

Nocturia: Current Evaluation and Treatment for Urology

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Abstract Nocturia is a very common yet a highly underreported entity. Recently, there has been an increasing interest in nocturia because of its association with serious adverse health conditions such as diabetes, heart disease, elevated BMI, and mortality. Frequency volume charts are the cornerstone of initial assessment and are pivotal in determining the type of nocturia and associated causes. The diagnostic evaluation is aimed at clarifying the underlying cause: sleep disturbances, reduced bladder capacity (functional or extrinsic), and increased urine production (nocturnal or daily). Obstructive sleep apnea is an important cause of nocturnal polyuria and should always be considered. Management is focused on treating the underlying cause; a range of behavioral and pharmacologic options are available.

Keywords Nocturia · Obstructive sleep apnea · Frequency · Frequency volume charts · Polyuria

Introduction

Nocturia is an extremely common entity that is generally regarded as a natural consequence of aging [1]. The incidence of nocturia is alarmingly high, reported to be up to 60 % in patients >70 years old by the National Health and Nutrition

Examination Survey (NHANES) [2] and other auxiliary national surveys [3]. A systematic review on this subject showed that of men in their 70s and 80s, 68.9–93 % reported at least 1 void per night, and 29–59.3 % reported at least 2 voids per night [3]. This high prevalence rate is seen in populations of various ethnicity [4] and nationality throughout the world.

Nocturia is commonly assumed to occur in older men secondary to prostatic obstruction or in women because of an overactive bladder. Patients tend to dismiss nocturia as an expected consequence of growing older and therefore underreport its presence to their physicians [5, 6]. Historically, there has been a false perception among both patients and physicians that nocturia is more annoying than serious [3]. This under-appreciation of the health consequences of nocturia has led to relative disregard and a lack of attention that it deserves.

Recently, there has been an increasing interest in nocturia and the adverse effects with which it has been linked. Nocturia is associated with decreased quality of life, daytime function disturbances, heart disease, diabetes, and an elevation in BMI, mortality, reduced health-related quality of life, mood disturbances, reduced work productivity, increased falls, increased fractures, and increased mortality [7–9, 10]. While much research has shown these associations, more is needed to show that the adverse effects related to nocturia do in fact disappear if we successfully treat nocturia over a long period of time. In this article, we aim to highlight some of the published studies that indicate the importance of diagnosing, investigating, and treating nocturia.

Definition

The International Continence Society (ICS) defines nocturia as “individual has to wake at night one or more times to void”

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Table 1 Definitions of common acronyms

Acronym	Definition	Comments
NUV	Nocturnal urine volume	Total volume of urine passed during the night, including the first morning void
MVV	Maximal voiding volume	Reflects the functional bladder capacity. Nocturia occurs when NUV exceeds MVV
Ni	Nocturia index	NUV divided by MVV. Ni is positive if >1.
NBC	Nocturnal bladder capacity	Nocturia occurs when the nocturnal bladder capacity (NBC) is overwhelmed by the amount of urine entering the bladder during the night
NBCi	NBC index	Corresponds to the actual number of voids minus the predicted number of voids. The predicted number of voids is obtained by subtracting 1 from Ni. NBCi >0 means that voids at night occur below the MVV, indicating that the bladder itself cannot store the amount of urine produced at night.

[11]. Each void must be preceded and followed by sleep. The ICS standardization report also defines 24-h polyuria as a urine output exceeding 40 ml/kg bodyweight per 24 h and nocturnal polyuria (NP) as a nocturnal urine output (including the first morning void) of >33 % of the total 24-h voided volume [12, 13]. Various tools, such as the International Prostate Symptom Score (IPSS) and the American Urological Association symptom score (AUA-SS), are utilized by many providers to help identify and quantify nocturia in their patients [14]. Other relevant assessment tools include the Overactive Bladder Questionnaire (OAB-q) and the Medical Outcomes Study (MOS) sleep scale [15]. Table 1 summarizes the definitions of common acronyms used in nocturia literature.

