symptoms. *BJU Int*. 2010;105:1141-1146.
33. Schatzl G, Madersbacher S, Lang T, et al. The early postoperative morbidity of transurethral resection of the prostate and of 4 minimally invasive treatment alternatives. *J Urol*. 1997;158:105-110; discussion 110-111.
34. Simaioforidis V, Papatsoris AG, Chrisofos M, et al. Tamsulosin versus transurethral resection of the prostate: effect on nocturia as a result of benign prostatic hyperplasia. *Int J Urol*. 2011;18:243-248.
35. Tacklind J, Macdonald R, Rutks I, et al. Serenoa repens for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2012;12:CD001423.
36. Barry MJ, Meleth S, Lee JY, et al. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial. *JAMA*. 2011;306:1344-1351.
37. Wilt T, Ishani A, Mac Donald R, et al. *Pygeum africanum* for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2002:CD001044.
38. Wilt T, Mac Donald R, Ishani A, et al. Cernilton for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2000:CD001042.
39. Kaye M. Nocturia: a blinded, randomized, parallel placebo-controlled self-study of the effect of 5 different sedatives and analgesics. *Can Urol Assoc J*. 2008;2:604-608.
40. Takami N, Okada A. Triazolam and nitrazepam use in elderly outpatients. *Ann Pharmacother*. 1993;27:506-509.
41. Drake MJ, Mills IW, Noble JG. Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. *J Urol*. 2004;171:1199-1202.
42. Tikkinen KA, Auvinen A, Johnson TM, et al. A systematic evaluation of factors associated with nocturia—the population-based FINNO study. *Am J Epidemiol*. 2009;170:361-368.
43. Asplund R, Henriksson S, Johansson S, et al. Nocturia and depression. *BJU Int*. 2004;93:1253-1256.
44. Yoshimura K, Terada N, Matsui Y, et al. Prevalence of and risk factors for nocturia: analysis of a health screening program. *Int J Urol*. 2004;11:282-287.
45. DasGupta R, Fowler CJ. Bladder, bowel and sexual dysfunction in multiple sclerosis: management strategies. *Drugs*. 2003;63:153-166.
46. Tikkinen KA, Auvinen A, Tiitinen A, et al. Reproductive factors associated with nocturia and urinary urgency in women: a population-based study in Finland. *Am J Obstet Gynecol*. 2008;199:153.e1-153.e12.
47. Torimoto K, Hirayama A, Samma S, et al. The relationship between nocturnal polyuria and the distribution of body fluid: assessment by bioelectric impedance analysis. *J Urol*. 2009;181:219-224.
48. Fitzgerald MP, Litman HJ, Link CL, et al. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. *J Urol*. 2007;177:1385-1389.
49. Krystal AD, Preud'homme XA, Amundsen CL, et al. Detrusor overactivity persisting at night and preceding nocturia in patients with overactive bladder syndrome: a nocturnal cystometrogram and polysomnogram study. *J Urol*. 2010;184:623-628.
50. Thakar R, Ayers S, Clarkson P, et al. Outcomes after total versus subtotal abdominal hysterectomy. *N Engl J Med*. 2002;347:1318-1325.
51. Alling Møller L, Lose G, Jørgensen T. Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. *Obstet Gynecol*. 2000;96:446-451.
52. Soda T, Masui K, Okuno H, et al. Efficacy of nondrug lifestyle measures for the treatment of nocturia. *J Urol*. 2010;184:1000-1004.