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LOWER URINARY TRACT SYMPTOMS & VOIDING DYSFUNCTION (J SANDHU, SECTION EDITOR)

Management Strategies for Nocturia

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Abstract

Purpose of Review Nocturia is defined as awakening due to the desire to void during a period of intended sleep. The pathophysiology of nocturia is multifactorial and management remains a challenge. Herein, we provide an overview of the management strategies for nocturia and summarize the existing evidence for treatment of nocturia across the condition's broad etiologic categories: nocturnal polyuria, diminished bladder capacity, and global polyuria.

Recent Findings Treatment should begin with behavioral modification. A high level of evidence supports the efficacy of desmopressin in the treatment of nocturnal polyuria. Data supporting the efficacy of α-blockers, antimuscarinics, and surgical bladder outlet procedures in the treatment of nocturia remains limited.

Summary Treatment options for nocturia are determined by underlying mechanism. Desmopressin is effective in treating nocturnal polyuria. Surgical intervention, α-blockers, and antimuscarinics may improve nocturia when associated with lower urinary tract symptoms or overactive bladder in the setting of diminished bladder capacity.

Keywords Nocturia · Nocturnal polyuria · Diminished bladder capacity · Global polyuria · Nocturia management · Nocturia treatment

Introduction

Nocturia, defined as awakening due to the desire to void during a period of intended sleep, is a multifactorial, highly prevalent, and morbid condition that has proven to be a therapeutic challenge for many experts in the field of urology. One in every five to six people between the age of 20 and 40 and up to three in every five people over the age of 70 wake from sleep to void at least two times nightly [1]. The condition has tremendous individual and societal costs. Nocturia is highly associated with decreased quality of life and has been linked to early mortality [2]. This is thought to be due to sleep impairment, including reduced sleep duration, which has been linked to the development of metabolic syndrome [3, 4]. Furthermore, nocturia is often a symptom of underlying comorbid conditions including hypertension, diabetes mellitus, heart disease, kidney disease, and obstructive sleep apnea [5, 6]. The societal costs are substantial, with an estimated $61 billion productivity loss attributable to nocturia in 2008 [7].

The cause of nocturia is often multifactorial; however, distinct pathophysiological mechanisms have been delineated which may be identified after a thorough clinical examination and voiding diary analysis (Table 1). These include (1) global polyuria or an overall increase in urine production, (2) nocturnal polyuria or an increase in urine production only at night, (3) diminished bladder capacity, and (4) primary or secondary sleep disorders. The etiology of nocturia frequently does not occur in isolation, and patients often present with many medical comorbidities, complicating both diagnosis and therapeutic management.

Treatment of nocturia is dependent upon underlying mechanism, which first needs to be delineated with a thorough clinical assessment and analysis of a voiding diary. Management strategies may include lifestyle and behavioral modification, treatment and optimization of contributory medical comorbidities, medical therapy, or surgical intervention. The latest evidence supporting management strategies for

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Table 1 Diary-derived nocturia diagnosis with associated medical conditions

Diary-derived nocturia diagnosis	Associated medical conditions
Nocturnal urine overproduction	Behavioral (too much intake) Leg edema Obstructive sleep apnea syndrome Glycosuria Cardiac dysfunction
Low 24-h or nocturnal bladder capacity	Ureteral stones Bladder stones Pharmaceuticals Pelvic floor dysfunction Lower urinary tract cancer Neurogenic bladder Nocturnal detrusor overactivity Urethral obstruction
Polyuria	Diabetes mellitus Primary polydipsia Diabetes insipidus

nocturnal polyuria, diminished bladder capacity, and global polyuria will be discussed. As management options continue to evolve, a consensus on the most effective and safe management techniques based on underlying mechanism will aid in developing improved treatment algorithms.

Treatment of Nocturnal Polyuria

Nocturnal polyuria is defined as increased production of urine at night and a 24-h urine production within normal limits [8]. On voiding diary analysis, nocturnal urine volume exceeds 20% of 24-h urine volume in younger patients, or 33% of 24-h urine volume in people aged over 65 years [9]. An alternative definition of nocturnal polyuria is a nocturnal urine production greater than 90 ml/h [10]. Nocturnal polyuria is one of the most common causes of nocturia in adults and is caused by a blunting in production of arginine vasopressin, excess production of atrial natriuretic peptide, peripheral edema, increased nighttime fluid intake, and as an adverse effect of certain medications such as diuretics [3].

