

Nocturia: Focus on Etiology and Consequences

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Nocturia is a condition characterized by the need to awaken ≥ 1 times per night to void. Although nocturia is a multifactorial condition that can coexist with other lower urinary tract symptoms, the most common causal factor is nighttime overproduction of urine. Many people with nocturia do not seek help, accepting it as a natural consequence of aging. However, nocturia is common in men and women of all ages and has a profound impact on quality of life, especially in the young, that may be associated with increased morbidity and mortality. Nocturia as a condition deserves public health attention.

[Rev Urol. 2012;14(3/4):48-55 doi: 10.3909/riu0576]

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KEY WORDS

Nocturia • Quality of life • Sleep disruption • Nighttime urine overproduction

Nocturia is defined as the need to awaken ≥ 1 times per night to void.¹ It is divided into two main categories: upper urinary tract and lower urinary tract dysfunction. However, nocturia has long been considered one of a range of symptoms associated with well-recognized lower urinary tract symptoms (LUTS), such as benign prostatic obstruction (BPO) and overactive bladder (OAB). This assumption is not surprising, given that BPO and OAB are generally associated with urinary frequency. However, although nocturia is urinary frequency that occurs during nighttime sleep, it is not necessarily driven by a lower urinary tract

dysfunction involving the bladder, prostate, or urethra; it may be driven instead by nighttime urine overproduction, or nocturnal polyuria (NP), resulting from renal, cardiovascular, or pulmonary factors.

Although nocturia has been shown to be one of the most bothersome LUTS^{2,3} and despite much emphasis placed on the need to improve patient-reported outcomes in all LUTS, nocturia has not received the clinical attention that it deserves.⁴ In trials reporting the impact on nocturia of BPO and OAB medications, such as α -antagonists and antimuscarinics, the clinical significance of the reductions in nocturnal voids, although in some

cases demonstrating statistical significance, is yet to be determined.⁵ Many clinicians consider nocturia to be of minor concern and do little to dispel the myth that nocturia is a normal part of aging.^{4,6}

Nocturia is, however, an important condition that warrants specific clinical attention. Repeated nocturnal voiding can result in chronically

Nocturia Is the Most Common LUTS

Although its prevalence is generally underestimated, nocturia is in fact an extremely common condition, affecting both men and women of all ages. Almost 69% of men and 76% of women (aged ≥ 40 years) in the United States, United Kingdom, and Sweden, randomly selected

Repeated nocturnal voiding can result in chronically disturbed sleep, which in turn negatively affects a patient's quality of life and general health.

disturbed sleep, which in turn negatively affects a patient's quality of life (QoL) and general health. In addition to daytime lack of vitality and the overall bother caused by waking at night to void, poor sleep can contribute to the exacerbation of existing health conditions. Furthermore, there is mounting evidence that nocturia may be associated with an increased mortality risk, via its detrimental effects on sleep and other associated comorbidities. This article reviews current knowledge of the prevalence, etiology, and impact of nocturia.

from Internet-based panels (20,000 participants in the United States, 7500 in the United Kingdom, and 2500 in Sweden), reported ≥ 1 nocturnal voids.³ In a review of 43 studies of the prevalence of nocturia around the world, Bosch and Weiss recently reported that, although nocturia is most prevalent in older people, it also affects a significant proportion of younger individuals.⁷ For instance, 4% to 18% of women in their 20s and 30s were affected by ≥ 2 voids per night, increasing to 28% to 62% for women in their 70s and 80s (Figure 1). Similar

ranges were reported in men. The proportion of men aged 20 to 30 years reporting ≥ 2 voids per night was 2% to 17%, rising to 29% to 59% in men aged 70 to 80 years. In European Pain in Cancer (EPIC), a population-based, cross-sectional telephone survey of 19,165 adult men and women in five countries (Canada, Germany, Italy, Sweden, and the United Kingdom), 13% to 17% of adults aged < 40 years reported ≥ 2 nocturnal voids, increasing to 20% to 21% of middle-aged men and women and 35% to 36% of adults aged ≥ 60 years.⁸ The condition, therefore, can affect up to one in five or six younger adults, as well as up to one-third of older people.^{8,9}

