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Review Article

Nocturia, nocturnal polyuria, and nocturnal enuresis in adults: What we know and what we do not know

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Abstract

Nocturia is defined as the nocturnal frequency of one or more voiding episodes per night. It increases with aging and has an impact on sleep quality and the risks of falling and mortality. Nocturia disorder involves nighttime frequency, nocturnal polyuria, and nocturnal enuresis. In older adults with nocturia disorder, multiple factors could contribute to nocturia severity and characteristics, including poor sleep quality, lower urinary tract dysfunction, and excessive fluid output. Several nonurological medical diseases have been found to result in nocturia, such as hypertension, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, metabolic syndrome, and diabetes. Urological and medical assessments should be performed to diagnose nocturia disorder. A frequency volume chart to evaluate the nocturnal polyuria index, functional bladder capacity, and urodynamic study can reveal the presence of nocturnal polyuria and lower urinary tract dysfunction. Treatment should be based on multiple nocturia etiologies, and a combination of multiple therapies for individual pathophysiology will achieve a better treatment outcome.

Keywords: *Bladder outlet obstruction, Lower urinary tract dysfunction, Nocturnal incontinence, Urinary frequency*

Introduction

Lower urinary tract symptoms (LUTS) are bothersome in older people. Among the LUTS, the prevalence of nocturia is not higher than that of hesitancy, intermittency, and incomplete emptying; however, the percentage of patients who perceive it as more than just a problem is as high as 70% [1]. Nocturia is defined as frequent wakening to void for one or more times [1,2]. The prevalence of nocturia is high in men and women and increases with aging with much higher rates in those aged >60 years [3], and nocturia significantly affects the quality of life (QoL) and even increases mortality [4,5].

Epidemiological studies have revealed that nocturia is positively associated with depressive syndrome [6]. Patients with metabolic syndrome and smoking may have persistent nocturia after transurethral resection of the prostate [7]. The improvement of nocturia episodes in the International Prostate Symptom Score (IPSS) has been found to have a maximal influence on the change in the QoL score in patients with LUTS [8]. A community health survey in Boston also revealed that nocturia is significantly associated with increased bothersome and depressive symptoms and QoL [9]. This article reviews recent evidence on the pathophysiology and treatment of nocturia, nocturnal polyuria, and nocturnal enuresis in adults.

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Clinical characteristics of nocturia

Clinical characteristics of nocturia include nocturnal frequency of two or more episodes per night, which is found in 49.4% of patients with LUTS, including 32.9% with one episode and 16.5% with two or more episodes [10]; nocturnal polyuria and nocturnal urinary incontinence [11]; global polyuria with day and night polyuria of >40 mL/kg/24 h [12]; and decreased global or nocturnal bladder capacity [13]. Poor sleep quality is also involved in the nocturia pathophysiology. Nocturnal polyuria is defined as having a nocturnal urine output of >90 mL/h or a nocturnal polyuria index (NPI) of >33% of daily urine [11]. Using a frequency volume chart to record daytime and nighttime urinary frequency and voided volume is a pivotal tool in the clinical assessment of nocturia, nocturnal polyuria, and reduced bladder capacity and helps detect urological and nonurological etiologies [2].

The pathophysiology underlying nocturia is multifactorial [14]. Any systemic disease or lower urinary tract dysfunction affecting

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urothelial cell function, receptor sensitivity, circadian rhythm, chronic inflammation, or oxidative stress can cause nocturia [15]. Therefore, the possible nocturia pathophysiology includes detrusor overactivity, bladder hypersensitivity, bladder outlet obstruction (BOO), nocturnal polyuria, small bladder capacity and contracted bladder, anxiety and depression, sleep disorder and insomnia, and medical diseases such as diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease (CKD).

Nocturia in the geriatric population

The prevalence of nocturia increases with age, with a prevalence of >50% in patients aged 80 years [1,4]. Nocturia is also the most common cause of disturbed sleep patterns in older people [16]. Due to sleeping time deprivation, older patients with nocturia are likely to experience fatigue and are exposed to serious health risks [17]. Traumatic injury due to falling also increases in elderly patients with nocturia [18]. Patients with overactive bladder syndrome (OAB) usually strongly desire to void at daytime or during sleep [19]. Patients with OAB due to idiopathic etiology, BOO, central nervous system diseases, or systemic diseases affecting the bladder are often bothered by nocturia with or without nocturnal polyuria. OAB is also positively associated with circadian syndrome in adults in the USA [20]. Medical or minimally invasive treatment for OAB can also effectively decrease nocturia episodes [21].

