CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will ask their elderly patients about symptoms of nocturia

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Nocturia in the elderly: A wake-up call

ABSTRACT

Nocturia is a condition that health providers must seek out and address in older adults. Since it adversely affects quality of life and carries a risk of morbidity and of death (often because of falling), this symptom must be elicited during the physician-patient encounter. Understanding its underlying causes, risk factors, and consequences is essential in formulating the most suitable management strategy. Drug and nondrug treatments target the individual disorders that contribute to nocturia.

KEY POINTS

Nocturia is multifactorial and is caused by factors that increase urine production and others that decrease the bladder's ability to hold urine.

The first priority in treating nocturia is to identify and treat concomitant conditions that may be contributing to it, such as diabetes mellitus, diabetes insipidus, urinary tract infections, hypercalcemia, and hypokalemia.

Nonpharmacologic measures can help, but by themselves usually do not solve the problem.

Drug therapies for nocturia include desmopressin (DDAVP), antimuscarinic agents, alpha-blockers, and 5-alpha reductase inhibitors.

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Nocturia is common, but elderly patients infrequently volunteer this complaint, and even when they do, some clinicians may dismiss it as simply a part of aging. Nevertheless, nocturia causes significant distress and impairment of quality of life. It is associated with very serious consequences such as depression, social isolation, and a higher risk of death.

In this article, we review the concepts behind frequent nighttime voiding in older adults. We will start with two case scenarios to aid in understanding these concepts; near the end of the article, we will discuss the most appropriate management strategies for these two patients.

CASE SCENARIOS

Case 1: An 82-year-old man with fatigue

An 82-year-old obese white man with a history of hypertension, diabetes, and benign prostatic hyperplasia comes in to see his primary care provider, complaining of fatigue. He wakes up tired and has difficulty completing his daytime tasks. He gets up every 1 to 2 hours at night to urinate and has slow urinary flow and a feeling of incomplete bladder emptying.

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He says his wife has been increasingly bothered by his loud snoring. Recently, he had a car accident when he fell asleep while driving.

Case 2: An 85-year-old woman with incontinence

An 85-year-old white woman is in her family physician's office with a primary complaint of waking up at least four times at night to uri-

TABLE 1

Pathophysiology of nocturia in the elderly

Nocturnal polyuria
Low levels of antidiuretic hormone at night
Altered circadian rhythm in plasma vasopressin levels
Increased sodium excretion at night
Decreased nocturnal bladder capacity
Comorbid conditions (diabetes mellitus, benign prostatic hyperplasia)
Increased irritative symptoms
Overactive bladder
Age-related changes
Decreased functional bladder capacity
Decreased maximum urinary flow rate
Decreased ability to postpone urination
Increase in postvoid residual volume
Diminished bladder compliance
Detrusor overactivity
Decreased renal ability to concentrate urine
Others
Increase in nighttime plasma natriuretic peptide
Increase in blood pressure
Increase in nighttime catecholamine levels
Decrease in plasma melatonin levels
Mobilization of edema fluid
Autonomic dysfunction

nate, and often ends up soaking her bed or adult diapers. She is bothered by urinary urgency and frequency during the day as well. She denies dysuria and hematuria.

She has a history of hypertension and urinary incontinence, and she has seven children. Her current medications are diltiazem (Cardizem), metoprolol (Toprol), and oxybutynin (Ditropan).

In these two cases, what would account for the nocturia? What would be the best way to help these patients?

THE NORM, NOT THE EXCEPTION

Although nocturia is defined as an awakening by the need to urinate even once in a night, many experts consider that it begins to be clinically significant only when the patient voids at least twice during the night.[1]

In older adults, nocturia is the norm rather than the exception. Studies done between 1990 and 2009 found that 68.9% to 93% of men age 70 and older get up at least once a night to void. The prevalence in women is somewhat lower, at 74.1% to 77.1%.[2] Clinically significant nocturia is present in a majority of the elderly: more than 60% of both men and women.[3]

An Austrian study[4] reported that elderly men got up to urinate a mean of 2.8 times per night, while women got up significantly more often—3.1 times. Women were also bothered more by this symptom, and their quality of life was significantly more decreased.