In addition to nocturia prevalence increasing with age, it is also common in certain racial and patient populations. Data from the National Health and Nutrition Examination Survey demonstrated that non-Hispanic black men are at greater risk for nocturia even when controlling for other factors, such as education and income.⁹ Almost 84% of patients in an OAB

Figure 1. Prevalence of nocturia in men (A) and women (B) from a meta-analysis of epidemiology studies, by number of nocturia episodes per night. Reproduced with permission from Bosch JL, Weiss JP.⁷

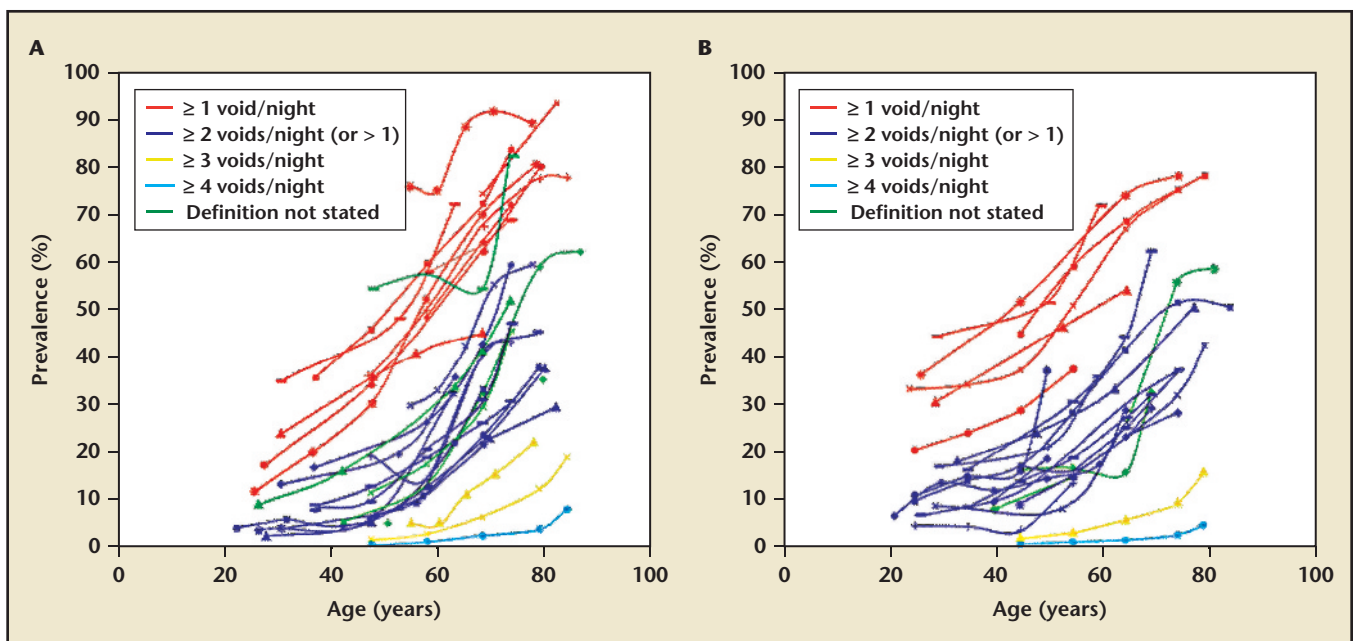


TABLE 1

Causes of Nocturia

Urologic Conditions	Nonurologic Conditions
<ul style="list-style-type: none"> • LUTS (OAB, BPH) • Neurogenic voiding dysfunction • Idiopathic nocturnal detrusor overactivity • Bladder cancer • Nocturnal polyuria 	<ul style="list-style-type: none"> • Chronic heart failure • Diabetes mellitus (uncontrolled) • Diabetes insipidus • Hypoalbuminemia • Sleep apnea • Multiple sclerosis • Depression • Chronic pain • Inadequate fluid intake

