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PHARMACOTHERAPIES AND DRUG DEVELOPMENT/AGENTS (ES ROVNER, SECTION EDITOR)

Nocturia: Evaluation and Management

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Abstract

Purpose of Review Nocturia, defined as waking to pass urine during the main sleep period, is among the most common and bothersome lower urinary tract symptoms. In this review, the current literature as it pertains to the etiology, evaluation, and management of nocturia is addressed.

Recent Findings Over the past decade, there has been increased interest in nocturia as a specific lower urinary tract symptom, with efforts made to improve understanding of underlying mechanisms and consequences. Several publications now classify nocturia according to underlying cause (such as nocturnal polyuria), in that what was a previously overlooked and understudied topic, emerges as a distinct urinary complaint carrying significant morbidity. Multiple randomized controlled trials demonstrate effective medical and surgical therapy and provide the basis for modern guidelines.

Summary Nocturia is a highly prevalent symptom associated with reduced quality of life, morbidity, and mortality. Proper evaluation including analysis of a frequency-volume chart, will determine treatment options based on underlying etiology including nocturnal polyuria, global polyuria, and reduced bladder capacity. Desmopressin is shown to be an effective treatment for nocturnal polyuria. Evidence supporting other treatment options including surgical intervention, α-blockers, and antimuscarinics remains limited. Further research is needed to integrate and emphasize the importance of a proper evaluation of nocturia and its subsequent management for use in modern guidelines.

Keywords Nocturia · Nocturnal polyuria · Frequency-volume chart · Nocturia management · Nocturia treatment · Desmopressin

Introduction

Nocturia, defined as waking to pass urine during the main sleep period, is among the most common and bothersome lower urinary tract symptom (LUTS) in the general population [1]. Nocturia occurs owing to an abnormality of the genitourinary tract, an underlying medical condition, use of certain medications, or by insomnia and behaviors that adversely impact proper sleep. The etiology is multifactorial and may be attributable to a broad range of urologic and systemic comorbidities, medication use, and modifiable behaviors. Therefore, identifying the etiology of a person's nocturia and selecting an appropriate treatment are challenging both diagnostically and therapeutically. Management of nocturia requires a systematic approach. A thorough history and physical examination is essential to assess for other LUTS, to uncover contributing medical conditions or behaviors that may be neurologic, cardiac, pulmonary, or psychiatric in nature, to assess current medications, and should also include a basic evaluation for sleep including quality and duration. A frequency-volume chart (FVC) will aid in the identification of a specific underlying mechanism. There is an array of therapeutic options including behavioral modification, pharmacotherapy, and invasive procedures, which when chosen appropriately and combined with an accurate diagnosis will lead to effective clinical treatment and improved quality of life.

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Consequences of Nocturia and Rationale for Management

Nocturia is associated with poor quality of life secondary to associated degree of bother, as well as increased morbidity and mortality secondary to reduced sleep quality. The current definition of nocturia does not take into consideration a person's degree of bother. While previously deemed not clinically significant unless a patient voids two or more times per night, one void meets the widely accepted International Continence Society's (ICS) definition of nocturia [1]. A person may be significantly bothered from a single void during the main sleep period, while another person who voids many times may report little bother. Quality of life is strongly linked to a person's degree of bother. In a large population-based study of 5502 men and women aged 30–79 years, nocturia was associated with increased prevalence of depressive symptoms and decreased quality of life in both men and women [2••]. Compared with those with low bother, patients reporting high levels of nocturia-specific bother were found to have more difficulty initiating sleep, returning to sleep, and experienced greater morning fatigue.

Multiple studies have linked nocturia to early mortality. In the Third National Health and Nutrition Examination Survey (NHANES III), a US-based sample of 15,988 men and women aged 20 years or older, nocturia was a strong predictor of mortality. The association was stronger in younger men and women than in the elderly, with a dose-response pattern linking increased mortality risk with increasing number of voiding episodes nightly [3]. A 5-year observational study of 784 elderly men in Japan reported higher risk of both fractures and death in those with nocturia than those without. When controlling for confounding variables such as diabetes, smoking, coronary artery disease, renal disease, stroke, use of tranquilizers, hypnotics, and diuretics, the positive relationship was unchanged [4].

