Nocturia: diagnosis and management for the primary care physicians

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Primary care physicians commonly see men or women with nocturia (or nocturnal polyuria). Nocturia can have a dramatic impact on a patient's physical and emotional quality of life, including work performance or ability to function, because of the interrupted sleep patterns. It has also been determined that the most important sleep interval is the time from first falling asleep until first awakening. Nocturia is one of the most common and most bothersome symptoms of lower urinary tract symptoms (LUTS). In a man, LUTS is most commonly caused by benign prostatic obstruction (BPO) related to the enlargement of the prostate. In a woman, the most common cause of LUTS is overactive bladder (OAB). This article first explores the different causes and types of nocturia, then describes how to diagnose different types of nocturia (including use of frequency-volume charts), and last, discusses different approaches for managing nocturia (including the use of desmopressin), depending on the type and cause.

Key Words: nocturia, nocturnal polyuria, LUTS, BPH, BPO, frequency-volume charts (FVC), desmopressin

Introduction

Lower urinary tract symptoms

Lower urinary tract symptoms (LUTS) in men and women include frequency, urgency, hesitancy, urgency incontinence, and nocturia. According to the American Urological Association (AUA) Symptom Index (SI), symptoms fall into the urine storage (irritative), urine voiding (obstructive), or post-micturition categories. A patient work up helps clinicians determine the cause of the symptoms as well as the degree of bother to the patient. Patients generally only accept treatment for symptoms that are bothering them.[1]

Overactive bladder (OAB), which by definition consists of symptoms of urgency and frequency with or without urgency incontinence and nocturia, is very common in men and women. In 2004, based on earlier surveys, Corcos and colleagues,[2] estimated that the prevalence of OAB in Canada was 14.8% in men and 21.2% in women, whereas in 2008, Hershorn and colleagues reported a somewhat lower estimate of OAB prevalence: 13.1% in men and 14.7% in women.[3]

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In a study based on a survey of more than 1400 people who were diagnosed with OAB with bothersome symptoms, the combination of urgency plus nocturia was the most bothersome symptom combination. More than 75% of survey respondents reported having nocturia (defined as getting up 1 or more times in the night to void), and 53% of men and almost 60% of women reported getting up 2 or more times in the night to void.[4]

Daytime urinary frequency associated with OAB in women or benign prostatic obstruction (BPO) in men can usually be treated with standard medications for OAB[5] or benign prostatic hyperplasia (BPH).[6]

Unfortunately, nocturia that is commonly associated with these conditions does not usually resolve with these treatments. Studies have not consistently shown that standard 5-alpha reductase inhibitors (5-ARIs), alpha blockers, anticholinergics, or beta 3 agonists improve nocturnal polyuria.[7]

Nocturia

According to the International Continence Society (ICS), nocturia is defined as "The complaint that the individual has to wake at night one or more times to void. Each void is preceded and followed by sleep."[8]

Nocturia can be due to urologic and non-urologic causes. The non-urologic medical causes should be addressed, and the patient should be referred to a specialist, if needed, as shown in Table 1.[9]

If the urologic causes of nocturia are related to "urine storage" problems, then the classic medical management for OAB or BPH can be employed, but often, the patient may still have nocturnal polyuria.

By definition, a patient who excretes more than 40 cc/kg in a 24-hour period has global polyuria. A person has nocturnal polyuria if he or she produces an abnormally large volume of urine from the time of first sleep until the time of first void after rising in the morning.

The International Continence Society established criteria for an abnormal nocturnal polyuria index (NPI), where NPI is nocturnal urine volume divided by 24-hour urine volume. Younger adults are considered to have an abnormal NPI if their nocturnal urine volume exceeds 20% of total 24-hour urinary output; and older adults are considered to have an abnormal NPI if their nocturnal urine volume exceeds 33% of their total 24-hour urinary output.[8]

If nocturia is not treated, it can have a significant impact on the patient. Nocturia is a leading cause of sleep disturbance in patients who are older than 50, and it is an independent predictor of poor sleep.[10-13] Nocturia may be a sign of early disease, and it may decrease a person's health status and quality of life. It has a greater impact on younger adults, and interfere with work and increase sick leave. In older adults it can lead to falls and fractures.[11,14]

Diagnosis of nocturia

When taking a patient history, it is important to determine the onset and severity of the nocturia, and also find out if the nocturia is consistent or intermittent. The physician also needs to look for any medical conditions, as mentioned in Table 1, or drugs that may cause nocturia.