In another study,[5] whites had a significantly higher nocturia ratio (ratio of nighttime urine volume to the 24-hour urine volume) than Asians. Asians, on the other hand, had a significantly higher nocturnal bladder capacity index than whites. (See below for definitions of the various indices of nocturia.) This information implies that nocturia may be a more prominent problem for elderly whites than for other racial groups.

In an epidemiologic study in Sweden,[6] the death rate was as much as twice as high in both men and women who had three or more nocturnal voids, even after taking into account the influence of cardiac disease, diabetes mellitus, and stroke.

If nocturia is not addressed in the physician-patient encounter, patients may try to "self-manage" it by restricting their fluid intake or by limiting their social exposure,[7] with limited success and with unwanted social isolation.

WHAT CAUSES NOCTURIA?

In almost all cases of nocturia in elderly people, the cause is multifactorial (TABLE 1).

Advancing age is primary among these factors. Age-related structural changes in the urinary system include decreased functional

bladder capacity, a decreased maximum urinary flow rate,[6] a decreased ability to postpone urination,[8] and an age-related increase in postvoiding residual urine volume.[9] The aging kidney is also less able to concentrate urine. Also implicated are histologic changes in the detrusor muscle[10] that lead to diminished bladder compliance and, together with detrusor overactivity, result in increased urinary frequency.

Nocturnal polyuria or nocturnal urine overproduction is common in patients with nocturia.[11]

Although the pathophysiology of nocturnal polyuria is still unclear, some investigators believe that low levels of antidiuretic hormone (ADH) at night are involved, reflecting an alteration in the circadian rhythm seen in diurnal plasma arginine vasopressin levels.[12] In patients with nocturnal polyuria, ADH levels drop to very low or undetectable levels at night, which increases nocturnal urine output. In some extreme cases, the low to absent levels of ADH increase nocturnal voiding to 85% of the total 24-hour urine volume.[13]

Other causes of nocturnal polyuria include mobilization of fluids in patients with edema,[14] and autonomic dysfunction. Other biochemical changes that contribute to nocturia include a decrease in nighttime plasma melatonin levels, an increase in nighttime plasma catecholamine levels, an increase in nighttime plasma natriuretic peptide levels, an increase in blood pressure, and an increase in total urine volume.[15]

A decreased ability to store urine also leads to nocturia. This is caused by decreased nocturnal bladder capacity, more irritative symptoms, and comorbid conditions such as overactive bladder, pelvic floor laxity resulting in pelvic organ prolapse, and, in men, benign prostatic hyperplasia.

Neural inputs to the bladder can also be impaired, as in patients who have diabetes mellitus or spinal stenosis, leading to chronic urinary retention, detrusor dysfunction, nocturia, and incontinence.

WHICH PATIENTS ARE AT RISK?

Nocturia is associated with a number of risk factors (TABLE 2).

TABLE 2

Risk factors for nocturia

Older age
Obesity
Nocturnal eating and poor daytime appetite
Obstructive sleep apnea
Depression
Frequent napping
Congestive heart failure
Hypertension
Prostatic enlargement
Diabetes mellitus
Spinal stenosis
Recurrent cystitis
Lung disease
Drugs: cholinesterase inhibitors, beta-blockers, calcium channel blockers, antihistamines

Obesity is associated with a higher incidence of moderate to severe nocturia.[15] Studies have shown that the higher the body mass index, the greater the number of nighttime voids, especially in women.[16]

Habitually eating at night, with poor daytime appetite, is shown to be associated with increased nighttime diuresis.