Nocturia is an important predictor of poor sleep in the elderly population and is often overlooked [5]. The impact of nocturia on survival is thought to be secondary to sleep impairment, specifically through a reduction of slow-wave sleep [6]. Slow-wave sleep is the restorative deep stage sleep, which predominates earlier during the night. The first episode of nocturia occurs on average during the first 3 hours of sleep, often interrupting slow-wave sleep. Shorter time to the first nighttime void is associated with lower sleep quality, shorter sleep duration, poorer sleep efficiency, and greater daytime dysfunction [7]. When slow-wave sleep is interrupted, both glucose tolerance and insulin sensitivity are impaired [8]. Therefore, aging individuals with impaired slow-wave sleep are at higher risk for developing metabolic syndrome. In a cross-sectional community-based cohort of 1214 participants, sleep duration less than 6 h was observed as a component of metabolic syndrome [9].

In the elderly, self-reported insomnia is strongly associated with nocturia [2••, 3]. Sleep is vital for physical and mental well-being and 7 to 8 h is generally accepted as necessary for restorative effect. Interrupted or insufficient sleep has been strongly linked to numerous physical and mental health disorders including major depression, mood alterations, and poor job performance [10, 11].

Epidemiology and Risk Factors

Nocturia is exceptionally common and affects men and women of all ages and ethnicity across the world. A review of 43 pertinent articles demonstrates a prevalence rate of one or more voids in 11–35% of young men (20–40 years) and two or more voids in 2–17%. In elderly men (> 70 years), rates of one or more voids were 69–93% and two or more voids were 29–59%. In young women, prevalence rates of one or more voids are 20–44% and two or more voids 4–18%. In elderly women, the rates of one or more voids were 74–77% and two or more voids 28–62%. Overall, one in every five or six young people wakes two or more times to void, and three in every five people older than 70 years voids two or more times nightly [12••].

A population-based study including 4427 men and women reported a prevalence of 47% at baseline and 50.3% 1 year later [13]. Nocturia incidence was 20% and remission was 15.4%. Epidemiologic studies of nocturia are limited by how the data is acquired. In a longitudinal, community-based study among 1688 men aged 50–78 years, nocturia as a component of the International Prostate Symptom Score (IPSS) overestimated the percentage with nocturia three times or more compared with recordings on voiding diaries in younger men less than 60 years. Meanwhile, in elderly men, IPSS underestimates true nighttime voids [14].

The most important risk factor for nocturia in men and women in population-based studies is age [6]. The prevalence of nocturia also increases with age [12••]. Because of a perceived correlation of nocturia with increasing age, nocturia is often viewed as a natural part of aging, and patients are less likely to either report nocturia or seek help. Risk factors also include gender, with prevalence rates in younger people greater among women and older people greater among men [12••]. Nocturia is also more common in people of African descent; however, several confounding variables including associated medical comorbidities may influence this relationship [7]. Nocturia is also linked to obesity, metabolic syndrome, hypertension, toxic habits, reproductive history in women, testosterone deficiency, and low vitamin D levels [12••, 15–21].

Evaluation

The wealth of evidence demonstrating the severe potential sequelae of nocturia provides a basis for consideration of thorough clinical assessment of nocturia at the time lower urinary tract systems is divulged by patients. The evaluation of nocturia should be systematic, beginning with a complete history and physical. A validated questionnaire such as the IPSS should be utilized to assess for other LUTS. Initial assessment of nocturia is often limited to the patient's self-reported or estimated number of nighttime voids noted during a clinical history or as part of the IPSS. Degree of bother specific to nocturia should be elucidated. The patient's medication history should be reviewed exhaustively. Evaluation should assess for associated medical comorbidities; pertinent medical history may include peripheral edema, congestive heart failure, peripheral vascular disease or venous stasis, hepatic failure, nephrotic syndrome, urolithiasis, malnutrition, diabetes mellitus, diabetes insipidus, obstructive sleep apnea, and chronic obstructive pulmonary disease. Associated neurologic comorbidities may include prior cerebrovascular accident (CVA), spinal cord injury, multiple sclerosis, Parkinson disease, or neurogenic bladder. Contributing behaviors should be identified such as the patient's overall and evening fluid intake as well as alcohol or caffeine consumption. A basic evaluation of sleep should also be performed, with special note to the patient's bedtime, duration, and quality of sleep. Both psychiatric and sleep disorders such as depression, anxiety, insomnia, narcolepsy, and excessive snoring are important to rule out as they may contribute directly to nocturia without an observed abnormality on a frequency-voiding chart. Pertinent physical findings may include peripheral edema suggestive of cardiac, vascular, or renal disease, enlarged prostate on digital rectal exam suggestive of benign prostatic hyperplasia, or obesity and short neck suggestive of obstructive sleep apnea (OSA).