BPH, benign prostate hyperplasia; LUTS, lower urinary tract symptoms; OAB, overactive bladder.

study reported nocturia among their urinary symptoms,¹⁰ and 71% of patients with benign prostatic hyperplasia (BPH) experienced frequent nighttime voiding (ie, 2 or more episodes per night).¹¹

Nocturia Is a Multifactorial Condition

The pathophysiology of nocturia is complex and multifactorial, which may partly explain why the condition has not received appropriate attention as a disorder in its own right. The underlying causes may be urologic or nonurologic in origin and may be described in terms of the broad categories listed in Table 1.⁴

Although the causes of nocturia may differ among patients, multiple factors may underlie the cause of nocturia in any given patient. Failure to incrementally evaluate the potential underlying factors may lead to poor clinically relevant outcomes because the major causes of nocturia may not be addressed. Therefore, it is paramount that clinicians are aware of the multiple potential contributing factors in any given patient, in order to

enable optimal treatment decisions that address each issue adequately. Nevertheless, nocturnal overproduction of urine at night (> 20% to 33% of daily total urine volume depending on age),¹ also known as NP, has been implicated as a significant causal factor in up to 88% of nocturia cases.¹²

Nocturia is common among patients suffering from BPO or OAB,^{10,11} and their nocturnal urinary frequency may be an extension of their daytime symptoms because of diminished bladder storage capacity. However, the modest clinical improvement of nocturia in patients receiving BPO or OAB medications⁵ suggests that the key underlying cause of nocturia in these patients, as just mentioned, may not solely be their enlarged prostate or bladder dysfunction. A review of eight trials or groups of trials with antimuscarinics for OAB found that drug treatment did not significantly reduce the mean number of nocturnal voids in two of the trials.⁵ The other six trials did demonstrate a significant reduction in nocturnal voids from baseline, but when

a placebo group was included, the maximum reduction in nocturnal voids was only 0.2 voids compared with placebo. Similar results were seen in the review of nocturia endpoints in six trials for BPH medication such as α -antagonists or 5- α reductase inhibitors or combination therapy.⁵ Numerically similar reductions in the number of nocturnal voids were seen across the trials, and when a placebo group was included, a further reduction of 0.05 to 0.3 nocturnal voids occurred compared with placebo.⁵ Even in a trial with a reduction in number of nocturnal voids relative to placebo, there was no change in time to first void.⁵

Overproduction of urine at night may result from a number of factors, such as evacuation of daytime third-space fluid sequestration with peripheral edema due to a recumbent position for sleep, excessive production of atrial natriuretic peptide due to sleep apnea or congestive heart failure, abnormalities in antidiuretic hormone arginine vasopressin (AVP) secretion, external factors such as medications (eg, diuretics), or lifestyle factors such as fluid intake at night.^{1,4,13}

Mechanism of Urine Production and Nocturnal Overproduction of Urine

AVP is involved in the regulation of many organ systems and functions including body fluid osmolality, blood volume, blood pressure, cell contraction, cell proliferation, and adrenocorticotrophic hormone secretion.¹⁴ In particular, AVP plays a key role in the control of urine production by increasing water absorption and thus concentration of urine at night. AVP release is modulated by plasma osmolality mediated by specialized cells in the hypothalamus.¹⁵ Although AVP mediates its effects via the stimulation of specific