Obstructive sleep apnea[17] and **untreated depressive symptoms** such as frequent napping[18] are also associated with moderate to severe nocturia.[19]

Higher systolic blood pressures are associated with more urine production at night. Plasma ADH regulation is also altered, which contributes to nocturnal polyuria.[21]

Other comorbid conditions associated with nocturia include recurrent cystitis, lung disease, congestive heart failure, neurodegenerative conditions (eg, Alzheimer disease and parkinsonism), and chronic kidney disease.[21]

Drugs associated with nocturia include cholinesterase inhibitors (for dementia),[22] beta-blockers,[23] and calcium channel blockers.[24]

Lifestyle factors. Alcohol and coffee have shown either no or only a mild diuretic effect.

Nocturia is common, but patients rarely volunteer this complaint

TABLE 3

Consequences of nocturia

Higher incidence of falls
Higher incidence of hip fractures, with consequent immobility and debility
Altered conception of one's age
Poorer sleep quality
Increased fatigue
Depression
Obesity
Higher rate of death in patients with coronary heart disease

Smoking has not been shown to be associated with nocturia.[15]

Seasonal differences also exist, with increased frequency of nocturia in the winter.[25]

WHAT ARE THE CLINICAL CONSEQUENCES OF NOCTURIA?

The cost of nocturia-related falls is about $1.5 billion a year

Nocturia's effects are varied and are very important to address (TABLE 3).

Quality of life can be profoundly affected, and if nocturia is left untreated, it may lead to morbidity and even death. Elderly patients may feel simultaneously debilitated, frustrated, distressed, and puzzled. Nocturia may also increase their fear of falling and may negatively affect personal relationships.[26]

Falls, injuries. Nocturia exposes elderly patients to injuries such as hip fractures due to falling, significantly increasing the incidence of this injury.[26] This occurs as elderly patients get up from bed and walk to the bathroom to void.[27] In addition, during the day, superficial and fragmented sleep leads to daytime sleepiness and impaired perception and balance, also increasing the risk of falls.[28] The complications of immobility and the need for surgery in many cases lead to debility, increased risk of infections, decubitus ulcers, and death. The risk of hip fractures can lead elderly patients with nocturia to associate this symptom with a fear of falling and can alter their concept of their own age ("Nocturia makes me feel old"),[29] further diminishing quality of life.

The estimated medical cost of nocturia-associated falls in the elderly is about $1.5 billion per year, part of the $61 billion in lost productivity due to nocturia in adults.[30]

Long-term complications (eg, debilitation, poor sleep, obesity, decreased energy), increase the overall mortality rate, especially in patients who report voiding more than three times per night.[29] Elderly patients with nocturia also have a greater need for emergency care.[31]

Nocturia also complicates other comorbid conditions, such as dementia, which increases the risk of urinary incontinence.[32] In patients who have had a stroke, nocturia is the most frequent lower urinary tract symptom, and represents a major impact on daily life.[33]

Sleep disturbance is another important consequence. In one survey,[34] nocturia was cited as a cause of poor sleep four times more often than the cause cited next most often, ie, pain. Because the elderly patient is awakened from sleep numerous times throughout the night, nocturia leads to more fatigue,[35] lower energy levels, and poorer quality of sleep.[36] Depression may be linked to poor sleep, as men with two or more nocturnal episodes were shown to be six times more likely to experience depression.

The patient is not the only person who loses sleep: so do the patient's family members or sleeping partner.[7] It is therefore not surprising that sleep disruption caused by nocturia has been cited as a principal reason for admitting older relatives to care homes.[37]

The risk of death is higher for elderly patients with coronary heart disease if they have nocturia. The causative link is the hemodynamic changes (increases in blood pressure and heart rate) that accompany awakening and arising, which may cause cardiovascular strain and lead to cardiovascular events. The 12-year survival rate has been shown to be significantly lower in patients with nighttime voiding, making nocturia a highly significant independent predictor of death in coronary heart disease patients.[38]

HOW TO EVALUATE AN OLDER ADULT WHO PRESENTS WITH NOCTURIA

A thorough history and physical examination are crucial in diagnosing nocturia. The goal is

to identify any treatable underlying condition, such as diabetes mellitus, obstructive sleep apnea, diabetes insipidus, overactive bladder, benign prostatic hyperplasia, urinary tract infection, and congestive heart failure. Laboratory tests and imaging studies can help rule out these underlying conditions.