Classification

Nocturia can occur in a patient for one, two, or all of the following three reasons: (1) Sleep disturbances (waking up at night because of a sleep disturbance followed by voiding); (2) Reduced bladder capacity, functional, or extrinsic, (a) only at night or (b) both day and night; and (3) Increased urine production (a) only at night or (b) over 24 h [16, 17].

(1) Sleep disturbances

Sleep disturbances lead to patients waking up from sleep in the middle of the night, at which point they may feel a sensation of fullness in the bladder and elect to void [11]. The primary cause of awakening in these cases is not bladder fullness but rather sleep disturbances. Sleep disorders are classified into either primary (such as insomnia and narcolepsy) or secondary disorders (such

as cardiac failure, chronic obstructive pulmonary disease, and endocrine disorders.) Other conditions that can result in sleep disturbances include neurologic conditions (e.g., Parkinson disease, dementia, epilepsy), psychiatric conditions (e.g., depression, anxiety), chronic pain disorders, use of alcohol, or drugs (consumption or withdrawal) and/or secondary to certain medications (e.g., corticosteroids, diuretics).

(2) Reduced bladder capacity

Reduced bladder storage leads to frequent voiding of low volumes, either because of urgency (overactive bladder) or simply a frequent urge to void. Patients with the inability to completely empty their bladder might complain of frequency due to a high post-voiding residual volume and decreased functional bladder capacity. This might happen only at night or at night and during the day. If the bladder has a reduced capacity, nocturia occurs even without an over-production of urine at night [18–20].

(3) Increased urine production (polyuria)

Polyuria refers to either making too much urine over a 24-h period (24-h polyuria) or making too much urine only at night (nocturnal polyuria) [19].

(a) Twenty-four-hour polyuria (increased urine production during the day and at night)

Twenty-four-hour polyuria is defined as an overall urine volume of >40 ml/kg in adults as determined by frequency volume charts (FVC) [11]. Twenty-four-hour polyuria is classically seen in individuals suffering from diabetes mellitus but can also be a symptom of diabetes insipidus, polydipsia, the use of certain drugs, or medication or simply a voluntary excessive fluid intake [16]. Polydipsia is usually seen in patients with 24-h as a drive by the body to prevent circulatory collapse. An overnight water deprivation test can be performed to distinguish between diabetes insipidus and primary polydipsia [21].

(b) Nocturnal polyuria (increased urine production at night)

Nocturnal polyuria is defined by the ICS as a nocturnal urine volume (NUV) >20–33 % of total 24-urine volume (in other words, the nocturnal urine output rate exceeds the daily one) [11]. This proportion is called the nocturnal polyuria index (NPI). The first void after the morning wakeup is included in the NP definition. Nocturnal polyuria may be caused by multiple factors—some easily managed by behavioral modifications (e.g., limiting excessive fluid intake prior to bedtime) [22••] and others that require more extensive workup and management (e.g., obstructive sleep apnea leading to a nocturnal over-production of atrial natriuretic peptide production)

[23] One of the most common causes in the older patient population is chronic heart failure, leading to a nighttime evacuation of daytime third spaced fluid sequestration with peripheral edema and the use of diuretics [16]. A rare cause is a disturbance of the pattern of endogenous production of arginine vasopressin (AVP) hormone by the posterior pituitary [11].