Conservative management including behavioral and lifestyle modification should be considered first-line treatment of nocturnal polyuria, although to date there are no randomized controlled trials supporting its efficacy. Behavioral modifications include evening fluid restriction, compression stockings for patients with peripheral edema, optimizing sleep hygiene, adjustment of hypertension medications to the mid-afternoon, and elimination of medications that can contribute to nocturnal polyuria [3]. Diuretics, selective serotonin reuptake inhibitors, calcium channel blockers, lithium, and tetracyclines are examples of medications that increase urine output and may contribute to nocturnal polyuria [11–15]. It is recommended to administer diuretics in the mid-afternoon, thus allowing for elimination of fluids prior to sleep [3]. Treating patients with nocturnal polyuria with diuretics 6 h prior to sleep has been proven to reduce nocturia episodes and nighttime voided volume [16].

Comorbid conditions including peripheral edema, obstructive sleep apnea (OSA), diabetes mellitus, congestive heart failure, and hypertension are important causes of nocturnal polyuria and should not be overlooked when considering therapeutic management of nocturia. OSA is an especially important medical condition, for which treatment with continuous positive airway pressure (CPAP) has been proven to improve nocturnal polyuria. Nocturnal polyuria secondary to OSA is caused by increases in atrial natriuretic peptide due to increased right atrial pressures, which in turn results in increased sodium and water excretion. A significant decrease in the number of nightly voids has been attributable to treatment of OSA with CPAP [17].

Hypertension (HTN) has also been linked to nocturnal polyuria. A recent cross-sectional study conducted amongst black men aged 35–49 years old found uncontrolled hypertension to be an independent determinant of nocturia [18••]. Blunting of nocturnal blood pressure dipping amongst hypertensives often results in "pressure natriuresis" with increased urine output during hours of sleep; this is known as non-dipping hypertension [19]. This cross-sectional study importantly found that men with treated but uncontrolled HTN had an adjusted odds ratio for nocturia greater than that of men with normal blood pressure and men with untreated hypertension, likely secondary to medication side effects [18••]. Episodes of nocturia were significantly lower amongst patients with well-controlled blood pressure on antihypertensive therapy. Further studies into the relationship between HTN and nocturnal polyuria are ongoing.

Desmopressin may be considered in all cases of nocturnal polyuria. As an antidiuretic and synthetic analogue of vasopressin, it has been used in the treatment of nocturnal polyuria by increasing water permeability and reabsorption within the renal collecting duct. A significant amount of high-level evidence supports the efficacy and safety of desmopressin over placebo in the treatment of nocturia. Desmopressin may be administered as intranasal spray, oral tablets, or orally disintegrating tablets (melt). Studies of desmopressin tablets have found a reduction in nocturnal voids compared with baseline (48–58% for men and 55–59% for women) and increases in initial sleep period by 2 h [20, 21]. More recent studies have examined the efficacy of a desmopressin melt and found that increasing doses were associated with greater proportions of patients with more than 33% reduction in nocturnal voids [22]. Furthermore, men prescribed 50 μg and women prescribed 25 μg had significantly increased odds of having a period of first uninterrupted sleep $\geq$ 4 h compared with placebo [23, 24]. A meta-analysis of desmopressin for

treatment of nocturia shows a significant increase in quality of life and overall supports the use of desmopressin for the treatment of nocturnal polyuria in adults [25••]. Adverse effects most frequently described include hyponatremia, headache, hypertension, edema, nausea, and abdominal pain. Most cases of hyponatremia are asymptomatic; however, close monitoring of serum sodium levels after initiation of desmopressin therapy is recommended. Administration of 50 μg of desmopressin melt for males and 25 μg for females has significantly reduced the number of nightly voids (− 0.37 difference in reduction of nightly voids amongst males and − 0.22 amongst females versus placebo) without significant drops in sodium levels [23, 24]. This reflects the increased sensitivity to desmopressin amongst women in terms of decreasing nocturnal production of urine and to the duration of action of the medication [26, 27].

Alternative medical therapy may be considered for cases of nocturnal polyuria refractory to conservative management or for patients who are not candidates for desmopressin. These medications include α-blockers, antimuscarinics, and imipramine. Limited data support the use of these medications, as nocturia is rarely used as a primary endpoint in studies of these drug classes. The vast majority of studies have been conducted in the context of benign prostatic hyperplasia, lower urinary tract symptoms, and overactive bladder management, with nocturia being assessed as a part of an International Prostate Symptom Score (IPSS) or similar questionnaire.

