Supplement Article

Management of Nocturia and Nocturnal Polyuria

Jeffrey P. Weiss and Karel Everaert

Nocturnal polyuria (NP), characterized by overproduction of urine at night (greater than 20%-33% of total 24-hour urine volume depending on age), is a major contributing factor in most nocturia cases. Nocturia can be caused by intake, urological, nephrological, hormonal, sleep, and cardiovascular factors. It is therefore important to accurately diagnose both the type of nocturia and the potentially associated medical conditions to determine appropriate treatment. Diagnostic tools, in addition to a thorough history and physical examination, include voiding/bladder diary analyses and questionnaires to diagnose nocturia type (NP, diminished nocturnal/global bladder capacity, global polyuria) and causative factors. Lifestyle modifications are the first intervention implemented for the management of nocturia and NP but, as symptoms progress, such measures may be insufficient, and pharmacotherapy may be initiated. While drugs for benign prostatic hyperplasia and overactive bladder have demonstrated statistically significant reductions in nocturnal voids, patients often fail to achieve a clinically meaningful response. Antidiuretic treatment is warranted for patients with nocturia due to NP because, in many patients, it treats the underlying cause (ie, insufficient secretion of antidiuretic hormone arginine vasopressin) that leads to overproduction of urine at night and has been shown to provide statistically significant reductions in nocturnal voids. Desmopressin, a synthetic analog of arginine vasopressin, is the only antidiuretic treatment indicated specifically for nocturia due to NP. Overall, the pathophysiology of NP is complex and differs from that of other types of nocturia. A multidisciplinary approach is necessary to effectively diagnose and manage this bothersome condition. UROLOGY 133: 24–33, 2019. © 2019 Elsevier Inc.

Nocturia is a highly prevalent and bothersome medical condition characterized by the need to wake up to pass urine during the main sleep period, with each urination followed by sleep or the intention to sleep, as per the International Continence Society (ICS) 2018 definition.[1] Awakening 2 or more times per night to void may also be considered a clinically relevant definition, according to the International Consultation on Incontinence Research Society 2018 definition.[2] Overproduction of urine at night (greater than 20%-33% of total 24-hour urine volume depending on age)[3] is known as nocturnal polyuria (NP) and has been shown to be a major contributing factor in nocturia cases.[4]

NP can be associated with a variety of medical conditions including congestive heart failure (CHF), diabetes mellitus, obstructive sleep apnea, peripheral edema, and excessive nighttime fluid intake.[5] Overproduction of urine at night may also result from abnormalities in antidiuretic hormone arginine vasopressin (AVP) secretion. NP "syndrome" is defined as NP in the absence of identifiable medical conditions[6] and is thought to be due to impaired circadian release of AVP, which plays a key role in the control of urine production by increasing water absorption and concentration of urine at night.[7]

The quality of life of patients with nocturia can be profoundly impaired through a decline in both mental and physical health, primarily due to sleep interruption.[8] Patients with nocturia also have a higher mortality rate, an increased risk of falls and fractures,[9] and an increased mortality risk with increasing number of voiding episodes at night.[10] Thus, the management of such a bothersome condition is an important issue to patients and a matter of public health concern.[11]

This review focuses on methods for the evaluation, diagnosis, and management of NP, as the main contributing factor to nocturia, based on the multiple causative factors that require assessment. It is one of a series of articles published in this supplement that summarizes the presentations and discussions from a roundtable meeting focused on nocturia and NP.

PREVALENCE OF NOCTURIA AND NP

The prevalence of nocturia and NP reported in studies varies depending on the definition used. In a literature

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review focusing on prevalence, nocturia was seen in a substantial proportion of all populations studied, and across nationalities, and sex and age groups; rates varied based on the different assessment parameters utilized.[12] For example, in the younger population (20-40 years), prevalence rates in men were 11%-35.2% based on ≥1 voids and 2%-16.6% based on ≥2 voids; the rates in women were 20.4%-43.9% based on ≥1 voids, and 4.4%-18% based on ≥2 voids. In the older population (≥70 years), rates in men were 68.9%-93% based on ≥1 voids, and 29%-59.3% based on ≥2 voids; the rates in older women were 74.1%-77.1% based on ≥1 voids, and 28.3%-61.5% based on ≥2 voids.[12] As demonstrated, nocturia increases with age, but younger adults are also affected; with the more clinically meaningful cut-off of ≥2 nightly voids, nocturia occurs in 15%-20% of young adults. Additionally, in clinical practice, it has been reported that up to 1 in 5 or 6 younger adults consistently wake to void at least twice per night.[12] Overall results of a population-based study in Finland showed that approximately 40% of men and women reported 1-2 voids per night. However, based on more detailed age-specific analyses, differences between the sexes emerged and nocturia was more common among young women than young men, but the prevalence of nocturia in men reached that of women in the middle age and exceeded it after the age of 60 years.[13]

In another study of NP prevalence, the proportion of adults with nocturia (≥2 nightly voids) due to NP, defined as nocturnal urine volume (NUV) greater than 33% of 24-hour volume including the first morning void, was investigated in 2 cohorts from the United States and Europe. Patients recorded time and volume of each void for 3-7 days. Based on diary recordings, most patients in the first cohort (76% [641 of 846]) had NP and, similarly in the second cohort, 88% (806 of 917) of patients had NP. It was also shown that, while the prevalence of NP was seen to increase with age, it was high in all age and ethnic groups in both cohorts.[4] Overall, 66%-83% of patients younger than 65 years and 90%-93% of patients ≥65 years had NP. The high prevalence in each cohort and all subgroups further supports the evidence that NP is a leading cause of nocturia in men and women of all ages and across different ethnic groups.[4]