Other important facets in the history that must be elicited are medication use, patterns of fluid intake, and a history of other urinary complaints.[39]

A voiding diary and indices of nocturia

A voiding diary is extremely useful and should be used whenever possible. Episodes of incontinence, time of voids, volume voided, and frequency and volume of fluid intake are recorded. From the raw data, one can determine the following:

Total nocturnal urine volume, ie, the sum volume of the nighttime voids

Maximum voided volume, ie, the largest single recorded volume voided in a 24-hour period

Nocturia index, ie, the total nocturnal urine volume divided by the maximum voided volume. A nocturia index greater than 1 shows that nocturnal urine production is greater than the functional bladder capacity. Clinically significant nocturia is observed in patients with a nocturia index of 2.1 or greater.

Nocturnal polyuria index, ie, total nocturnal urine volume divided by the 24-hour urine output. A nocturnal polyuria index higher than 33% implies nocturnal polyuria.[40]

Nocturnal bladder capacity index, ie, the actual number of nightly voids minus the predicted number of nightly voids, which in turn is calculated as the nocturia index minus 1.

It is especially important to encourage patients to make a voiding diary, as some patients may find this cumbersome, and compliance can be low unless its importance is emphasized. A diary over 7 days usually gives meaningful data. The results from the diary typically confirm the presence of nocturnal polyuria or a decrease in bladder capacity, influencing management.[41]

WHAT ARE THE TREATMENT OPTIONS?

Therapy must be directed at the primary cause, addressing any underlying conditions that can contribute to nocturia. Examples[39]:

- Tight control of blood sugar for patients with diabetes mellitus
- Treatment of diabetes insipidus
- Referral for patients with primary polydipsia
- Management of hypercalcemia and hypokalemia
- A survey of medications
- Treatment of infections.

TABLE 4

Management strategies for nocturia

General approach
Address underlying causes: ie, treat diabetes mellitus, diabetes insipidus, infections; address benign prostatic hyperplasia; correct metabolic disorders
Survey the patient's medications
Refer to specialists (eg, a pulmonologist for obstructive sleep apnea, a urologist for benign prostatic hyperplasia)
Nonpharmacologic measures
Avoiding nighttime fluid intake, including alcohol and caffeine
Compression stockings
Leg elevation during the afternoon
Continuous positive airway pressure for obstructive sleep apnea
Moderate exercise
Reducing nonsleep time in bed
Sleeping in a warm bed
Phototherapy
Pharmacologic therapies
Desmopressin (DDAVP)
Antimuscarinic agents: oxybutynin (Ditropan), tolterodine (Detrol), solifenacin (Vesicare), propiverine (not available in United States)
Alpha-blockers and 5-alpha-reductase inhibitors for benign prostatic hyperplasia
Diuretics: hydrochlorothiazide, furosemide (Lasix)
Cyclo-oxygenase-2 inhibitors: celecoxib (Celebrex) Other nonsteroidal anti-inflammatory drugs: diclofenac (Voltaren), loxoprofen (not available in United States)
Botulinum toxin

Nonpharmacologic measures

Tailored behavioral therapy can also be instituted, but the patient needs to have realistic expectations, as these measures are rarely effective alone.

Avoiding nighttime fluid intake, including alcohol and caffeine, has shown promise.

Wearing compression stockings and elevating the legs in the afternoon decrease the retention of fluid that otherwise would return to the circulation at night.