The 24-h frequency-voiding chart (FVC) is the cornerstone of nocturia evaluation [22]. The FVC is more accurate than patient self-reporting on the IPSS and is the basis for identifying a specific nocturia subclassification for focused treatment [23]. The FVC demonstrates the true actual number of nightly voids (ANV) on a given night, while questionnaires typically involve recall of the symptom over a period of several weeks. The sum of all nocturnally voided volumes plus the volume of the first morning void is the nocturnal urine volume (NUV). The maximum voided volume (MVV) is the largest voided volume during a 24-h period. Nocturia occurs when NUV exceeds MVV and is characterized in an FVC analysis by nocturia index (Ni). Ni is calculated as NUV divided by MVV. When the Ni is greater than 1, nocturia must occur if the patient awakens, and if not, enuresis will occur. A FVC will aid in identifying a specific etiology of nocturia, which can be divided into distinct categories: (1) nocturnal polyuria (NP); (2) reduced bladder capacity (functional or extrinsic); and (3) 24-h or global polyuria (Table 1).

Nocturnal polyuria is characterized by an increased nocturnal urine output, counterbalanced by lower daytime urine production, such that 24-h urine volume remains normal. It is defined as a nocturnal polyuria index (NPi) greater than 20% in young adults and greater than 33% in patients older than 65 years when 24-h urine production is within normal limits [24]. NPi is calculated as NUV divided by total 24-h urine volume. Other proposed definitions for NP include nocturnal urine production greater than 90 ml/h, NUV greater than 6.4 ml/kg or nocturnal urine output > 0.9 ml/min [25, 26].

Reduced bladder capacity results from either a global decrease in bladder capacity, expressed as a low MVV, or as a decrease in nocturnal bladder capacity. Nocturia will occur when NUV exceeds nocturnal bladder capacity and the patient awakens to void. This relationship is expressed by the nocturnal bladder capacity index (NBCi), which corresponds to the ANV minus the predicted number of voids (PNV). The PNV is obtained by subtracting 1 from Ni. When NBCi is greater than 0, voids at night occur below the MVV; the higher the NBCi, the more nocturia is due to nocturnal voiding at volumes lower than MVV [27].

Global polyuria causes both nocturia and daytime urinary frequency and is defined as 24-h urine output in excess of 40 ml/kg [28]. When combined with a focused history and physical examination, the FVC will lead to a more accurate diagnosis of global polyuria, NP, reduced bladder capacity, and associated medical conditions. The FVC therefore is a key component facilitating appropriate clinical management of nocturia.

Management of Nocturnal Polyuria

Nocturnal polyuria is present in most patients with nocturia regardless of age, gender, ethnicity, or country of origin. It is one of the most frequent causes of nocturia in adults, especially the elderly, given its prevalence increases with age. The pathophysiology of NP stems from multiple possible factors including disruption in the arginine vasopressin (AVP) system, excess production of atrial natriuretic peptide in patients with OSA or congestive heart failure, nighttime mobilization and subsequent diuresis of daytime-acquired peripheral edema, behaviors such as excessive nighttime fluid intake, or medication side effects [29].

Treatment of nocturnal polyuria begins with a conservative approach including behavioral and lifestyle modification. There is limited data to support the efficacy of conservative management; however, suggested recommendations are at low risk and may result in clinical improvement. Oral hydration should be ceased at least 4 h prior to the patient's self-reported bedtime. Patients with peripheral edema of the

Table 1 Frequency-volume chart derived nocturia diagnosis with associated medical conditions

Frequency-volume chart–derived nocturia diagnosis	Associated medical conditions
Nocturnal polyuria	Behavioral (too much intake)
	Leg edema
	Obstructive sleep apnea syndrome
	Glycosuria
	Cardiac dysfunction
Low global or nocturnal bladder capacity	Ureteral stones
	Bladder stones
	Pharmaceuticals
	Pelvic floor dysfunction
	Lower urinary tract cancer
	Neurogenic bladder
	Nocturnal detrusor overactivity
	Urethral obstruction
Global polyuria	Diabetes mellitus
	Primary polydipsia
	Diabetes insipidus

bilateral lower extremities should be offered compression stockings. Optimizing sleep hygiene is an important part of patient counseling, and individuals suffering from insomnia may benefit in terms of a reduction in nocturia episodes from behavioral therapy directed solely at insomnia [30].