EVALUATION AND CLASSIFICATION OF NOCTURIA AND NP

Typically, patients with nocturia are first evaluated with a thorough history and physical examination focusing on their sleep quality, fluid intake, urinary complaints, cardiac abnormalities, medication timing, prior lower urinary tract surgery, and other comorbidities that could cause increased urine output during night, detrusor overactivity, or bladder sensory dysfunction.[5] Classification of nocturia is based on various applied parameters and definitions that are often derived from voiding diary analyses and are presented in Table 1.

Table 1. Voiding diary parameters and definitions

Parameter	Definition
NUV	Total volume of urine passed during the night, including the first morning void. The last void prior to going to bed is not included
MVV	The largest single voided volume in 24 hours
Ni	Ni = NUV/MVV; when Ni >1, NUV exceeds maximum storage capacity and nocturia occurs. In clinical practice, Ni >1.3 is suggested as a cut-off and in the elderly with nocturnal LUTS the cut-off should be 1.8[14]
NPi	NPi = NUV/(24-hour urine volume); if NPi >0.20−0.33 (age dependent), patient has NP
NUP	NUP = NUV/(#hours asleep); if NUP >90 mL/h, patient has NP

LUTS, lower urinary tract symptoms; MVV, maximum voided volume; Ni, nocturia index; NP, nocturnal polyuria; NPi, nocturnal polyuria index; NUP, nocturnal urine production; NUV, nocturnal urine volume.
Sources: Epstein et al,[45] with information also from Denys.[14]

Patients ≥65 years old with nocturnal lower urinary tract symptoms (LUTS) have shown an important excess in nocturnal diuresis and sodium loss at night as compared with patients without nocturnal LUTS.[14] The nocturia index (Ni) cut-off for validating nocturnal LUTS is much higher in the elderly patients (Ni >1.8).[14]

NP has been defined based on studies showing that the mean NP index (NPi) was 14% in individuals <25 years old and 34% in those over 65 years old.[2] Although NPi >20% in the young and NPi >33% (NPi33) in the old is often considered as a definition of NP in studies and clinical practice, several other definitions exist, including those that are based on absolute definitions with urine production per kg or time unit (NUP >90 mL/h [NUP90], NUP >0.9 mL/min, NUP >6.4 mL/kg).[2]

In a retrospective study reviewing 200 consecutive patients with nocturia,[15] 13 (7%) were diagnosed with NP (in which voided urine volume during the hours of sleep exceeded 35% of the 24-hour output), 111 (57%) with nocturnal detrusor overactivity (NDO; defined as nocturia due to diminished bladder capacity during sleep), and 70 (36%) had a mixed etiology of nocturia (both NP and NDO). Overall, 83 (43%) patients were found with either pure NP or mixed etiology (both NP and NDO); in these patients, NP was at least a component of the etiology of nocturia.

In the Krimpen study,[16] the NPi33 and NUP90 definitions were compared in a 50-78 years old, male population; NP prevalence was 78% according to NPi33 definition, and 15% according to NUP90 definition. NPi33 was seen in 92% of men with at least 2 nightly voids, and in 70% of those without nocturia, suggesting that NPi33 has a limited discriminative value for diagnosing NP as a nocturia cause. NUP90 was shown in 28% of men with nocturia and in 8% of those without nocturia.[2]

NUP90 has been considered a benchmark characterization of NP, as it is based upon absolute diuresis independent of 24-hour urine production[17] and prior studies comparing the definitions of NP with renal function profiles demonstrated a higher specificity for the NUP90 than the NPi >20%-33% according to age (NPi20−33) definition.[18] This has been observed in a population of asymptomatic community-dwelling men with a chief complaint of LUTS and more severe nocturia. The study included review of 285 voiding diaries from 170 patients with a mean age of 69.6 years and a mean number of nocturnal voids of 2.89. The percentage (and number) of voiding diaries in each ordinal nocturia severity category that returned a diagnosis of NP based on NP33, NUP90, and both NP33 and NUP90 are summarized in Table 2.

According to the results, when the rates of diagnosis of NP, as a function of nocturia severity, were compared based on NP33 vs NUP90, NUP90 consistently returned fewer diagnoses of NP than NP33 for the same voiding diaries. However, the more severe the nocturia, the more likely for either definition to return a diagnosis of NP, which demonstrates a convergence in both definitions as a function of nocturia severity. Further studies are needed to clarify the responsiveness of each NP definition to better diagnose NP and determine the best treatment choice.[17]

In efforts to provide further clarity and user-friendly definitions to aid clinical practice and research, the ICS report on the terminology for nocturia and nocturnal lower urinary tract function (2019) suggests that NP be redefined as "excessive production of urine during the individual's main sleep period"; this should be quantified using a bladder diary.[1]

There is continued interest in the accuracy of proposed definitions of NP as a definition should not be too inclusive so that it has a low positive predictive value, or too exclusive (that it omits NP) based on a lack in sensitivity in detecting respective symptoms.[19]