Nocturnal polyuria and obstructive sleep apnea

More and more evidence is being published supporting the role of sleep disordered breathing in the presence of nocturia. The most notable of the sleep disordered breathing group is obstructive sleep apnea (OSA). The prevalence of OSA has been reported to range from 3 to 7 % for men and 2 to 5 % for women to >50 % in certain patient groups [24]. OSA is a chronic disorder characterized by repetitive episodes of complete or partial obstruction of the upper airway during sleep and is an independent risk factor for several other conditions including systemic hypertension, cardiac disease, stroke, and impaired glucose tolerance [25]. The association between OSA and nocturia has been recognized for a long time; however, only recently have we begun to uncover the complex pathophysiology behind this association [23]. This is of particular importance to a urologist evaluating patients with nocturia because of the very high prevalence of undiagnosed OSA. For example, Finkel and his colleagues demonstrated that in a cohort of 2877 patients, 24 % screened at high-risk for OSA, of whom 81 % did not carry a diagnosis of OSA [26]. The leading theory of OSA-induced nocturia is increased nocturnal urine production. Hypoxia and hypercapnea from apnea/hypopnea result in vagal bradycardia and pulmonary vasoconstriction causing a sympathetic response and tachycardia. The sensation of cardiac fluid overload leads to an elevated secretion of atrial natriuretic peptide (ANP), which in turn suppresses desmopressin, (ADH) resulting in nocturia [23, 27, 28]. Given the under diagnosis of OSA, it seems clear physicians cannot rely on the patient's established past medical history, alone, to determine the presence of OSA. While there are many known risk factors for OSA, including obesity, snoring, acromegaly, asthma, hypertension, diabetes, and craniofacial abnormalities [29], there are increasingly more associations being discovered. The authors have previously demonstrated that nocturia and other voiding symptoms, such as frequency, predict a positive Berlin score (a screening tool for OSA), and vice versa [30]. A patient who screens positive on the Berlin Questionnaire is

recommended to seek evaluation with a sleep medicine specialist and be considered for a polysomnographic sleep study, the test required to determine a definitive diagnosis for OSA. It stands to reason that patients reporting nocturia to their physician should therefore also complete a Berlin Questionnaire. Treating OSA with CPAP has been demonstrated to reduce nocturnal urine production, with resultant decrease in episodes of nocturia, lending support to the consideration of identifying OSA in patients with nocturia [31, 32].

Bladder hypoxia and nocturnal frequency

An additional mechanism linking OSA and nocturia is bladder hypoxia [33]. Animal models have shown that exposure of the bladder to cycles of hypoxia and re-oxygenation results in neurodegeneration, fibrosis, smooth muscle injury, and contractile dysfunction leading to decreased bladder compliance and detrusor overactivity [34–36]. This concept is supported by observations in a rabbit model showing that chronic moderate bladder ischemia and oxidative stress results in detrusor overactivity and urinary frequency [33, 36, 37]. These findings suggest that more than just the annoyance of increased urine production at night, OSA can cause structural changes to the bladder that may not be reversible.

Evaluation

The first step in evaluating patients complaining of nocturia is classifying the patient's condition into the correct nocturia category or categories. Past medical history should uncover possible underlying diseases, such as cardiovascular disease, and fluid intake (e.g., alcoholic and caffeinated beverages). A 3-day FVC should be completed with the patient recording the volume and timing of each void during the day and night [38]. A 3-day FVC seems to be preferable to questionnaires in terms of patient compliance and because of lack of recall-bias [14]. Urinalysis, urine culture, and cytology should also be carried out. Screening with a Berlin Sleep Questionnaire [39] can be done, followed by evaluation of sleep with polysomnography in patients suspected to have sleep disordered breathing [29]. Of note, sleep evaluations no longer require an overnight stay in a sleep lab in most cases and can be performed at home using a portable sleep monitor. These tests can be performed by the primary care physician or through a referral to a sleep medicine specialist. Lastly, the Health Related Quality of Life (HR QoL) instrument is useful when quantifying the effect of nocturia on the patient's daily

life and determining how bothered they are by their symptoms.