Pathophysiology associated with nocturia

Benign prostatic hyperplasia and nocturia

Benign prostatic hyperplasia (BPH) should be first considered in older male patients with LUTS and nocturia; thus, they were prescribed alpha blockers to relieve BOO. Patients with BPH with storage symptoms posttreatment with alpha blockers could have improved LUTS after adding on OAB medication or desmopressin [22]. However, the improvement of nocturia episodes in men treated for 2 years was only significant in men aged <80 years, and 62% of patients treated with alpha blockers and 5-alpha-reductase inhibitors still had nocturia more than twice [23]. This result further implies that nocturia in elderly men is caused by several factors other than BPH or BOO. The common causes of nocturia unrelated to BOO include nocturnal polyuria, idiopathic detrusor overactivity, reduced bladder capacity, or bladder hypersensitivity with aging [15]. In patients with unimproved nocturia after a combined alpha-blocker and antimuscarinic therapy for clinical BPH, detailed examinations for persistent BOO, nocturnal polyuria, neurogenic OAB, or inflammatory bladder dysfunction should be performed to identify the etiologies and provide appropriate treatment [24].

Hypertension and nocturia

Hypertension is highly prevalent in older people. The association between nocturia and hypertension has been widely reported but poorly characterized [25]. Nocturia has been reported in various systemic diseases, including diabetes, cardiovascular disease, and hypertension. Elevated blood pressure was strongly associated with nocturia as determined by both voiding diary and self-report, with renal hyperperfusion as the main mechanism [26]. The Nagahama study revealed that nocturia may represent a potential risk for circadian bladder pressure abnormality, with a slight nocturnal blood pressure drop in participants with nocturia [27]. Nocturia may be a marker for cardiovascular disease risks. Frequent nocturnal urination was independently associated with arterial stiffness measured by the brachial-to-ankle pulse wave velocity in older men [28]. Inadequate reduction of nocturnal blood pressure has been associated with nocturnal polyuria in men [29]. Silodosin has been reported as an effective treatment for male LUTS, including nocturia, in men with clinical BPH, possibly related to a reduction of nocturnal blood pressure [30].

Cardiovascular, kidney, and pulmonary diseases and nocturia

In addition to hypertension, heart disease, especially congestive heart failure (CHF), is closely associated with nocturia, typically nocturnal polyuria [31]. The atrial natriuretic peptide levels were elevated in patients with CHF and nocturnal polyuria. Patients with nocturia and high plasma levels of atrial natriuretic peptide might have subclinical heart failure and should be referred for cardiologic treatment [32]. CKD is also a risk factor for developing nocturnal polyuria through the osmotic diuresis mechanism. Reduced renal function could impair salt and water homeostasis, causing nocturnal polyuria and hence nocturia in patients with CKD [33]. Treatment of nocturnal polyuria in patients with CKD should aim at reducing salt intake, promoting fluid control, and identifying urological diseases. In patients with obstructive sleep apnea syndrome (OSAS), nocturia is a symptom that increases the disturbance with disease severity [34]. Patients with OSAS are easily awake and have increased bladder filling due to polyuria. Treatment with continuous positive airway pressure can reduce the nocturia episode by one or more voids and improve the QoL of patients with OSAS [35].

Dietary salt control is important in patients with salt-sensitive hypertension and nocturia [36]. When patients consume too much salty food during daytime and cannot excrete salt, they are likely to excrete salt at nighttime, causing increased urine output during sleeping time and resulting in nocturia. In patients with CHF, a supine position during sleep further increases central fluid volume by increasing venous return, stretching the atria and ventricles, and increasing atrial natriuretic peptide. Treatment with thiazide and loop diuretics in the morning may be effective in reducing nocturia and nocturnal urine output. A small functional bladder capacity may exacerbate the nocturia severity, particularly in older people with CHF, CKD, or OSAS [37].

Diabetes, metabolic syndrome, and nocturia

Diabetes is strongly associated with nocturia [38]. Sleep and circadian rhythm disturbances are common in people with diabetes, which are associated with an increased risk of developing type 2 diabetes and poor treatment outcomes. Appropriate treatment of disturbed sleep and circadian rhythm could improve diabetes outcomes [39]. Nocturia is also positively associated with depression in Japanese women with

type 2 diabetes [6]. Metabolic syndrome is defined by a group of cardiovascular risk factors, including impaired glucose tolerance, central obesity, hypertension, and dyslipidemia. Metabolic syndrome is also associated with LUTS, especially nocturia [40]. OAB is more prevalent in patients with metabolic syndrome than in controls [41]. The common pathophysiology of OAB and metabolic syndrome includes autonomic dysregulation, chronic ischemia, inflammation, and dysregulation of nutrient-sensing pathways [42]. Patients with OAB refractory to currently available medications should be appropriately managed by targeting metabolic syndrome.