Imipramine has been proven to improve nocturnal polyuria in children due to the antimuscarinic effect and modulation of antidiuretic hormone secretion [28]. However, the side effect profile of imipramine is significant, with EKG changes (QTc prolongation) as well as reports of torsades de pointes and sudden death [29, 30]. Efficacy of antimuscarinics in the treatment of nocturnal polyuria is still under question. Four pooled 3-month phase III RCTs found no significant decrease in episodes of nocturia amongst patients with nocturnal polyuria administered solifenacin, an antimuscarinic [31]. A single randomized controlled trial compares an α-blockers with placebo with nocturia as a primary outcome. This study found no statistical difference in the decrease in number of nocturnal voids for tamsulosin (1.1) compared with placebo (0.7) [32]. The use of α-blockers and antimuscarinics will be further discussed in the section below.

Diminished Global and Nocturnal Bladder Capacity

Nocturia occurs when the nocturnal urine volume exceeds the nocturnal bladder capacity. Diminished bladder capacity may be secondary to a wide variety of causes including infravesicular obstruction or bladder outlet obstruction (including benign prostatic hyperplasia); detrusor overactivity; cystitis (bacterial, interstitial, tuberculosis, radiation); neurogenic bladder; malignancy of the urethra, bladder, or prostate; learned voiding dysfunction; psychological disorders; calculi of the bladder or ureter; and certain medications (xanthines, beta-blockers) [3]. Management of nocturia secondary to diminished global and nocturnal bladder capacity is dependent on the underlying etiology. A rational strategy for the treatment of nocturia in patients with low bladder capacity includes the various options discussed above for treatment of nocturnal polyuria, that is, to decrease nocturnal urine output to better align output with functional bladder capacity [33]. Again, conservative measures should be considered first-line.

Elevated post-void residual urine volume and reduced detrusor contractility are frequently seen with bladder outlet obstruction (BOO) and can be treated surgically or medically. The treatment of BOO improves nocturia via multiple mechanisms including decreasing post-void residual volume, urinary frequency, and stimulation of afferent nerves in the bladder neck and prostatic urethra, while also increasing functional capacity of the bladder [34–36]. When symptoms are secondary to BOO, both tamsulosin and transurethral resection of the prostate (TURP) have been shown to decrease nocturia episodes in 17.9% and 32.2% of patients, respectively [37]. Furthermore, simple prostatectomy significantly decreased the average number of nocturia episodes by 0.8 and significantly increased hours of uninterrupted sleep by 0.91 postoperatively [35]. A retrospective analysis of treatments for BPH including watchful waiting, alpha-blockers, TURP, and transurethral microwave treatment (TUMT) found a reduction in episodes of nocturia by 7%, 17%, 75%, and 32%, respectively [38]. Improvement in hours of uninterrupted sleep was noted in patients treated with both tamsulosin and TURP, with neither treatment proving to be more efficacious than the other in this measure [39].

Medical therapy plays a key role in the treatment of nocturia secondary to decreased bladder capacity, as lower urinary tract symptoms and overactive bladder often coincide. One study conducted amongst men with BPH comparing the efficacy of terazosin, finasteride, combination, or placebo found the greatest reduction in nocturia episode amongst men administered terazosin only. However, the net reduction in nocturia episodes amongst men administered terazosin was only 0.3 episodes compared with placebo [40]. Consistent throughout the literature, α-blockers are associated with only minor clinical improvements in nocturia [41].

Additional studies were conducted on the efficacy of tolterodine, trospium chloride, and fesoterodine, all of which are antimuscarinic agents, in the management of nocturia. One randomized control study found that while 4 mg of tolterodine extended-release did not significantly reduce the number of nocturia episodes, it did have a significant effect on reducing nocturia episodes related to overactive bladder [42]. This suggests that nocturia related to detrusor overactivity can be

therapeutically managed with antimuscarinics. A randomized controlled trial of trospium chloride 20 mg bid found a decrease in the number of episodes of nocturia of 0.57 versus 0.29 for placebo. While there are some contrasting studies about whether fesoterodine decreases nocturnal voids, a recent study did find a significant reduction in both nocturnal urgency episodes (− 1.29 in the fesoterodine group vs. − 1.06 in the placebo group, $p = 0.0030$) and in nocturnal voids (− 1.02 in the fesoterodine group vs. − 0.84 in the placebo group, $p = 0.0112$) [43].