Management

When managing patients with nocturia, the degree of bother often dictates the intensity of the workup, bearing in mind that the number of awakenings sufficient for a patient to express a feeling of bother is generally considered to be 2–3 [3]. That said, bother by nocturia is highly variable and even among patients who do not complain, work up may be indicated in those with a high nocturia score. Depending on the category of nocturia being experienced by the patient, the clinician determines its cause(s) and manages the patient accordingly. Behavioral modifications should be attempted before implementing other treatments [40] and include dietary fluid restrictions prior to bedtime, preemptive voiding before going to bed, nocturnal “dehydration,” and diuretics timing in the midafternoon, rather than immediately prior to sleep [41]. If the patient has 24-h polyuria on FVC’s, referral to an endocrinologist for a diabetes insipidus workup is indicated. Patients with nocturnal polyuria due to congestive heart failure or peripheral edema may be advised to elevate their legs 2–3 h prior to bedtime to mobilize third space fluids and should be referred to their PCP for further evaluation. For patients on diuretics, it is recommended to time diuretics during the mid-to-late afternoon to produce a diuresis before going to bed [41]. Patients with low nocturnal bladder capacity should be evaluated for urologic causes such as poor bladder compliance, decreased ability to store, bladder cancer, neurogenic bladder, obstruction with secondary detrusor overactivity, or a stone. Medications may be appropriate and helpful, in these situations. Patients with severe, frequent nocturnal urgency might benefit from a trial of a standard treatment regimen for overactive bladder (e.g., antimuscarinic agent or a beta-3 agonist). As antimuscarinic agents only work for patients with overactive bladder and severe nocturnal urgency, urodynamics to assess bladder capacity and the presence of bladder overactivity may be prudent [42].

Despite what is often reported by patients and observed by physicians in practice, studies show that alpha-1-blockers seem to be ineffective in treating nocturia [43, 44]. 5-alpha reductase inhibitors either alone or in combination with an alpha-blocker have also been shown to have clinically negligible improvements in nocturia [45]. Irrespective of these findings, patients with bladder outlet obstruction should be considered for trials of alpha blockers and/or 5 alpha reductase inhibitors, in the case of the latter medication—only if the prostate is over 40 g. If a male patient has a large residual urine volume related to bladder outlet obstruction, he might benefit from surgical reduction of the prostate, such as

transurethral resection (TUR) of the prostate [46]. Lastly, studies do not support the use of melatonin for nocturia [47].

In Europe (but not in the USA), anti-diuretic therapy with the synthetic analog of arginine vasopressin, desmopressin, is approved for nocturia [48]. Desmopressin aims at concentrating the urine at night by way of an action on V2 receptors present in the distal collecting tubules. Desmopressin can be administered by intranasal spray, oral tablets, or newly released orally disintegrating tablets. Side-effects related to desmopressin include hyponatremia, hypertension, dry mouth, insomnia, headaches, abdominal pain, peripheral edema, and nausea [48, 49]. Hyponatremia is the most concerning side-effect and is most frequent in men >65 years of age [50].

No surgical or interventional therapy (including bladder outlet obstruction surgery) is indicated for nocturia as a sole indication [46]. Botulinum toxin detrusor injections, sacral neuromodulation, or tibial electric nerve stimulation are used to treat patients with OAB, but nocturia is regarded as a secondary outcome [51]. While surgical therapy may be effective in treating some patients with nocturia, urodynamics to determine the presence of obstruction, and/or overactivity, is warranted—and other concomitant causes should be considered. Like all voiding dysfunction, the etiology of nocturia could be multifactorial.

Conclusions

Nocturia is a highly prevalent symptom associated with myriad of different disease processes and is associated with significant sequelae, morbidity, and an increase in mortality. Success is relative to each patient and depends on the baseline condition and root cause. For effective evaluation and management, it is important to understand and document patients’ baseline, degree of bother and expectations, correctly identify which category of nocturia a patient’s symptoms belong to, and plan a treatment regimen accordingly. In addition to a thorough history and clinical examination, frequency volume charts are the cornerstone of initial assessment and are pivotal in determining the type of nocturia and associated causes. Obstructive sleep apnea is an important cause of nocturnal polyuria and should always be considered. Patients can be screened with the Berlin questionnaire and should undergo polysomnography and treatment with CPAP if an OSA diagnosis is confirmed. As the treatment options for nocturia are largely determined by the nocturia category into which a patient falls (nocturnal polyuria, 24-h polyuria, reduced bladder capacity, sleep disordered breathing, etc.), it is incumbent upon the physician to identify the cause. Continued efforts to bring nocturia into the forefront with primary care physicians may help to identify any unrecognized

underlying conditions and improve a patient's overall health status.