The diagnostic performance of 7 different definitions of NP was investigated in a systematic review.[19] Three of the definitions were based on elderly males only, and the remaining definitions were developed in a mixed population but a small sample size. Applying the definitions to populations other than the original has shown low accuracy. The ICS definition is the most widely evaluated and it has high sensitivity but low specificity as it cannot distinguish subjects with NP from those without NP. Prevalence studies have found many subjects without nocturia to have NP, which is evidence of moderate accuracy and the possibility of having a fair amount of false positive subjects. Overall, diagnostic performance characteristics for the proposed definitions of NP demonstrated poor to modest discrimination and were not based on a sufficient level of evidence from representative, multiethnic, population-based data from females and males of all adult ages.[19]

Table 2. Diagnosis of NP based on NP33, NUP90, and both definitions—voiding diaries were stratified based on nocturia severity represented by the number of nocturnal voids

No. of Nocturnal Voids	Percent (No.) of FVCs With		
	NPi >0.33	NUP >90	NPi >0.33 and NUP >90
1	38 (23)	23 (14)	15 (9)
2	53 (43)	33 (27)	22 (18)
3	71 (51)	46 (33)	39 (28)
4	88 (28)	56 (18)	53 (17)
5	85 (17)	70 (14)	70 (14)
6	90 (9)	90 (9)	80 (8)
7	100 (4)	100 (4)	100 (4)
8+	83 (5)	83 (5)	83 (5)

Reprinted with permission from Cherian J, et al.[17]

Table 3. A lower maximum voided volume is the difference between continuous and fluctuating nocturia

	Fluctuating nocturia	MVV NPi	Continuous nocturia	
Higher NPi Fluid intake ↓	0	=	0	↓ *Lower MVV Higher NPi Fluid intake*
	1	=	1	
	≥2	=	≥2	

MVV, maximum voided volume; NPi, nocturnal polyuria index.
Source: Personal communication, M Denys based on published data.[20]

Another factor in the classification of nocturia is its differentiation between continuous and fluctuating.[20] The NPi is thought to increase with fluid intake in both fluctuating and continuous nocturia, however, the latter pattern is further characterized by a lower maximum voided volume (MVV) (Table 3).

The potential of algorithms to substitute definitions for the diagnosis of nocturia has been explored in a post-hoc analysis of 3 prospective, observational studies.[21] The analysis showed that cut-off values depending on multiple factors could be replaced by statistical models that could possibly render voiding diaries redundant for many patients. The multivariate model that was used consisted of factors including voided volume, 24-hour diuresis, age, and body mass index; however, the model requires confirmation in other databases and ideally in databases that include a therapeutic arm.

MEASUREMENT OF DIURESIS RATE IN PATIENTS WITH NOCTURIA

Nocturnal diuresis rate (DR) has been moderately associated with nocturia severity; however, the degree of association between DR and urge to void varies between individuals. Measuring the DR in patients with nocturia is important as it may identify a cohort of patients with LUTS that would benefit from treatment to reduce the rate of frequency, urgency, and nocturia.[11] The impact of DR, calculated by dividing each voided volume by the time elapsed from the previous void,[11] on the presence of LUTS and the associated bother based on a Likert scale

(0 = no bother; 10 = maximal bother) was recently investigated in healthy volunteers and patients referred for a urologic consultation. Based on the Likert scale, 3 groups were defined: "*bother* ≤*2*" for no/mild bother, "*3*≤ *bother* ≤6" for moderate bother, and "*bother* ≥*7*" for strong bother. Participants with a strong bother related to LUTS showed a significantly higher fluid intake than those without bother (≤2 on the Likert scale; 1640 mL vs 1800 mL during the daytime, $P = .007$). Higher DR was associated with more bother related to LUTS, with an increase in bother by 1 on the Likert scale when diuresis increased by 100 mL/hr.[22]

Additionally, a retrospective study analyzed voiding diaries of men and women with a chief complaint of LUTS in an ambulatory urology clinic to assess the relationship between urinary diuresis rate and the desire to void. Spearman's rank correlation coefficient rho was used to relate DR to urgency perception score (UPS), with a graded response from 0 to 4, where 0 is zero desire to void and 4 is a severe urgency. Correlations of DR, UPS, and nocturia severity were then calculated for both the entire cohort and individual subjects. A total of 202 diaries from 136 unique patients (110 men, 26 women, mean age of 65 years) were analyzed with a mean number of voids of 10.2 per diary.[11] Nocturnal DR correlated with nocturia severity but not with nocturnal UPS. The relationship between DR and UPS was not strong for all subjects: 19% of subjects showed a moderate correlation (Spearman's rho 0.3-0.5) and 17% showed a strong correlation (rho >0.5), indicating that 36% of the subjects demonstrated a relationship between DR and the degree of desire to void.[11]

While nocturnal DR was moderately correlated with nocturia severity, the degree of correlation between DR and UPS varied significantly between individuals.[11] Furthermore, another study in patients with LUTS comparing urgency and nonurgency groups per UPS reported a low correlation between UPS and voided volume suggesting that there are factors other than voided volume that cause the urge to void.[23]

Taken together, these findings suggest that although there is a relationship between voided volume and urgency, it is variable, and urgency may be multifactorial. Approximately one-third of patients experience a relationship between diuresis rate and the perception of the urge to void, which presents a potential substrate for treatment of nocturia in this subset by influencing the rate of urine production. Strategies such as alteration of diuretic choices, intake, timely administration of antidiuretics, and certain antihypertensive medications need investigation as to potential efficacy in such subjects.