Nocturia is influenced by a number of medications that are often prescribed for common medical conditions. Drugs that globally increase urine output include diuretics, selective serotonin reuptake inhibitors (SSRIs), calcium channel blockers, tetracyclines, and lithium. SSRIs block AVP secretion [31]. Calcium channel blockers increase ANP and inhibit sodium reuptake in the proximal tubule of the nephron [32]. Tetracyclines inhibit sodium reuptake and attenuate AVP [33], while lithium downregulates aquaporin channel expression in the renal medullary collecting duct [34]. Medications with central nervous system effects may contribute to insomnia; these include CNS stimulants such as dextroamphetamine or methylphenidate, antihypertensives such as α-blockers or β-blockers, and hormones such as corticosteroids or levothyroxine. Timing of these medications is important for limiting nocturnal urine output. In a randomized, double-blind, placebo-controlled trial of an afternoon dose of the diuretic furosemide taken 6 h before bedtime, there was a significant reduction of both nocturia episodes and percentage of nighttime voided volume [35]. Patients on diuretics should therefore be advised to take short-acting diuretics 6 h prior to their reported bedtime.

Patients with associated medical comorbidities such as OSA, hypertension, diabetes mellitus, congestive heart failure, or nephrotic syndrome should be referred to appropriate providers for optimal treatment. Treatment of OSA with continuous positive airway pressure (CPAP) is strongly associated with an improvement in nocturia. In a prospective study of 88 men with OSA, nocturia episodes were significantly reduced after treatment with CPAP [36]. These findings were also observed in women [37]. The link between hypertension and nocturia is currently an area of significant research. A recent cross-sectional study in black men aged 35–49 years old found uncontrolled hypertension to be an independent determinant of nocturia [38•]. Men with untreated hypertension were 39% more likely than men with normotension to report nocturia ($P = 0.02$), whereas men whose hypertension was treated and controlled were no more likely than normotensive men to report nocturia ($P = 0.69$). In normotensives, blood pressure dips during sleep; however, blunting of nocturnal blood pressure dipping among hypertensives results in "pressure-natriuresis" and consequently increased nocturnal urine output. This process is known as non-dipping hypertension [39, 40].

In the absence of identifiable contributory comorbidities, adverse effects from medications, or modifiable behaviors, increased nocturnal diuresis is thought to be due to dysfunction in the arginine vasopressin system (AVP) [24]. When AVP concentration is low, the renal collecting duct is less permeable to water due to a reduction in stimulation of V_2-receptors on the basolateral membrane of the renal tubular cell. V_2-receptors are responsible for intercalation of aquaporin channels into the apical membrane of the renal tubules, resulting in passive water reabsorption. AVP inhibition therefore leads to a larger volume of urine produced (Fig. 1). In healthy adults, the amount of circulating AVP is increased at night, leading to a physiologic decrease in nocturnal urine production [40]. In some elderly patients, this normal diurnal rhythm of plasma AVP concentration is blunted, leading to

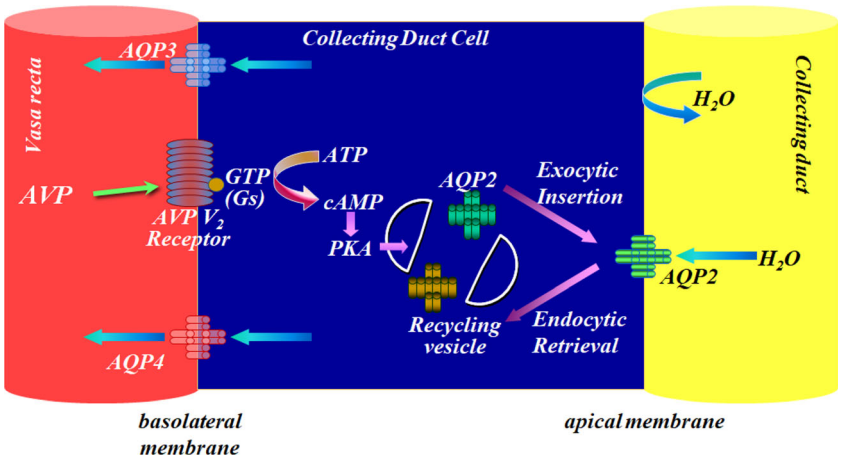

Fig. 1 Arginine vasopressin regulation of water reabsorption from renal tubular cells

increased nocturnal diuresis, and therefore, nocturia episodes [41]. Factors that may increase AVP inhibition include increased atrial natriuretic peptide (ANP) and prostaglandin E-2, hypercalemia, hypokalemia, lithium, and tetracyclines.