Compliance with Ethics Guidelines

Conflict of Interest Tony Nimeh, Pedro Alvarez, Naem Mufarreh, and Lori B. Lemer each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

- van Dijk L, Kooij DG, Schellevis FG, et al. Nocturia: impact on quality of life in a Dutch adult population. *BJU Int.* 2004;93:1001–4.
- Markland AD, Vaughan CP, Johnson 2nd TM, et al. Prevalence of nocturia in United States men: results from the National Health and Nutrition Examination Survey. *J Urol.* 2011;185:998–1002.
- Coyne KS, Zhou Z, Bhattacharyya SK, et al. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. *BJU Int.* 2003;92:948–54.
- 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;177:1385–9.
- Umlauf MG, Goode S, Burgio KL. Psychosocial issues in geriatric urology: problems in treatment and treatment seeking. *Urol Clin North Am.* 1996;23:127–36.
- MacDiarmid S, Rosenberg M. Overactive bladder in women: symptom impact and treatment expectations. *Curr Med Res Opin.* 2005;21:1413–21.
- Asplund R. Hip fractures, nocturia, and nocturnal polyuria in the elderly. *Arch Gerontol Geriatr.* 2006;43:319–26.
- Parsons JK, Mougey J, Lambert L, et al. Lower urinary tract symptoms increase the risk of falls in older men. *BJU Int.* 2009;104:63–8.
- Temml C, Ponholzer A, Gutjahr G, et al. Nocturia is an age-independent risk factor for hip-fractures in men. *Neurourol Urodyn.* 2009;28:949–52.
- Lightner DJ, Krambeck AE, Jacobson DJ, et al. Nocturia is associated with an increased risk of coronary heart disease and death. *BJU Int.* 2012;110:848–53.
- Van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardization of terminology in nocturia: report from the standardization subcommittee of the International Continence Society. *BJU Int.* 2002;90 Suppl 3:11–5.
- Asplund R. The nocturnal polyuria syndrome (NPS). *Gen Pharmacol.* 1995;26:1203–9.
- Carter PG, Cannon A, McConnell AA, et al. Role of atrial natriuretic peptide in nocturnal polyuria in elderly males. *Eur Urol.* 1999;36:213–20.
- Yap TL, Cromwell DA, Brown C, et al. The relationship between objective frequency-volume chart data and the I-PSS in men with lower urinary tract symptoms. *Eur Urol.* 2007;52:811–8.
- Kim SO, Choi HS, Kim YJ, et al. Impact of nocturia on health-related quality of life and medical outcomes study sleep score in men. *Int Neurourol J.* 2011;15:82–6.
- Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. *BJU Int.* 2011;107:702–13.
- Koseoglu H, Aslan G, Ozdemir I, et al. Nocturnal polyuria in patients with lower urinary tract symptoms and response to alpha-blocker therapy. *Urology.* 2006;67:1188–92.
- Weiss JP, Wein AJ, van Kerrebroeck P, et al. Nocturia: new directions. *Neurourol Urodyn.* 2011;30:700–3.
- Weiss JP, Blaivas JG, Stember DS, et al. Nocturia in adults: etiology and classification. *Neurourol Urodyn.* 1998;17:467–72.
- Norgaard JP. Pathophysiology of nocturnal enuresis. *Scand J Urol Nephrol Suppl.* 1991;140:1–35.
- Abyholm G, Monn E. Intranasal DDAVP-test in the study of renal concentrating capacity in children with recurrent urinary tract infections. *Eur J Pediatr.* 1979;130:149–54.
- Cho SY, Lee SL, Kim IS, et al. Short-term effects of systematized behavioral modification program for nocturia: a prospective study. *Neurourol Urodyn.* 2012;31:64–8.
- Yalkut D, Lee LY, Grider J, et al. Mechanism of atrial natriuretic peptide release with increased inspiratory resistance. *J Lab Clin Med.* 1996;128:322–8.
- Lurie A. Obstructive sleep apnea in adults: epidemiology, clinical presentation, and treatment options. *Adv Cardiol.* 2011;46:1–42.
- Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* 2008;5:136–43.
- Finkel KJ, Searleman AC, Tymkew H, et al. Prevalence of undiagnosed obstructive sleep apnea among adult surgical patients in an academic medical center. *Sleep Med.* 2009;10:753–8.
- Clark BA, Elahi D, Fish L, et al. Atrial natriuretic peptide suppresses osmostimulated vasopressin release in young and elderly humans. *Am J Physiol.* 1991;261:E252–6.
- Umlauf MG, Chasens ER. Sleep disordered breathing and nocturnal polyuria: nocturia and enuresis. *Sleep Med Rev.* 2003;7:403–11.
- Partinen M. Epidemiology of obstructive sleep apnea syndrome. *Curr Opin Pulm Med.* 1995;1:482–7.
- Rai A, Nimeh T, Sood A, et al. Could nocturia be an indicator of an undiagnosed sleep disorder in male veterans? *Urology.* 2015;85:641–7.
- Guilleminault C, Lin CM, Goncalves MA, et al. A prospective study of nocturia and the quality of life of elderly patients with obstructive sleep apnea or sleep onset insomnia. *J Psychosom Res.* 2004;56:511–5.
- Margel D, Shochat T, Getzler O, et al. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. *Urology.* 2006;67:974–7.
- Azadzi KM, Radisavljevic ZM, Siroky MB. Effects of ischemia on tachykinin-containing nerves and neurokinin receptors in the rabbit bladder. *Urology.* 2008;71:979–83.
- Azadzi KM, Yalla SV, Siroky MB. Oxidative stress and neurodegeneration in the ischemic overactive bladder. *J Urol.* 2007;178:710–5.
- Azadzi KM, Radisavljevic ZM, Golabek T, et al. Oxidative modification of mitochondrial integrity and nerve fiber density in the ischemic overactive bladder. *J Urol.* 2010;183:362–9.
- Azadzi KM, Chen BG, Radisavljevic ZM, et al. Molecular reactions and ultrastructural damage in the chronically ischemic bladder. *J Urol.* 2011;186:2115–22.
- Azadzi KM, Tarcan T, Kozlowski R, et al. Overactivity and structural changes in the chronically ischemic bladder. *J Urol.* 1999;162:1768–78.
- Blanker MH, Bohnen AM, Groeneveld FP, et al. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. *J Urol.* 2000;164:1201–5.
- Zebede S, Lovatsis D, Alarab M, et al. Prevalence of obstructive sleep apnea detected by the Berlin Questionnaire in patients with nocturia attending a urogynecology unit. *Int Urogynecol J.* 2015.