Poor sleep pattern and nocturia

Nocturia is bidirectionally associated with depression [43]. A previous study reported that moderate-to-severe depression is prevalent in women with OAB, mainly associated with urgency incontinence and nocturia [44]. Many, but not all, women with OAB experienced interrupted sleep due to bladder symptoms. Some women had nocturia due to poor sleep quality because of anxiety or depression [45]. Therefore, clinicians should not conclude that all nocturia is caused by bladder symptoms. Among women with urgent urinary incontinence, poor sleep quality is common, and these patients should be queried about their sleep patterns [46]. In addition to antimuscarinic agents prescribed for OAB, appropriate intervention for poor sleep patterns should be concomitantly offered.

Nocturnal polyuria

Nocturia can be caused by high fluid intake, nephrological, cardiovascular, hormonal, urological, or sleep factors [47]. For patients with nocturia not responding to the first medical treatment for OAB or BOO, nocturnal polyuria should be considered the etiology. Nocturnal polyuria is a condition with excessive urine production at night [1]. Patients with nocturnal polyuria usually have nocturnal urine amounts of >33% of the daily urine amount, termed a NPI of >0.33. In addition to a high NPI, patients generally have abnormal lower urinary tract function such as OAB or BOO, and some may also have medical diseases causing polydipsia or osmotic diuresis [48]. The common pathophysiology of nocturia and nocturnal polyuria is listed in Table 1.

Table 1: Common causes and pathophysiology of nocturia and nocturnal polyuria

Cause of nocturnal polyuria	Underlying pathophysiology
Poor sleep pattern	Mental or physical ill health
LUTD	Incomplete voiding
	Bladder outlet obstruction
	Detrusor underactivity
	Bladder overactivity
	Bladder hypersensitivity
	Neurogenic LUTD
Excessive fluid output	Primary polydipsia
	Drugs, diuretics, alcohol, and caffeine
	Circadian changes to arginine vasopressin secretion
	Diabetes insipidus, DM
	Hypercalcemia, hyperuricosemia

DM: Diabetes mellitus, LUTD: Lower urinary tract dysfunction

Treatment of nocturia and nocturnal polyuria

Patients with nocturia which affects the sleep quality and bothersome should be treated. Treatment of nocturia should start with lifestyle modification and behavioral changes, followed by medication for underlying medical or urological conditions, including OAB, BOO, poor sleep pattern, nocturnal polyuria, and medical diseases [49]. The treatment strategy should include the following: (1) water restriction for patients with polydipsia and salt restriction for hypertension; (2) good control of diabetes, hypertension, CHF, CKD, or OSAS; (3) tranquilizer for insomnia and consultation with a psychiatrist for poor sleep patterns; (4) treatment of BPH and BOO, if any, with alpha-blockers with or without 5-alpha-reductase inhibitors; (5) addition of antimuscarinics or beta-3 adrenoceptor agonists; (6) addition of desmopressin or afternoon diuretics for nocturnal polyuria; and (7) combination therapy for patients with multiple factors. Personalized treatment is essential based on patients' age, sex, medical comorbidity, and underlying pathophysiology [49,50] [Table 1]. Because the nocturia pathophysiology is usually multifactorial, medical treatment for LUTS in men with nocturia is usually not significantly better than placebo [51]. However, efforts should be made to find the appropriate medication or treatment for nocturia after the first trial has failed.

Desmopressin

If the voiding diary has revealed the presence of nocturnal polyuria (NPI, ≥0.33), antidiuretic therapy can effectively reduce nocturnal urine production and hence decrease the nocturia episodes [48]. Currently, desmopressin is the only synthetic analog of arginine–vasopressin specifically indicated for patients with nocturnal polyuria [50]. In a Japanese multicentric clinical study, desmopressin of 25 and 50 μg had been shown effective for male patients with nocturnal polyuria. Nocturia episodes decreased from 4.1 ± 1.3 at baseline to 2.9 ± 1.4 at 1 month ($P < 0.01$) and 2.6 ± 1.3 at 23 months ($P < 0.01$). Patients with nocturia reduction of two or more episodes had larger nighttime voided volume at baseline [52]. Our previous study also confirmed that 66.7% of patients aged >65 years with severe nocturnal polyuria were effectively treated with desmopressin. Nocturnal frequency decreased from 5.2 ± 1.16 at baseline to 2.24 ± 1.12 times at 1 month, and nocturnal urine volume decreased from 955.6 ± 255.9 mL at baseline to 522.8 ± 210.5 mL at 1 month. The posttreatment nocturnal bladder capacity also increased in patients effectively treated but not in those who failed treatment. The adverse event of hyponatremia was noted in only 1 (3.3%) patient [53].