DIAGNOSIS AND MANAGEMENT OF NOCTURIA AND NP

Several tools are available to accurately diagnose the underlying causes of nocturia, a process critical to manage this condition effectively. In addition to a thorough medical history and physical examination, and disease-specific questionnaires, a key diagnostic tool to identify patients with nocturia is the frequency-volume chart or voiding/bladder diary, a record of the volume and timing of daytime and nighttime voids for 1-3 days, allowing clinicians to analyze voiding patterns and further investigate the complex etiology of nocturia. Analysis of the patient's voiding diary facilitates diagnosis by identifying the main cause of nocturia from 4 basic categories, as presented in Table 4.

Although the use of the 24-hour voiding diary is standard, it is time consuming and often difficult for patients to record the volume and timing of every void in a 24-hour period. A study at a Veterans Affairs urology clinic examined whether a nocturnal-only voiding diary could provide a suitable alternative to the 24-hour diary in a retrospective review of 285 voiding diaries submitted by men

Table 4. Main categories of nocturia and respective characteristics

Nocturia Category	Main Characteristics	Phenotypes
Low NBC or low global bladder capacity	Characterized by reduced voided volume, indicating a reduced capacity of the bladder to store urine, which may occur exclusively during the hours of sleep or globally	Overactive bladder, bladder outlet obstruction, detrusor underactivity
Global polyuria	Characterized by a 24-hour urine volume of more than 40 mL/kg, representing excessive urine production during the day and night	Diabetes mellitus, diabetes insipidus
NP	Characterized by NUV >20%-30% of total 24-hour urine volume (age dependent)	Loss of circadian rhythm in water diuresis (inborn, aging), cardiovascular diseases (edema, hypertension, heart failure), sleep disorders
Mixed etiology	Comprising combinations of the foregoing criteria	Mainly older age with nocturnal incontinence or extremely invalidating nocturia

NBC, nocturnal bladder capacity; NP, nocturnal polyuria; NUV, nocturnal urine volume.
Sources: Weiss et al,[30] Van Kerrebroeck et al,[3] Oelke et al,[8] Everaert et al.[11]

≥18 years with ≥1 nocturnal voids. Entries were analyzed based on the 24-hour voiding diary, the nocturnal-only diary, and the nocturnal voiding diary plus availability of the 24-hour urine volume. Both types of nocturnal voiding diaries detected all etiologies with high specificity, except for decreased global bladder capacity. Overall, results showed acceptable sensitivity and specificity from the nocturnal voiding diary in comparison with the standard voiding diary. Therefore, a nocturnal-only voiding diary may provide an alternative option for patients with nocturia who have had global polyuria ruled out as a possible etiology.[2]

As per the ICS consensus on the diagnosis and treatment of nocturia, bother and severity of nocturia should be evaluated with a symptom score and, if needed, accompanied by directed questioning. Nocturia-specific questionnaires include the international consultation on incontinence questionnaire-nocturia, the nocturia quality of life questionnaire (N-QoL), and the nocturia impact diary.[24] As nocturia is a symptom of many conditions, it is encountered across various health disciplines. Optimal management of nocturia requires comprehensive evaluation to identify all potential etiologies, including and beyond the lower urinary tract. To this end, a robust screening metric for use in identifying nonlower urinary tract comorbidities in patients with nocturia was developed entitled TANGO, **T**argeting the individual's **A**etiology of **N**octuria to **G**uide **O**utcomes.[25]

The TANGO Short Form (TANGO SF) consists of 22 statements across 4 domains: (1) the Cardio/Metabolic domain, referring to disorders that contribute to 24-hour polyuria and NP; (2) the Sleep domain, assessing quality of sleep, quantifying the initial sleep period before first awakening to void, identifying causes for waking in the night apart from nocturia and likely sleep disordered breathing; (3) the Urinary tract domain, detecting LUTS of clinical relevance to nocturia; and (4) the Wellbeing domain, including poor health, the occurrence of falls, excessive daytime sleepiness, and loss of enthusiasm.[11,25] As an assessment tool for nocturia, TANGO can be used in combination with a 24-hour and nocturnal voiding diary to improve assessment and subsequent treatment of patients with nocturia.[25]

The multifactorial nature of nocturia involves several causative factors or etiologic "packages" including urological, nephrological, hormonal, sleep, cardiovascular, and intake that require multidisciplinary assessment as described below and illustrated in Figure 1.[11]

Urological factors that may lead to nocturia require assessment of the function of the lower urinary tract, including the bladder, prostate, and urethra, which are anatomically involved in the micturition process.[11]

Nephrological evaluation should assess the patient's renal function profile[11,26] as nocturia can be the result of nephrogenic diabetes insipidus, hypercalciuria, or polyuria due to renal disease.[11]

Changes in sex hormone levels in menopausal women and during andropause in men must also be considered due to the impact of hormone changes on sodium excretion/reabsorption via the renin-angiotensin-aldosterone system as well as water excretion via the antidiuretic hormone AVP.[11]