Desmopressin (DDAVP), a synthetic form of vasopressin with selective activity for the V_2-receptor but lacking its unwanted pressor activity at the V_1 receptor, has been demonstrated in multiple clinical trials to be a safe and effective treatment for nocturia. It is currently the only pharmaceutical treatment for nocturia with Grade A (level 1 evidence) recommendations from the ICS [42] and Grade A (level 1b evidence) recommendations from the European Association of Urology (EAU) [43].

DDAVP comes in multiple dosage forms, including tablets, orally disintegrating preparations or "melts," and most recently, nasal spray. In a prospective, randomized, double-blinded clinical trial of 757 patients with nocturia (90% of whom had nocturnal polyuria), the efficacy of 10, 25, 50, or 100 μg of DDAVP melt was compared with placebo. Increasing doses of desmopressin were associated with decreasing numbers of nocturnal voids and voided volume, greater proportions of subjects with > 33% reduction in nocturnal voids, and increased duration of first sleep period. Improvements were clinically significant, meaning that patients had fewer nightly voids [44••]. In both men at a moderate dose (50 μg) and women at a low dose (25 μg) DDAVP melt, the rate of increasing the first uninterrupted sleep period to 4 h or longer was significantly greater than placebo at 1 week and after months 1, 2, and 3 ($P < 0.0001$) [45]. Additional studies have concluded that 50 μg of desmopressin melt may be the lowest therapeutically beneficial dose for men. In a 3-month, randomized, double-blind study of 385 men, 50 μg and 75 μg DDAVP were compared with placebo. The 50- and 75-μg doses significantly reduced the number of nocturnal voids (− 0.37, $P < 0.0001$ and − 0.41, $P = 0.0003$, respectively) and increased the odds of a 33% or greater response (OR 1.98, $P = 0.0009$ and OR 2.04, $P = 0.0004$, respectively) compared with placebo during the 3-month period. Desmopressin 50 and 75 μg increased the time to first void from baseline by approximately 40 min compared with placebo ($P = 0.006$ and $P = 0.003$, respectively). The response to desmopressin was seen by 1 week of treatment and was sustained. Significant increases in health-related quality of life and sleep quality were observed compared with placebo [46].

DDAVP in nasal spray formulation has been utilized for treatment of diabetes insipidus, primary nocturnal enuresis, hemophilia A, and von Willebrand disease. While efficacy of DDAVP is well documented, hyponatremia is a well-known adverse effect and is of the most concern. A novel permeation-enhancing nasal formulation of desmopressin acetate designed to reduce risk of hyponatremia was approved by the Food and Drug Administration in 2017 for treatment of patients with nocturnal polyuria. A low dose (0.83 μg) and a high dose (1.66 μg) of DDAVP nasal sprays were tested in two 12-week, randomized, placebo-controlled clinical trials of 1333 patients 50 years of age and older with nocturic voids greater than 2 per night. Nadir serum sodium levels were studied and it was found that 0.2% of patients receiving placebo, 0% of patients receiving the low dose, and 1.1% of patients receiving the high dose developed hyponatremia (as defined by a serum sodium of 126–129 mmol/l with symptoms, or a serum sodium of < 126 mmol/l with or without symptoms). Efficacy at high dose and low dose showed statistically significant reduction in mean nocturic episodes over placebo (− 1.4 with 0.83 μg and − 1.5 with 1.66 μg versus − 1.2 with placebo; $P < 0.0001$). 48.7%, 37.9%, and 30.3% of patients had a 50% or greater reduction in mean nocturic episodes per night with the 1.66-μg dose, 0.83-μg dose, and placebo respectively. Results also corresponded to quality of life measures, showing statistically significant improvements in the high-dose group over placebo [47•].