Recently, low-dose oral desmopressin has been used for the treatment of men with nocturia associated with BPH. A systematic review revealed desmopressin alone or in combination with an alpha blocker effectively reduced nocturia in 43% and 64.3% of men with LUTS and nocturia, respectively [54]. Another systematic review confirmed the

efficacy of desmopressin in improving nocturia, QoL, and IPSS storage subscore. However, short-term adverse events such as nausea, headache, dizziness, and hyponatremia should be cautiously monitored [55]. However, a comprehensive review revealed that the efficacy of reducing nighttime frequency is similar to that of alpha blockers, and the combination of desmopressin with an alpha blocker or antimuscarinic agent did not provide additional benefits in the treatment of nocturia defined as one or more voids per night [56]. The treatment algorithm for nocturia and nocturnal polyuria is shown in Figure 1.

Due to potential adverse events of hyponatremia for the treatment with desmopressin, especially in patients aged >65 years, patients treated with desmopressin should be cautiously monitored for serum sodium levels [57]. The International Continence Society consensus on the diagnosis and treatment of nocturia has declared that serum sodium should be monitored at days 3–7 and 1 month, desmopressin therapy should be stopped if the serum sodium level is <130 mmol/L regardless of symptoms, and the treatment should be terminated if the serum sodium level is 130–135 mmol/L with symptoms of hyponatremia.

Nonpharmacological treatment of sleep quality in patients with nocturia

Several nonpharmacological treatments have been developed or applied to treat OAB and improve the sleep quality in women with OAB and nocturia. The treatments include pelvic floor muscle training [58], posterior tibial nerve stimulation [59,60], and percutaneous tibial nerve stimulation [61]. Nonpharmacological treatments using either method were equally effective in improving the sleep quality of women with nocturia [62].

Another nonpharmacological treatment for nocturia is continuous positive airway pressure (CPAP) devices. Patients with OSAS can be effectively treated with CPAP, and nocturia decreases by one or more episodes [35]. Urodynamic detrusor overactivity also decreased, and bladder compliance increased after the CPAP treatment [63]. A combination of the antimuscarinic agent tolterodine with CPAP could provide beneficial efficacy in OAB symptoms but not daily urine volume compared with CPAP treatment alone [64].

Nocturnal enuresis and urinary incontinence in adults

Nocturnal enuresis is commonly encountered in children aged <5 years. Nocturia is a maturation defect due to the lack of the circadian rhythm of arginine–vasopressin, resulting in urine overproduction during sleep [65]. In addition to nocturnal polyuria in children, other factors contribute to nocturnal enuresis in children, causing 20%–60% of children with monosymptomatic enuresis to be desmopressin-resistant [66]. In children with desmopressin-responsive nocturnal enuresis, nocturnal urine volume is greater at nights than at nights without enuresis, indicating other factors contributing to the occurrence of enuresis during sleep, such as high salt and water intake, deep sleep, and detrusor overactivity [67].

In older men and women with nocturnal urinary incontinence, increased nocturnal sodium diuresis and nocturnal polyuria are significant findings compared with those without nocturnal LUTS [68]. From the frequency volume chart, 84% of patients with nocturia can be categorized, and 95% of patients aged 60–80 years with nocturia can be categorized using a voiding diary and urodynamic study [69]. Among patients with nocturnal urinary incontinence, BOO due to BPH in men and dysfunctional voiding in women, detrusor overactivity, neurogenic OAB due to stroke and Parkinson's disease, and detrusor underactivity and overflow urinary incontinence after radical hysterectomy or abdominoperineal resection of the rectum are common diseases [70,71]. In addition, secondary causes of nocturnal enuresis, such as psychological distress, and contracted bladder with low