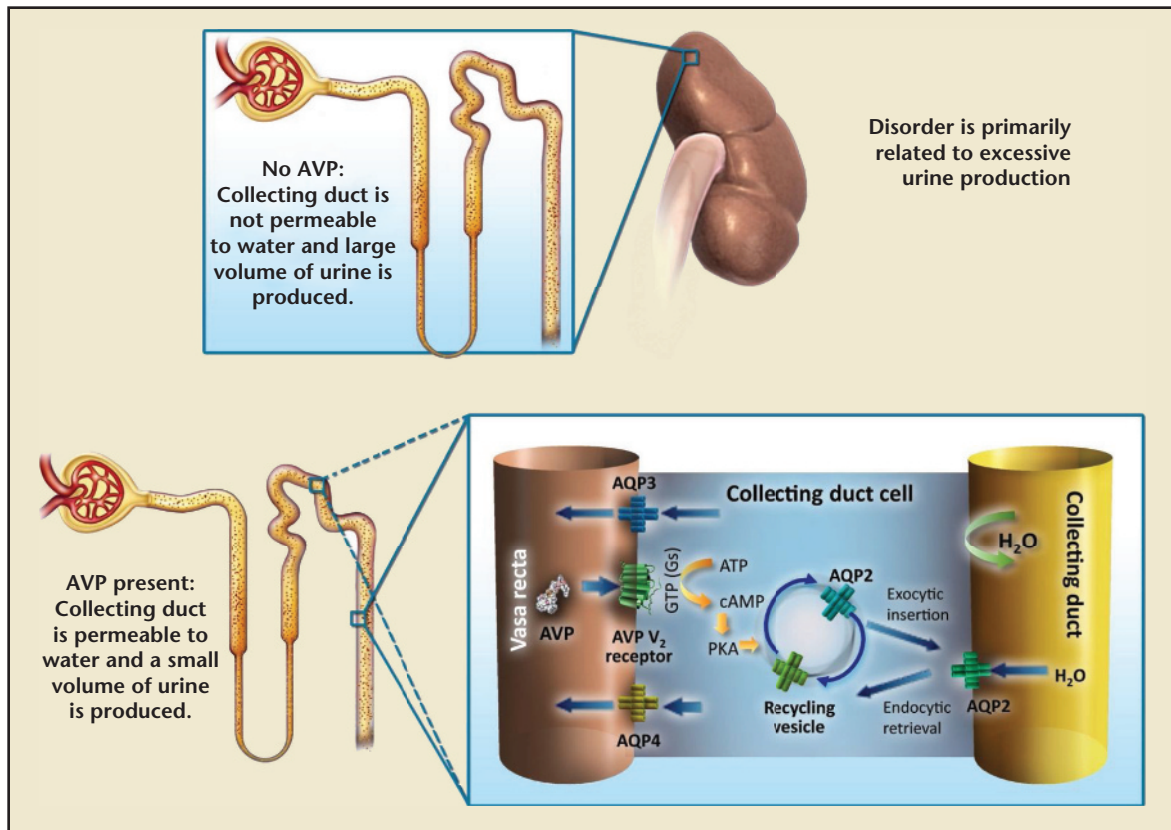


Figure 2. Mechanism of nocturnal overproduction of urine. AQP, aquaporin; ATP, adenosine triphosphate; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; GTP, guanosine triphosphate; PKA, protein kinase A. A portion of this image appears courtesy of Joseph Verbalis, MD, Georgetown University Medical Center, Washington, DC.

receptors throughout the body (V_1 vascular, V_2 renal, and V_3 pituitary), the antidiuretic effect of AVP (ie, regulation of water excretion) is achieved by the binding of AVP to the V_2 receptors primarily located in the connecting tubules and collecting ducts of the renal medulla in the kidney (Figure 2).^{14,15} Activating the V_2 receptors in the renal medulla induces the translocation of preformed water channels called aquaporins from a store in intracellular vesicles to the apical plasma membrane of the principal cells in the connecting tubules and collecting ducts of the nephron. These water channels increase the permeability of the distal tubules and collecting ducts, resulting in the osmotic reabsorption of water without solute, thereby increasing urine concentration and decreasing urine volume.¹⁶

Insufficient AVP in the kidneys, an impaired circadian rhythm of

AVP secretion, mutations of AVP receptors, or renal AVP resistance caused by intrinsic renal disease or exogenous factors such as medications or electrolyte abnormalities may all result in increased urine production and may be responsible for nighttime overproduction of urine.^{17,18}