Patients with sleep apnea should be identified since they present with impaired blood pressure dipping and nighttime natriuresis associated with an increased plasma level of atrial natriuretic peptide. Sleep disorders can be diagnosed clinically or through validated questionnaires including the Berlin sleep questionnaire, the Pittsburgh Sleep Quality Index, and the Epworth Sleepiness Scale. Diagnosis can be confirmed by polysomnography and actigraphy.[11]

Nocturia can also be associated with increases in diuresis following an increase in volume of the central vascular system (increase in end-diastolic/systolic volume or pressure including elevated blood pressure during the night), CHF, and lower limb venous insufficiency; therefore, assessment and diagnosis of these conditions are important.[11]

Assessment of food intake, including fluid and salt, and of conditions such as diabetes and obesity, which also increase diuresis rate or even alter the circadian rhythm of urine production, is required. Intake diaries and renal function profiles can be used to estimate dietary intake.[11,26]

Other factors that have been considered in the causation of nocturia and NP are an abnormality in nocturnal secretion or action of AVP, which describes classical NP syndrome, any edema-forming state (in addition to CHF, chronic renal disease, nephrotic syndrome, hypoalbuminemia, and liver failure), and comorbidities such as autonomic nervous system dysfunction, Alzheimer's disease, multisystem atrophy, stroke, and Parkinsonism.[27] Most importantly, how NP is defined vs other causes of nocturia should affect how it is treated.

As diagnosis and management of patients with nocturia is burdensome for both the physician and the patient, there is potential value in the development of data collection systems that pose less burden on patients, to enhance compliance and yield validated measurements. Wearable devices could be used for the collection and subsequent analysis of key data including micturition frequency and volume, sodium intake, blood pressure, and sleep patterns.

TREATMENT OF NOCTURIA AND NP

Nocturia and NP may improve via lifestyle and behavior modifications, which should be implemented initially and prior to pharmacotherapy. Potentially beneficial lifestyle modifications include minimization of fluid intake at least 2-hour before going to bed (particularly caffeine and alcohol), restriction of total fluid consumption to <2 L/day, emptying the bladder before going to bed, barrier-free access to a toilet or toilet chair, increasing exercise and fitness levels (including pelvic floor exercises, if indicated), reducing dietary salt intake, and weight loss for overweight patients. In addition, for patients with peripheral edema (lower extremities) due to CHF or chronic venous insufficiency, elevating the legs above heart level