Desmopressin is usually well tolerated but is associated with more adverse events than placebo. In studies of high-dose desmopressin tablets, 4.9% of all patients developed hyponatremia (defined as serum sodium < 130 mmol/l). Risk of hyponatremia increases with age, lower serum sodium

concentration at baseline, and higher baseline global urine production. Age was the single best predictor, with hyponatremia most frequent in patients over 65 years of age [48]. Similar results are seen in desmopressin melt prospective trials; in those treated with moderate dose (50 μg), 0% had serum sodium from 126 to 129 mmol/l, and 2% had serum sodium less than 125 mmol/L. In those treated with high dose (75 μg), 4% had serum sodium from 126 to 129 mmol/L, and 3% had serum sodium less than 125 mmol/L [46]. Most cases are not symptomatic, and assessment of serum sodium at 3–7 days after starting therapy is recommended in modern guidelines [49]. It is advisable to monitor the serum sodium 4 weeks after initial or incremental dosing, then continuing to check sodium levels every 6 months or more often as clinically indicated. In patients with nocturia related to nocturnal polyuria (especially that which is unassociated with demonstrable causes such as peripheral edema or heart failure), current literature supports desmopressin as the most appropriate therapy.

Management of Reduced Global and Nocturnal Bladder Capacity

Diminished bladder capacity may be secondary to chronic bladder outlet obstruction (BOO), detrusor overactivity, neurogenic bladder, cystitis, or lower genitourinary tract malignancy. Low bladder compliance is a risk factor for nocturia severity [50]. Other causes include behavioral or learned voiding dysfunction, anxiety, lower urinary tract calculi, and caffeine.

Nocturia secondary to reduced bladder capacity may be improved by treatment of bladder outlet obstruction. By lowering post-void residual bladder volume (PVR), functional bladder capacity is increased, and therefore, global urinary frequency is reduced. Treating BOO also attenuates input from bladder neck and prostatic urethral afferents [51]. In a study of 505 men with nocturia, tamsulosin therapy and transurethral resection of the prostate (TURP) significantly reduced the number of episodes of nocturia in 17.9% and 32.2% of patients, respectively [52]. Simple prostatectomy significantly reduces nocturia episodes, hours of uninterrupted sleep, and increases nocturia-specific quality of life [53]. Despite these findings, NHANES III showed that in patients who undergo TURP, nocturia as defined by 2 voids or more per night, persists for 41% of men aged 60–69 years, and 50% of men greater than the age of 70 years [54].

In a secondary analysis of the Veteran Affairs Cooperative Study Program Trial in which 1229 men with BPH aged 48–80 years were randomly assigned to receive terazosin, finasteride, combination therapy, or placebo, episodes of nocturia decreased from a baseline mean of 2.5 to 1.8, 2.1, 2.0, and 2.1 episodes in the terazosin, finasteride, combination, and placebo groups, respectively. Mean reduction of nocturia episodes from treatment with terazosin alone was significantly different from that with treatment with combination therapy ($P = 0.03$), finasteride ($P = 0.0001$), and placebo ($P = 0.0001$). Terazosin and combination therapy reduced the number of nocturia episodes in men with BPH, although the advantage of terazosin over placebo was only a net reduction of 0.3 episodes [55]. In a prospective, randomized controlled trial of 2583 men with nocturia followed over 4 years, doxazosin and combination therapy of doxazosin plus finasteride reduced nocturia episodes more than placebo ($P < 0.05$). The net benefit of medical therapy compared with placebo in this study was small, with a difference of less than 0.20 fewer nightly nocturia episodes at 1 and 4 years. This study confirmed that α-blockers alone are as effective as α-blockers in combination with 5α-reductase inhibitors (5-ARIs) for treatment of nocturia [56].

Antimuscarinics are often used in the treatment of lower urinary tract symptoms, including nocturia. Most of the studies on antimuscarinics were conducted in the context of management of overactive bladder (OAB). There are limited randomized controlled trials focusing on nocturia as a primary endpoint. In one 12-week randomized controlled trial, 850 men and women were given 4 mg tolterodine extended release (Tolt ER) or placebo once daily prior to bed. All subjects had 8 or more micturitions per 24-h with or without urge incontinence and nocturia (mean of 2.5 episodes per night) as evaluated by FVC. While tolterodine was associated with reduced OAB-specific symptoms, the difference between the two groups for nocturnal frequency was not statistically significant. Tolterodine did not affect non-OAB nocturnal micturitions, suggesting that antimuscarinic therapy may benefit nocturic voids that are characterized by severe urgency [57].