Impact of Nocturia on Overall Health and QoL

Although nocturia is defined as waking to void ≥ 1 time, a significant impact of nocturia on patient QoL is considered to be bothersome when ≥ 2 nocturnal voids are experienced.¹⁹ Sleep plays a vital role in physical and mental functioning, and repeated interruptions due to nighttime voiding can reduce the quantity and quality of sleep. For example, a cross-sectional analysis of the Sleep Heart Health study of 6342 men and women in the United

States demonstrated a significant association between self-reported nocturia and objective measures of sleep disruption, such as total sleep time, sleep efficiency, proportion of REM sleep, arousal index, and oxygen saturation as measured by polysomnography.²⁰ Given its high prevalence, nocturia is a major cause of sleep disturbance, which is a key factor in making nocturia one of the most bothersome LUTS.^{17,21} Nocturia was associated with significant decreases in 14 of the 15 domain scores reported by men and women in the Health-Related QoL (HR-QoL) questionnaire.¹⁹ For every increase in nocturnal voids above 1, further reductions in HR-QoL scores were seen.¹⁹

A causal relationship between nocturia and many disorders is suspected and nocturia is acknowledged to be a possible symptom of the primary illness—for example,

raised blood glucose in poorly controlled type 2 diabetes can lead to polyuria,¹ fluid accumulation in the lower extremities caused by right-sided congestive heart failure causes increased urine production upon attaining the recumbent position, and sleep apnea can increase renal sodium and water excretion due to elevated plasma atrial natriuretic peptide levels.^{4,18} A further complication in determining causality is that many epidemiologic studies have not adjusted for factors known

with all-cause mortality^{27,28} and sleep parameters such as sleep efficiency have been shown to independently predict mortality.²⁷

Overall, epidemiologic studies support that nocturia is not a trivial condition. Nocturia may be linked with increased morbidity and increased risk of mortality, and in some studies these relationships have been found to be independent of various confounding comorbidities and age.^{25,29} However, a recently reported 15-year follow-

A reduction in sleep quality is independently associated with indicators of poor health common to those associated with nocturia, including disturbed glucose homeostasis, diabetes, and hypertension.

to contribute to nocturia, such as sleep-disordered breathing. It has been shown that sleep-disordered breathing is independently associated with increased cardiovascular risk²⁰; thus, failure to exclude this or other known causes of nocturia may lead to erroneous associations between nocturia and certain morbidities.

A reduction in sleep quality is independently associated with indicators of poor health common to those associated with nocturia, including disturbed glucose homeostasis,²² diabetes,²³ and hypertension.²⁴ The direction of the cause-and-effect relationship between sleep and poor health is not always proven. The hypothesis that there may be a direct link between nocturia and mortality in an elderly population is supported by findings from the Olmsted County Study that showed an association of nocturia with mortality in men aged ≥ 60 years.²⁵ The increased mortality rate associated with nocturia was likely due to its association with impaired sleep, as well as the increased risk of falls and related fractures in patients with nocturia, especially elderly patients.²⁶ Poor sleep is associated

with all-cause mortality^{27,28} and sleep parameters such as sleep efficiency have been shown to independently predict mortality.²⁷ Overall, epidemiologic studies support that nocturia is not a trivial condition. Nocturia may be linked with increased morbidity and increased risk of mortality, and in some studies these relationships have been found to be independent of various confounding comorbidities and age.^{25,29} However, a recently reported 15-year follow-up of 1114 Dutch men, aged 50 to 78 years, challenges the association between nocturia and increased risk of mortality.³⁰ When age was taken into account, no association between nocturia and mortality risk existed. The multifactorial causes of nocturia, the increasing prevalence of the condition with age, and the frequent comorbidities in patients with nocturia make conclusions on the impact of mortality a challenge. Nocturia may impact health and survival because of the persistent negative effect frequent nocturnal

Given the multifactorial nature of nocturia, a thorough patient history assessment, including behavioral factors such as daily fluid intake, must be made to more clearly understand the patient's symptoms.

voiding has on sleep. Regardless of whether nocturia is a condition directly implicated in causing poor health, or whether nocturia is simply a symptom heralding the presence of another important underlying medical condition, the general finding of increased risk of significant illness associated with nocturia indicates that nocturia should be thoroughly investigated in each individual. Greater public health attention to nocturia is therefore needed.