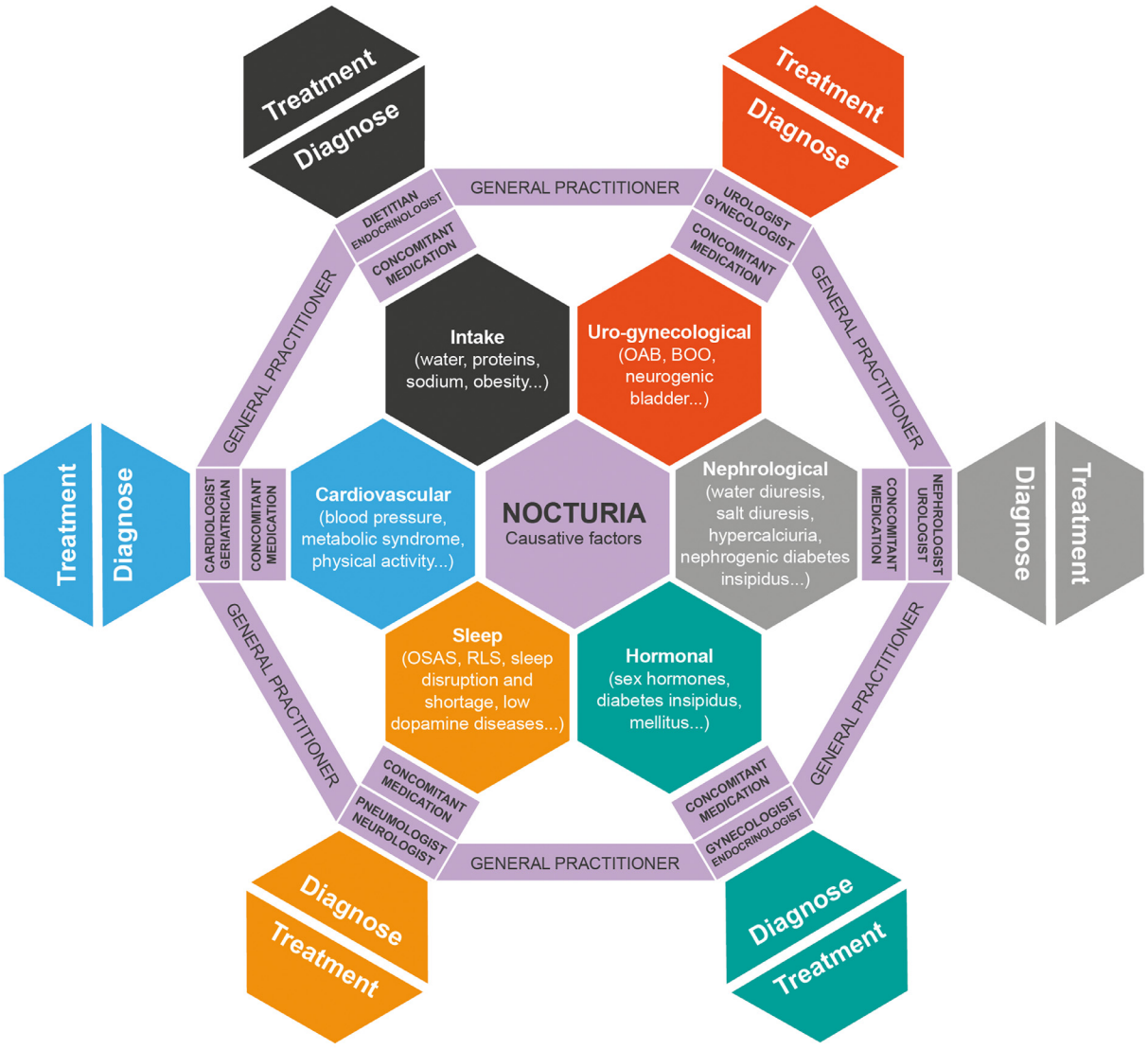

Figure 1. Diagnostic and therapeutic 'packages' of nocturia. BOO, bladder outlet obstruction; OAB, overactive bladder; OSAS, obstructive sleep apnea syndrome; RLS, restless leg syndrome. Adapted with permission from Everaert et al.[24]

for a few hours before going to bed could be of benefit. For those on diuretics, these could be taken midafternoon rather than prior to retiring, considering the half-life of the specific diuretic.[8]

As nocturia progresses and lifestyle changes may not bring desirable results, medical intervention is typically considered. The ideal treatment regimen must treat the underlying cause(s) and, accordingly, interventions should improve bladder emptying, thus improving nocturnal bladder storage capacity, and/or increase the volume at which bladder activity is elicited, and/or decrease urine production at night.[28] Medical interventions, including antimuscarinic agents and α-blockers used for the treatment of overactive bladder and benign prostatic hyperplasia, respectively, have often been used for nocturia as initial pharmacotherapy and have shown statistically significant reductions in the number of nocturnal voids (ranges 0.16-0.2 for antimuscarinics vs placebo and 0.1-0.3 for α-blockers vs placebo). However, these results may not be clinically relevant,[29] because of the reductions of only half of a void, or even less, per night.[28] Studies of antimuscarinics have shown that these agents are beneficial to patients with severe nocturnal urgency, but not necessarily to those with NP.[30] Statistically significant results in reducing nocturnal voids with α-blockers or combination therapy with α-blockers and 5α-reductase inhibitors have been demonstrated, where the authors subjectively designated a 50% reduction in nocturia as being a meaningful benefit. However, this only represented a 17% greater improvement in reducing nocturnal voids for the α-blocker over placebo.[30] Similarly, other pharmacologic therapies used for treating nocturia, including β_3-adrenoceptor agonists (mirabegron) for overactive bladder, and phosphodiesterase type 5 inhibitors and plant extracts for male LUTS/bladder outlet obstruction, have been shown to reduce

nocturnal voiding frequency to a limited clinical effect of −0.2 episodes per night on average (vs placebo).[8] Therefore, it is imperative to identify the underlying cause(s) of patients presenting with nocturia and manage accordingly.

For patients who have NP, treatment with an antidiuretic, desmopressin acetate, is warranted to address insufficient secretion of nocturnal AVP.[24] Desmopressin acetate, a synthetic analog of AVP, is a selective vasopressin receptor 2 (V_2) agonist that induces antidiuresis and has been shown to be effective and well-tolerated in adults with nocturia associated with NP. Desmopressin mimics the action of AVP, decreasing urine production and increasing urine osmolality.[29,31-33] Desmopressin has been used for more than 30 years for conditions including diabetes insipidus and primary nocturnal enuresis. Certain formulations have been approved in Europe for symptomatic treatment of nocturia due to idiopathic NP in adults,[34] and 2 formulations have been approved in the US for the treatment of nocturia due to NP in adults who awaken at least 2 times per night to void.[35,36]

Several studies support the use of desmopressin in nocturia associated with NP. In a meta-analysis by Cornu et al evaluating the efficacy and safety of desmopressin for the treatment of nocturia,[37] 5 studies were included based on a systematic review of English-language articles, published after 2000 through April 2012, with results of randomized controlled trials having nocturia as the primary endpoint.[37] The desmopressin formulations used in these studies included orally disintegrating tablets (ODTs) (melt formulation) 10, 25, 50, and 100 μg, and tablets 0.1 and 0.4 mg.[37] Results showed that desmopressin was superior to placebo as it reduced the overall number of nocturnal voids.[37] Overall, these results were in line with previous meta-analysis results reported by others and supported the recommendations for use of desmopressin in the treatment of NP in adults.[37]

Two formulations of desmopressin that were recently approved for the treatment of nocturia due to NP, a low-dose intranasal spray and an ODT, have been shown to be efficacious with an acceptable safety profile. The low-dose desmopressin intranasal spray formulation was evaluated in a pooled analysis of 2 studies (NCT01357356, NCT01900704), comparing 1.66 or 0.83 μg desmopressin vs placebo in 1333 patients of ≥50 years with 2.16 or more voids per night.[33] Coprimary endpoints were the mean change from baseline in nocturnal voids per night and the percentage of patients with a 50% or greater reduction in mean nocturnal voids per night. A significant reduction from baseline in mean nocturnal voids per night was seen at both doses vs placebo (−1.4 with 0.83 μg, and −1.5 with 1.66 μg, vs −1.2 with placebo, each dose P <.0001). A 50% or greater reduction in mean nocturnal voids per night was achieved by a significantly higher percentage of patients for the 1.66 μg dose vs placebo (48.7% vs 30.3%, P <.0001) and the 0.83 μg dose vs placebo (37.9% vs 30.3%, P = .0159). Furthermore, both doses resulted in a significant increase, vs placebo, in time from bedtime to the first nocturnal void, and in a significant decrease of NUV values. The higher (1.66 μg) dose corresponded with statistically significant improvements vs placebo in patients' QoL.[33]