Several studies have been conducted to evaluate the effectiveness of certain drug combinations with different mechanisms of action in the treatment of nocturia. A study was conducted to compare the efficacy of treatment with doxazosin, finasteride, combination therapy (doxazosin and finasteride), or placebo. After 1 year of treatment, there were significant reductions in nocturia episodes amongst the groups treated with doxazosin alone and combination therapy (doxazosin and finasteride). This study importantly found that the treatment of nocturia with alpha-blockers alone, such as doxazosin (reduction of nocturia episodes of 0.54 vs. 0.35 in the placebo group) was just as effective as treatment with a combination of an alpha-blocker and 5α-reductase inhibitors such as doxazosin and finasteride (reduction of 0.58 vs.0.35 in the placebo group) [44]. This important finding emphasizes that combining multiple medications is not always the most therapeutically beneficial option, especially amongst older patients in whom polypharmacy can be especially detrimental. In another study, the combination of tolterodine and tamsulosin did significantly reduce the number of nightly voids [45]. In general, medical management with α-blockers, 5α-reductase inhibitors, and antimuscarinics has been proven to statistically decrease nightly nocturia episodes. However, statistical significance is not always representative of clinical improvement. Overall, these studies highlight a minor clinical improvement in nocturia episodes.

It is also important to discuss alternative treatments that have been studied for nocturia. One study found that amongst patients taking Pygeum africanum, there was a reduction of 19% in nocturia episodes compared with placebo. However, this was not statistically significant ($p > 0.05$) [46]. Cernilton, a phytotherapy prepared from *Secale cereale*, was also studied and found to significantly improve nocturia compared with placebo (RR = 2.05; 95% CI, 1.41–3.00) [47]. However, it is important to note that these studies involving alternative therapies have significant quality limitations compared with other studies presented above.

Mixed Nocturnal Polyuria and Diminished Global and Nocturnal Bladder Capacity

As discussed above, many cases of nocturia are multifactorial and thus cannot be attributed to one clear underlying etiology. This makes the management of nocturia especially challenging. One review found that amongst 194 patients with nocturia, 36% had a "mixed" cause of their nocturia (thus, their symptoms could not be attributed to only nocturnal polyuria or decreased bladder capacity) [48]. In these cases, a combination of behavioral modification and medical management may be effective. As addressed above, lifestyle adjustments include reducing nighttime fluid and caffeine intake, improved sleep techniques, leg elevation, and compression stockings. Combining these behavioral modifications with medical management with terazosin for BPH symptoms, tolterodine for ≥ 8 nightly voids and zaleplon for extended episodes of awakening after voiding (≥ 30 min) proved to be efficacious for nocturia management [49]. Another study found that behavioral treatment (pelvic floor muscle training, delayed voiding, urge suppression) yielded greater improvement in nocturia compared with treatment with antimuscarinics amongst patients already on α-blockers [50]. Thus, while cases with mixed underlying etiologies may be difficult to manage, treatment should be initiated with lifestyle modification given the proven efficacy and low side effect profile of these techniques. Then, medical management should be added and titrated as necessary.

Global Polyuria

Polyuria, defined as a 24-h urine output ≥ 40 mL/kg, can be attributed to various medical conditions including uncontrolled diabetes mellitus, diabetes insipidus (central or nephrogenic), and primary polydipsia. Management of polyuria is largely dependent upon the underlying etiology. Polyuria secondary to osmotic diuresis caused by poorly controlled diabetes mellitus can be best managed by optimizing anti-diabetic medication regimens. Treatment of primary polydipsia can improve with water restriction and in the case of psychogenic polydipsia, referral for a psychiatric evaluation. One study found that by reducing food and water intake so that 24-h urine production < 30 mL/kg, there was a significant improvement in nocturnal urine volume and urinary frequency [51]. Central diabetes insipidus, caused by a deficiency in antidiuretic hormone, can improve with administration of synesthetic vasopressin analogues, such as desmopressin.

Conclusion

Nocturia is a morbid condition with significant impact both in terms of prevalence and effects on quality of life. The management strategies of the condition are dependent upon the underlying mechanism, which can be delineated with a thorough clinical assessment and voiding diary analysis. Behavioral modification should be considered as first-line

treatment. Comorbid conditions associated with nocturia should be treated and optimized. Desmopressin is effective in the treatment of nocturia due to nocturnal polyuria. Evidence supporting medical or surgical therapy for the treatment of nocturia secondary to nocturnal polyuria or diminished bladder capacity is limited and reveals mild clinical significance at best. Further research is necessary to reach a consensus in both diagnostic and treatment algorithms for nocturia based on the underlying mechanisms.

Compliance with Ethical Standards

Conflict of Interest Danielle J. Gordon, Curran Emeruwa, and Jeffrey P. Weiss each declares 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.

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