Clinical Considerations

Despite the prevalence of nocturia in the general population and associated recognized bother, clinicians should be aware that nocturia may be underreported for various reasons. Affected individuals may be reluctant to discuss their nocturia. In addition, many patients with nocturia consider nocturnal frequency to be a normal part of aging.^{4,6} Individuals with nocturia may not consider their condition to be sufficiently serious to warrant consulting a physician and, thus, may not seek medical attention for nocturia.⁶ Finally, patients may believe that nocturia cannot be treated.⁶

Given the multifactorial nature of nocturia, a thorough patient history assessment, including behavioral factors such as daily fluid intake, must be made to more clearly understand the patient's symptoms. The frequency volume chart (FVC) defined as a 24-hour evaluation of the time of urination (frequency) and the volume, is an invaluable tool in the diagnosis of the underlying causes of nocturia. It provides objective information on the characteristics of the patient's urinary frequency and volume, as well as timing and type

of fluid intake, all of which have a bearing on urine output (Figure 3).⁴

Analysis of the patient's FVC facilitates diagnosis of the main cause of nocturia from four main categories:

1. Reduced maximum voided volume (MVV), indicating a reduced capacity of the bladder to store urine, which may occur exclusively during the hours of sleep (low nocturnal bladder capacity [NBC]) or throughout the day and night⁴

Daytime (from waking up to going to bed)		Nighttime (from going to bed to waking up; includes first morning void)	
Time of waking up	Voided volume, mL	Time of going to bed	Voided volume, mL
7:00 AM		11:10 PM	
7:00 AM	200	1:00 AM	400
12:00 PM	350	3:00 AM	300
4:30 PM	450	6:00 AM	400
6:30 PM	300		
11:00 PM	300	Woke up at 8:00 AM next morning and voided 200 mL	

Figure 3. Example of a frequency volume chart.

- 24-hour urine volume of > 40 mL/kg, representing excessive urine production during the day and night (global polyuria)⁴
- Excessive production of urine at night (NP), in which nocturnal urine output (at any age) is > 33% of the 24-hour urine output and global urine production remains normal⁴
- Mixed etiology comprising combinations of the foregoing criteria⁴

Conducting simple mathematical analysis of the 24-hour FVC can help elucidate the etiology of nocturia. For instance, nocturnal urine volume (NUV) is defined as the total volume of urine produced between the time the individual goes to bed with the intention of sleeping and the time of waking with the intention of rising.¹ Thus, NUV does not include the last void before going to bed, but it

does include the first morning void. Nighttime overproduction of urine (NP) may be reported using the nocturnal polyuria index (NPi).³¹ The NPi is calculated by dividing NUV by total 24-hour urine volume. Thus, if 24-hour urine production is within normal limits, an NPi > 20% to 33% (age-dependent) indicates NP.¹ Nocturia index (Ni) is calculated by dividing NUV by MVV. If Ni > 1, nocturia occurs because the MVV is exceeded by the NUV. NBC is defined as the largest voided volume during the hours of sleep. The NBC index (NBCi) is used to address the degree to which nocturnal voided volumes vary from bladder capacity. NBCi is the actual number of nightly voids minus the predicted number of nightly voids. The predicted number of nightly voids is derived by calculating Ni and subtracting 1 (NBCi = Ni - 1). NBCi > 0, indicates nocturia at volumes less than MVV, implying bladder storage problems at night. An example of FVC analysis used to classify nocturia etiology is given in Table 2.