In clinical trials of fesoterodine for treatment of OAB, fesoterodine significantly improved all FVC parameters compared with placebo except for nocturnal voids and nocturnal urgency episodes [58–60]. However, in a study of the efficacy of fesoterodine on nocturnal urgency as a primary endpoint, the number of nocturnal urgency episodes and the number of nocturnal voids was decreased when compared with placebo. The mean reduction from baseline to week 12 in nocturnal urgency episodes per 24 h was statistically significantly greater with fesoterodine than placebo (− 1.29 vs. − 1.06, $P = 0.0030$). Mean reduction from baseline to week 12 in nocturnal micturitions per 24-h was significantly greater with fesoterodine than placebo (− 1.02 vs. − 0.84, $P = 0.0112$) [61].

In summary, bladder outlet procedures such as TURP and simple prostatectomy, α-blockers, 5-ARIs, and antimuscarinics have been found to have a statistically significant reduction in nocturia episodes, but clinical significance appears to be minimal. The optimal patients to treat with medications that target the bladder and the prostate appear to be those who have documented bladder outlet obstruction or severe nocturnal urgency.

Management of Global Polyuria

A global overproduction of urine in excess of bladder capacity leads to urinary frequency both day and night. Polyuria is normally associated with polydipsia once a steady state of urine production is reached; however, it may be associated with medical comorbidities such as diabetes mellitus and diabetes insipidus. Nocturia will manifest as a symptom of patients with polyuria of any cause. Treatment of polyuria should focus on underlying mechanism. If polyuria is suspected, an overnight water deprivation test (OWDT) should be performed. A normal OWDT means the cause is primary polydipsia, and fluid restriction would be first line treatment. If the OWDT is abnormal, the patient has diabetes insipidus. To distinguish central from nephrogenic diabetes insipidus, a renal concentrating capacity test (RCCT) may be performed by administering a dose of desmopressin and checking to see if urine osmolality increases beyond 800 mOsm/kg 4–6 h later. If the RCCT is normal, the patient has central diabetes insipidus and can be treated with desmopressin replacement therapy. If the RCCT is abnormal, the patient has nephrogenic diabetes insipidus, which has no specific treatment unless extrinsic causative factors such as lithium can be stopped [62].

Patients who have a 24-h urine production greater than 30 ml/kg may benefit from water restriction during the day and night. A small study showed that adjusting water and food intake so that 24-h urine production is less than 30 ml/kg reduced nocturnal urine volume and nocturnal urinary frequency with no adverse events [63]. This illustrates that guidance on water intake may be a safe and effective conservative lifestyle management strategy. A patient with primary (dipsogenic or psychogenic) polydipsia will have normal urine osmolality on water deprivation tests. Dipsogenic polydipsia is associated with a history of a central neurologic abnormality such as a history of brain trauma or radiation. Psychogenic polydipsia is a long-term behavioral or psychiatric disorder. It is important to identify the cause of a patient's polyuria to treat it effectively. For example, if a patient with polyuria has diabetes mellitus, controlling glycosuria may improve the polyuria. Central diabetes insipidus may be treated with synthetic vasopressin analogs. Patients without diabetes insipidus who are found to have polydipsia and are compulsive water drinkers may benefit from psychotherapy [62]. Nocturia as a manifesting complaint is expected to benefit from appropriate therapy for polyuria.

Conclusion

Nocturia is a highly prevalent and morbid symptom with identifiable underlying pathophysiologic mechanisms that have been thoroughly described in the literature. A focused history and clinical assessment in addition to frequency-volume chart analysis to identify nocturia etiology is suggested in all modern guidelines. Treatment options are determined by etiology, including nocturnal polyuria, global polyuria, reduced bladder capacity, or a combination of these. Desmopressin is an effective treatment for nocturia secondary to nocturnal polyuria. Evidence supporting alternative treatment options remains limited; however, conservative management, medical therapy with alpha blockers, antimuscarinics, and 5-alpha reductase inhibitors, or surgical outlet procedures may be considered.

Compliance with Ethical Standards

Conflict of Interest Dr. Curran J. Emeruwa and Danielle J. Gordon declare that they have no conflicts of interest. Dr. Jeffrey P. Weiss is a consultant for Ferring Pharmascience and the Institute for Bladder and Prostate Research.

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

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- • Of importance
- •• Of major importance

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