Identifying and eliminating nighttime influences that disturb sleep has variable efficacy. The use of continuous positive airway pressure helps to treat sleep apnea. Moderate exercise, reducing nonsleep time spent in bed,[42] and sleeping in a warm bed[43] to decrease cold diuresis have also been shown to improve sleep quality.[44] Patients with nocturia may have a disrupted circadian rhythm, and phototherapy may help resynchronize the diurnal rhythm and melatonin secretion.

Pharmacotherapy

Pharmacotherapy of nocturia includes desmopressin (DDAVP) to manage nocturnal polyuria and antimuscarinic agents to manage the patient's decreased ability to store urine. Alpha-blockers such as tamsulosin (Flomax) and 5-alpha-reductase inhibitors such as finasteride (Proscar) are used for men with benign prostatic hyperplasia. Novel and second-line therapies include diuretics such as furosemide (Lasix), cyclooxygenase-2 inhibitors, as well as botulinum toxin injected directly into the detrusor muscle for overactive bladder.[45]

Many experts consider nocturia clinically significant if it occurs at least twice a night

Desmopressin in a low oral dose (0.1–0.4 mg) at bedtime can be initiated and the response assessed. Patients with nocturnal polyuria and disorders of the vasopressin system have been found to be more sensitive to desmopressin therapy.[46] Fluid retention and hyponatremia can complicate therapy, and desmopressin must be avoided in patients with liver cirrhosis, renal failure, or congestive heart failure.[47]

Antimuscarinic agents are effective for patients who have lower urinary tract symptoms and for those with a diminished ability to store urine. They act by decreasing both voluntary and involuntary bladder contractions by blocking muscarinic receptors on the detrusor muscle. This reduces the bladder's ability to contract and the urge to urinate, thereby increasing bladder capacity.[48] These agents include oxybutynin (Ditropan), tolterodine (Detrol), solifenacin (Vesicare), and propiverine (not available in the United States).

Diuretics are being used as second-line agents or for patients who cannot tolerate desmopressin.[49] Hydrochlorothiazide is taken 8 hours before bedtime to prevent water accumulation before the early sleeping hours.[50] Furosemide has also led to a reduction in the mean number of nocturnal voids.[51] The effect of these drugs on nocturia are especially beneficial to patients with concomitant hypertension or cardiovascular disease.

Cyclo-oxygenase-2 inhibitors such as celecoxib (Celebrex)[52] and other nonsteroidal anti-inflammatory drugs such as diclofenac (Voltaren, others)[53] and loxoprofen (not available in the United States)[54] have been shown to decrease urine production, detrusor muscle tone, and inflammation, especially in men with benign prostatic hyperplasia.

Botulinum toxin has been used, usually in patients refractory to first-line treatment.[44]

Referral to specialists is guided by underlying causes. Referral to a pulmonologist or sleep specialist may be helpful if the patient has obstructive sleep apnea. Referral to a urologist may be prudent if the patient has benign prostatic hyperplasia, and a gynecologist can address issues such as pelvic relaxation.

TABLE 4 summarizes the treatment strategies for nocturia.

CASES REVISITED

The first patient described above has nocturia caused by several concomitant diseases, ie, hypertension, diabetes, benign prostatic hyperplasia, and obstructive sleep apnea. In addition to controlling his blood pressure and blood sugar, his primary care provider referred him to a pulmonologist, who confirmed obstructive sleep apnea with polysomnography and prescribed nightly use of a continuous positive airway pressure apparatus. A few weeks later, the patient's nocturia had improved significantly, and his level of fatigue had decreased.

Apart from hypertension, the second patient's nocturia was mostly attributed to her existing urinary incontinence. Recognizing that her current antihypertensive regimen may worsen nocturia, her family physician changed it to enalapril (Vasotec) and doxazosin (Cardura) and counseled her to restrict her fluid intake 2 hours before bedtime. She was also referred to a gynecologist, who found a moderate degree of cystocele and treated her with a collagen injection. Her nocturia improved significantly.

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