40. van Kerrebroeck P, Hashim H, Holm-Larsen T, et al. Thinking beyond the bladder: antidiuretic treatment of nocturia. *Int J Clin Pract.* 2010;64:807–16.
41. Weiss JP, Blaivas JG, Bliwise DL, et al. The evaluation and treatment of nocturia: a consensus statement. *BJU Int.* 2011;108:6–21.
42. 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;67:731–6. **discussion 736.**
43. Cornu JN, Abrams P, Chapple CR, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management—a systematic review and meta-analysis. *Eur Urol.* 2012;62:877–90.
44. MacDonald R, Tacklind JW, Rutks I, et al. Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review. *BJU Int.* 2012;109:1756–61.
45. Johnson 2nd 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;178:2045–50. **discussion 2050-2041.**
46. 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;18:243–8.
47. Drake MJ, Mills IW, Noble JG. Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. *J Urol.* 2004;171:1199–202.
48. Mattiasson A, Abrams P, Van Kerrebroeck P, et al. Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int.* 2002;89:855–62.
49. Lose G, Lalos O, Freeman RM, et al. Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am J Obstet Gynecol.* 2003;189:1106–13.
50. National Institute for Health and Clinical Excellence. Lower urinary tract symptoms: the management of lower urinary tract symptoms in men. NICE Clinical Guidelines.
51. Kurpad R, Kennelly MJ. The evaluation and management of refractory neurogenic overactive bladder. *Curr Urol Rep.* 2014;15:444.