TABLE 2

Patient Case Studies Using Frequency Volume Chart for Diagnosis

	Patient 1	Patient 2	Patient 3
24-h volume	1900 mL (no global polyuria)	6000 mL	2500 mL (no global polyuria)
Nocturia episodes	3	3	7
NUV, including first morning void	1200 mL	1500 mL	1500 mL
MVV	400	600	200
Ni (Ni = NUV/MVV; if Ni > 1, Nocturia due to NUV exceeding MVV)	3	2.5	7.5
NPi (NPi = NUV/24-h volume; if NPi > 33% at any age, NP is present)	63% (NP)	25% (normal)	60% (NP)
Diagnosis	NP	Global polyuria	Mixed etiology (NP and reduced voided volumes)

MVV, maximum voided volume; Ni, Nocturia index; NP, nocturnal polyuria; NPi, nocturnal polyuria index; NUV, nocturnal urine volume.

Classification of nocturia through the use of FVCs can disclose numerous potential underlying medical conditions that may contribute to the development of nocturia and thereby guide appropriate therapy. For example, NP carries differential diagnoses of sleep apnea, third spacing, cardiac dysfunction, and excessive evening fluid intake, whereas global polyuria may be caused by untreated diabetes mellitus or diabetes insipidus, chronic renal disease, pituitary dysfunction, or use of medications such as lithium.

Conclusions

Nocturia is the leading cause of sleep disruption with its subsequent negative impact on general health and QoL for a large proportion of the adult population.^{19,21,32} Nocturia is prevalent in men and women of all ages⁷ but may be particularly bothersome in younger adults, in whom the consequences of sleep disturbance may be more detrimental for daytime functioning and possibly for health and mortality.^{29,32,33} The underlying causes of nocturia obviously influence the efficacy of different treatment options. Because a major cause

of nocturia is overproduction of urine at night,¹² nocturia may not respond to treatments designed to reduce urgency and increase bladder capacity or increase urine flow, such as agents for the management of OAB or bladder outlet obstruction, respectively.⁵

Nocturia may be more than simply a patient inconvenience, in view of its association with increased risk of morbidity and mortality. Clinicians often underestimate the consequences of nocturia, however, and thus fail to perform a thorough evaluation of the condition and its causes. Patients with nocturia deserve full consultation and implementation of an appropriate management strategy to ensure that the specific underlying medical conditions associated with nighttime voiding are addressed. ■

Medical writing and editorial assistance, provided by ApotheCom ScopeMedical, were funded by Ferring Pharmaceuticals.

References

1. Van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21:179-183.

2. Chapple CR, Batista JE, Berges R, et al. The impact of nocturia in patients with LUTS/BPH: need for new recommendations. *Eur Urol Suppl*. 2006;5:12-18.
3. Coyne KS, Wein AJ, Tubaro A, et al. The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS. *BJU Int*. 2009;103(suppl 3):4-11.
4. Weiss JP, Blaivas JG, Bliwise DL, et al. The evaluation and treatment of nocturia: a consensus statement. *BJU Int*. 2011;108:6-21.
5. Smith AL, Wein AJ. Outcomes of pharmacological management of nocturia with non-antidiuretic agents: does statistically significant equal clinically significant? *BJU Int*. 2011;107:1550-1554.
6. Chen FY, Dai YT, Liu CK, et al. Perception of nocturia and medical consulting behavior among community-dwelling women. *Int Urogynecol J Pelvic Floor Dysfunct*. 2007;18:431-436.
7. Bosch JL, Weiss JP. The prevalence and causes of nocturia. *J Urol*. 2010;184:440-446.
8. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol*. 2006;50:1306-1314; discussion 1314-1315.
9. Markland AD, Vaughan CP, Johnson TM 2nd, et al. Prevalence of nocturia in United States men: results from the National Health and Nutrition Examination Survey. *J Urol*. 2011;185:998-1002.
10. Brubaker L, FitzGerald MP. Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. *Int Urogynecol J Pelvic Floor Dysfunct*. 2007;18:737-741.
11. Yoshimura K, Ohara H, Ichioka K, et al. Nocturia and benign prostatic hyperplasia. *Urology*. 2003;61:786-790.
12. Weiss JP, van Kerrebroeck PE, Klein BM, Nørgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. *J Urol*. 2011;186:1358-1363.
13. Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. *BJU Int*. 2011;107:702-713.
14. Vande Walle J, Stockner M, Raes A, Nørgaard JP. Desmopressin 30 years in clinical use: a safety review. *Curr Drug Saf*. 2007;2:232-238.
15. Nørgaard JP, Hashim H, Malmberg L, Robinson D. Antidiuresis therapy: mechanism of action and clinical implications. *Neurourol Urodyn*. 2007;26:1008-1013.
16. Nielsen S. Renal aquaporins: an overview. *BJU Int*. 2002;90(suppl 3):1-6.