In clinical trials (NCT00477490 and NCT00615836) of the desmopressin ODT (fast-dissolving melt formulation) comparing 10, 25, 50, or 100 μg desmopressin vs placebo in a broad age range of adults (≥18 years of age; 757 patients [416 men and 341 women]) with nocturia (≥2 voids per night), 2 coprimary endpoints were included: change in mean number of nocturnal voids from baseline, and proportion of patients with >33% reduction in mean number of nocturnal voids from baseline, both at 4 weeks of treatment. Desmopressin was associated with a dose-dependent decrease in numbers of nocturnal voids and voided volume, greater proportions of subjects with >33% reduction in nocturnal voids, and increased duration of first uninterrupted sleep period (FUSP).[31] At Day 28, significant mean decreases in the number of nocturnal voids were shown in the overall population with the 50 μg and 100 μg doses vs placebo (-1.18, P = .02, and -1.43, P <.0001, respectively). A post-hoc analysis indicated that females were more sensitive to desmopressin than males.[31]

To further establish dose recommendations in adults (≥18 years of age) with nocturia (≥2 voids per night), parallel 3-month randomized, placebo-controlled studies were conducted in 385 men (NCT01262456) to test the safety and efficacy of 50 μg and 75 μg ODT[38] and 261 women (NCT01223937) to confirm the safety and efficacy of 25 μg desmopressin ODT.[39] The 2 coprimary efficacy endpoints were change in mean number of nocturnal voids from baseline, and proportion of patients with at least a 33% reduction in mean number of nocturnal voids from baseline (33% responders) during a 3-month treatment period.[38,39]

In men, desmopressin in 50 μg and 75 μg doses, significantly decreased the number of nocturnal voids (−0.37, P <.0001 and −0.41, P = .0003, respectively) and increased the odds of a 33% or greater response (OR 1.98, P = .0009 and OR 2.04, P = .0004, respectively) vs placebo. Desmopressin 50 μg and 75 μg also increased the time to first nocturnal void from baseline by approximately 40 minutes compared with placebo (P = .006 and P = .003, respectively).[38] In women, desmopressin 25 μg significantly reduced the mean number of nocturnal voids (−0.22, P = .028) and increased the odds of a 33% or greater response (OR 1.85, P = .006) compared with placebo. Desmopressin also increased the mean time to first nocturnal void by 49 minutes compared with placebo (P = .003).[39]

Furthermore, treatment improvements were associated with QoL improvements in the studies reported above.[31,33,38,39] Results for the ODT formulation showed that 1 less nocturnal void was associated with an increase of 4.68 in the total N-QoL score (5.03 for bother/concern, 4.25 for sleep/energy; P <.05). An 1-hour increase in FUSP was related to an increase of 3.68 in total N-QoL score (4.05 for bother/concern score, 3.27 for sleep/energy;

P <.05).[31] For the intranasal spray, QoL, as measured by the nocturia-specific Impact of Nighttime Urination QoL questionnaire scores, showed significant improvements with 1.66 μg vs placebo in the overall impact score (−14.1 vs −11.5; P = .0255) and the nighttime domain score (−18.0 vs −14.5; P = .0118).[33] Taken together, these results show that improvements in nocturia may significantly improve QoL.[31,33] In an observational survey assessing the impact of nocturia on HR-QoL,[40] deterioration of HR-QoL was associated with increasing number of nightly voids, with significant differences between 0-1 and ≥2 voids (P <.001). Thus, a clear effect was seen at 2 voids per night, suggesting nocturia should be reduced below the bother threshold of 2 voids per night. Overall, from a safety perspective, cumulative patient exposure with desmopressin tablet and orally disintegrating sublingual tablet/melt formulations is estimated to have surpassed 25 million patients in 101 countries.[29] In the studies described above, adverse events related to the use of desmopressin (ODT formulation) included nausea, diarrhea, dizziness, blood sodium decreased, and hyponatremia.[31] Adverse events reported for the intranasal spray formulation included nasal-related events (nasal discomfort, nasopharyngitis), hypertension, and hyponatremia.[33] The safety data from the clinical studies described above showed desmopressin to have an acceptable safety profile and supported previous findings that hyponatremia is the main safety finding with this agent.[31,33,38,39] Hyponatremia has been reported in pediatric and adult patients treated with different desmopressin formulations (such as intranasal spray, oral tablet, and the orally disintegrating tablet/melt formulation) for enuresis or nocturia.[29,31-33,41,42] Hyponatremia has been seen mainly in older populations with earlier formulations of desmopressin (0.2 mg tablets).[24] Pooled data from 3 multicenter studies demonstrated a low incidence of clinically relevant hyponatremia with desmopressin; however, the risk of hyponatremia was seen to increase with increasing age and decreasing baseline serum sodium concentration.[43] Other risk factors for desmopressin-induced hyponatremia include baseline renal dysfunction, small body mass, and female sex. Therefore, the product information includes a black box warning for hyponatremia as desmopressin is contraindicated in patients with hyponatremia (eg, those with baseline serum concentrations below the normal range of 135 mmol/L). For those eligible for treatment, careful monitoring of serum sodium concentration is necessary first, prior to initiating treatment, then within 7 days and at 1 month after initiating/resuming treatment, and after a dose increment, and periodically (every 6 months) thereafter. In patients ≥65 years old, more frequent serum sodium monitoring is recommended.[35,36]