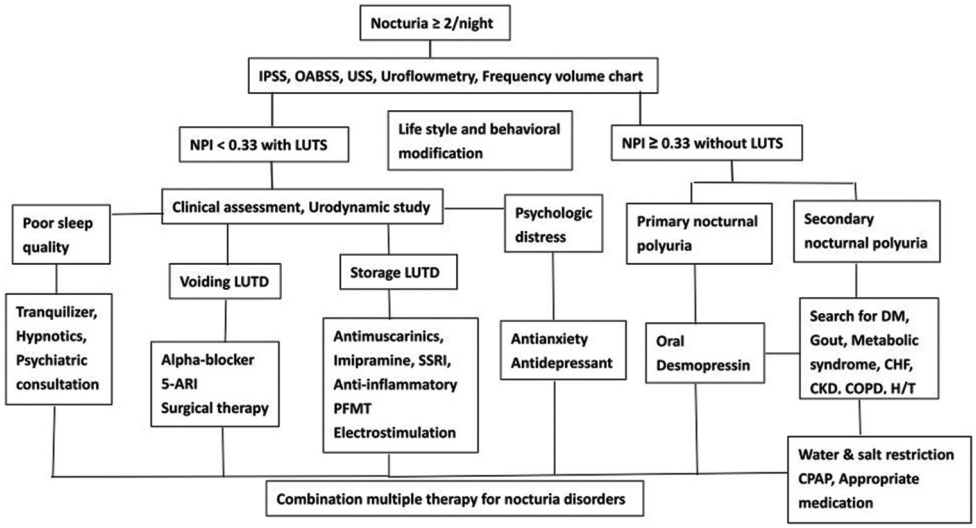

Figure 1: Diagnostic and treatment algorithm for adults with nocturia, nocturnal polyuria, and nocturnal enuresis. IPSS: International Prostate Symptom Score, OABSS: Overactive Bladder Symptom Score, NPI: Nocturnal polyuria index, LUTS: Lower urinary tract symptoms, LUTD: Lower urinary tract dysfunction, 5-ARI: 5-alpha-reduc tase inhibitor, PFMT: Pelvic floor muscle training, SSRI: Selective serotonin reuptake inhibitor, DML: Diabetes mellitus, CHF: Congestive heart failure, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, H/T: Hypertension, CPAP: Continuous positive airways pressure

bladder compliance are also possible causes of nocturnal urinary incontinence in adults [72,73].

Treatment for adult-onset nocturnal enuresis is similar to that for nocturia in adults. All patients with adult-onset nocturnal enuresis should be thoroughly worked up to identify possible etiologies of urinary incontinence, such as obesity, neurogenic disorders, bladder storage, and emptying dysfunction, by frequency volume chart, urodynamic study, neurological examinations, and cystoscopy [74,75]. Patients proven to have nocturnal polyuria should be treated with desmopressin. Antimuscarinic agents, such as tolterodine or solifenacin, can be added in patients with daytime and nighttime urinary incontinence. If a urodynamic study revealed BOO due to bladder neck dysfunction, BPH, or dysfunctional voiding, appropriate medication or surgical procedures are recommended. Imipramine or methylephedrine is helpful in male or female patients suspected of urethral sphincter incompetence. Pelvic floor muscle exercise or functional electrostimulation may also be helpful if medical treatment fails [76].

Future research topics for nocturia and nocturnal enuresis

Although extensive research has been performed to understand the pathophysiology of nocturia, nocturnal polyuria, and nocturnal enuresis in adults, several important questions remain to be solved. The role of desmopressin in adult nocturia without nocturnal polyuria should be determined. Will desmopressin affect bladder sensation, detrusor overactivity, or nocturnal urine output through unknown receptors in the bladder urothelium or kidney? How does desmopressin improve functional bladder capacity in patients who respond to treatment? Will bladder conditions such as detrusor overactivity change in pediatric nocturnal enuresis after long-term desmopressin therapy? What are the predictive factors for successful or failed desmopressin treatment for nocturia and nocturnal polyuria in adult patients? Will a combination of desmopressin and selective serotonin reuptake inhibitor have better therapeutic efficacy in adult primary nocturnal enuresis? All these questions deserve further clinical research to provide a better framework for the more effective treatment of adult nocturia.

Conclusion

Nocturia, nocturnal polyuria, and nocturnal enuresis in adults cause disturbed LUTS and are difficult to treat with currently available medications. Several different etiologies have been identified for nocturia disorders, including dietary imbalance, poor sleep quality, bladder storage and emptying dysfunctions, nocturnal polyuria due to vasopressin deficiency or secondary to medical diseases, and psychological distress. Detailed examination should be performed to identify possible causes and select appropriate treatment, including behavioral and lifestyle modification, appropriate medications, physiotherapy, and nonpharmacological therapies, to improve the QoL of adults with nocturia disorders.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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