MAIN POINTS

- Nocturia is a prevalent condition in men and women of all ages but is a major problem in the young.
- Nocturia, caused primarily by nocturnal overproduction of urine, or nocturnal polyuria, is primarily a kidney-driven urine production disease, as opposed to a bladder-driven urine storage disease. It is the underlying cause of nocturia in the majority of cases.
- Treatments designed for the management of other lower urinary tract symptoms, such as overactive bladder or benign prostatic obstruction, may only result in a modest clinical improvement of nocturia.
- Nocturia is the leading cause of sleep deprivation and has a detrimental effect on general health and quality of life. It also may be associated with an increased risk of morbidity and mortality.
- Clinicians underestimate the impact of nocturia, regarding it as an inconvenience for their patients rather than a condition in its own right that merits clinical attention. Patients with nocturia deserve a full consultation and appropriate management strategies to address the underlying causes of the condition.

17. Van Kerrebroeck P, Hashim H, Holm-Larsen T, et al. Thinking beyond the bladder: antidiuretic treatment of nocturia. *Int J Clin Pract.* 2010;64:807-816.
18. Schneider T, de la Rosette JJ, Michel MC. Nocturia: a non-specific but important symptom of urological disease. *Int J Urol.* 2009;16:249-256.
19. Tikkinen KA, Johnson TM 2nd, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol.* 2010;57:488-496.
20. Parthasarathy S, Fitzgerald M, Goodwin JL, et al. Nocturia, sleep-disordered breathing, and cardiovascular morbidity in a community-based cohort. *PLoS One.* 2012;7:e30969.
21. Bliwise DL, Foley DJ, Vitiello MV, et al. Nocturia and disturbed sleep in the elderly. *Sleep Med.* 2009;10:540-548.
22. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A.* 2008;105:1044-1049.
23. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med.* 2005;165:863-867.
24. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep.* 2006;29:1009-1014.
25. Lightner DJ, Krambeck AE, Jacobson DJ, et al. Nocturia is associated with an increased risk of coronary heart disease and death. *BJU Int.* 2012;110:848-853.
26. Nakagawa H, Niu K, Hozawa A, et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. *J Urol.* 2010;184:1413-1418.
27. Dew MA, Hoch CC, Buysse DJ, et al. Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosom Med.* 2003;65:63-73.
28. Ikehara S, Iso H, Date C, et al. Association of sleep duration with mortality from cardiovascular disease and other causes for Japanese men and women: the JACC study. *Sleep.* 2009;32:295-301.
29. Kupelian V, FitzGerald MP, Kaplan SA, et al. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. *J Urol.* 2011;185:571-577.
30. van Doorn B, Kok ET, Blanker MH, et al. Mortality in older men with nocturia. A 15-year followup of the Krimpen study. *J Urol.* 2012;187:1727-1731.
31. Weiss JP, Weinberg AC, Blaivas JG. New aspects of the classification of nocturia. *Curr Urol Rep.* 2008;9:362-367.
32. Kupelian V, Wei JT, O'Leary MP, et al. Nocturia and quality of life: results from the Boston area community health survey. *Eur Urol.* 2012;61:78-84.
33. Kobelt G, Borgström F, Mattiasson A. Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. *BJU Int.* 2003;91:190-195.