Sex differences to desmopressin treatment have shown that the minimum effective dose was lower for women than for men. In the ODT study described above, the minimum effective dose was 100 μg in men and 25 μg in women.[31] While no distinction was made between sex in reductions of internal voids, in the study with the intranasal spray formulation, the low, 0.83 μg, dose was associated with a statistically significant reduction from baseline in mean nocturnal voids vs placebo in both men and women.[33] In a post-hoc analysis, the relative male/female sensitivity to the antidiuretic effect of desmopressin (fast-dissolving melt formulation) in nocturia was 2.7, corresponding to a significantly higher desmopressin sensitivity in women than men.[44] This result supports lower, sex-specific dosing to reduce the risk of hyponatremia without compromising efficacy.[29,44]

Differential dosing between men and women may improve effectiveness and minimize sodium fluctuations.[29] A lower dose exerting an antidiuretic effect of 6-8 hours can be used for the older (especially female) population, in combination with serum sodium monitoring that is individualized based on patient-specific factors (age, concomitant medication) and comorbidities.[24]

OUTCOMES OF TREATMENT

Treating nocturia leads to reductions in voids as demonstrated by subsequent reductions in various diary-based parameters and improvements in nocturia. This has been observed in a retrospective analysis of 24-hour bladder diaries demonstrating reductions in NUV, Ni, NPi, nocturnal bladder capacity (NBC) index, NUP, and the number of voids in 24-hour in patients whose nocturia improved, whereas increases in the same parameters occurred in patients who did not respond to treatment. Nocturia improvement was not associated with changes in overall bladder capacity, as there was no difference in MVV in either group. However, there was considerable improvement in NBC in the improved group, as shown by a 72% decrease in NBC index compared with a 180% increase in the nonimproved group, suggesting that NBC as opposed to overall bladder capacity is a potential target for improving outcomes of nocturia treatment.[18]

Additionally, the association between voiding parameters and improvement in nocturia severity was shown in a retrospective study of 414 voiding diaries in a cohort of 105 men (treated with a variety of behavioral, pharmacologic [antimuscarinic, 5α-reductase inhibitor, α-blocker], and surgical treatments), where improvement in nocturia was accompanied by both reduced day and nighttime urine production. A decreased 24-hour volume (−310 mL vs +120 mL) and NUV (−290 mL vs +170 mL) was observed in the improved vs the nonimproved cohort and, at follow-up, in those who improved, a significant decline in the actual number of nightly voids (−1.8 vs +1.0) was seen. Also, FUSP increased significantly in the improved cohort (+1.8 hour) and decreased (−0.6 hour) in the nonimproved cohort, suggesting a potential for nocturia therapies to ameliorate impaired sleep architecture. Improvement in nocturia was further associated with a decrease in both 24-hour voided volume and NUV, but not MVV, suggesting that improved patients consumed less fluid and verifying the difficulty in increasing low

bladder capacity with any approach. A significantly decreased NBC index in the improved cohort (−0.99 vs +0.44 in nonimproved cohort) indicated that, irrespective of bladder capacity, a tendency to void at night at volumes *closer to* bladder capacity will yield diminished nocturia severity.[45] It may be suggested that patients who improved the most were those with a more severe nocturia at baseline compared with those who did not improve. Further studies are needed to investigate the degree of nocturia or NP that may potentially predict the degree of responsiveness to treatment.

CONCLUSION AND FUTURE LINES OF INVESTIGATION

Nocturia is a highly prevalent, bothersome medical condition that affects men and women of all ages. Nocturia is an important public health issue due to its profound impact on quality of life, work productivity, risk of falls and fractures, and mortality primarily due to sleep interruption. Appropriate assessment and diagnosis is imperative for treatment success, and the use of voiding diaries, along with comprehensive patient evaluation, is crucial to accurately identify the cause(s) of nocturia and thereby tailor an optimal management approach.[8] NP, the major causative factor of nocturia, presents in most patients with nocturia, and can be effectively managed with desmopressin if accurately diagnosed.

Further research is required to elucidate all the underlying mechanisms that lead to NP to achieve an accurate diagnosis, thus, leading to the right choice of treatment(s). Additionally, there is an increasing need for data collection systems that pose less burden on patients, thus, improving compliance. Rather than therapeutic approaches compartmentalized by specialty, the impact of patient-oriented treatment "packages" based on causative factors needs to be evaluated. Further research is necessary to improve the level of evidence for the already tested treatments and standardized quality of life outcome measures that need to be implemented to better evaluate existing treatment methods.[11]

A multidisciplinary approach is essential for the management of NP and this requires promotion of partnership between specialties with a focus on the development of more patient-specific therapy.

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