The physician should order a urinalysis, a urine culture and sensitivity test, and a urine cytology test (if indicated, because of hematuria). He or she should also order a serum creatinine test to rule out renal failure (if indicated).

When performing a clinical physical examination, ensure that the patient is not in retention (palpate supra-pubically), and ensure that a male patient has no signs of significant BPO by doing a digital rectal examination (DRE).

Order an abdominal and/or pelvic ultrasound test (if indicated).

TABLE 1. **Underlying conditions and management of nocturnal polyuria**

Cause	**Treatment**
Excessive fluid intake in the evening	Behavioral modification
Congestive heart failure	Refer to cardiology
Type 2 diabetes	Aim for optimal glycemic control
Suspected obstructive sleep apnea (snoring, obesity, short neck)	Sleep studies
Peripheral edema due to venous disease	Leg elevation/compression stockings
Impaired circadian rhythm of arginine vasopressin (AVP) secretion	Antidiuretic therapy

TABLE 2. **Patient frequency-volume chart results**

24-hour volume	1800 mL
Nocturnal urine volume (includes first morning void)	680 mL
Nocturia episodes	3
Nocturnal urine volume/ 24-hour volume (NPI) Abn: young > 20% old > 33% (> 55 y.o.)	38%
Maximum voided volume	225 mL

The simplest and most effective way to diagnose nocturnal polyuria is with a frequency-volume chart. The chart uses the patient's recorded responses for the frequency and total volumes voided and then calculates the nocturnal polyuria index to determine if the patient meets the criteria. Table 2 provides an example of a patient's frequency-volume chart results.

Although nocturia is a common complaint in patients diagnosed with OAB, the standard OAB treatments with antimuscarinic agents have only offered minimal, if any, improvement.[15] Since frequency-volume charts were not used in most of these trials, it was impossible to really tell if a patient really had nocturnal polyuria.[16]

To diagnose nocturia, the critical and simple question that we must pose to our patients is: "When you get up at night to void- do you pass a lot of urine each time or just a small amount?" A patient who passes small amounts of urine, most likely has OAB, but a patient who passes a large amount of urine each time has nocturnal polyuria.

Treatment of nocturia

Lifestyle changes

If a patient has just been diagnosed with nocturia, then the initial treatment should aim to try to diminish the amount of urine that is produced and/or excreted at night. The first approach to manage nocturia is to adopt certain lifestyle behaviors. as shown in Table 3.

Antidiuretic hormone therapy

The human anti-diuretic hormone (ADH)/arginine vasopressin (AVP), which is produced in the pituitary gland, stimulates reabsorption of fluid in the renal tubules at night, which prevents nocturnal polyuria. Desmopressin is a synthetic antidiuretic hormone. ADH/AVP and desmopressin both act on the collecting ducts of the nephrons to allow re-absorption of water at night, thereby reducing the amount of urine produced and nocturia.

ADH/AVP is a V1 and V2 receptor agonist, and has a V1 mediated vasopressor and uterotonic effect. Desmopressin is a selective V2 agonist with no vasoporessor or uterotonic effect. Both ADH/AVP and desmopressin act on V2 receptors in the distal renal tubules and collecting ducts to promote water reabsorption.[9]

Oral preparations of desmopressin have certain advantages and disadvantages. The advantages include demonstrated efficacy, a response that was observed within a week, and a prolonged initial sleep period.[9] The disadvantages include a risk of hyponatremia associated with higher doses of desmopressin. In addition, dosing titration may be required (0.1 mg (~60 µg ODT) at bedtime x 7 days; 0.2 mg (~120 µg ODT) at bedtime x 7 days; and 0.4 mg (~240 µg ODT) at bedtime). There is also a need for serum sodium monitoring at baseline and 3 days after initiation of therapy or an increase in dosage, as well as at other times during treatment as deemed necessary by the treating physician; patients who are over 65 years old or who are at risk of hyponatremia also require serum sodium monitoring monthly or every 2-3 months, depending on their risk of hyponatremia.[9]

Because of these problems with the older preparations at higher doses, a new preparation was developed. This oral disintegrating tablet (ODT) dissolves under

TABLE 3. **Lifestyle changes for patients with nocturia**

Lifestyle changes

- Void immediately before going to bed.
- Modify diet and restrict fluids (e.g., avoid caffeinated beverages and alcohol).
- Take diuretics in the mid-afternoon.
- Elevate the legs in the evening to mobilize fluids.
- Use sleep medications/aids.[9]

the tongue and has a higher bioavailability, providing for greater absorption of a much smaller dose than before. It is a freeze-dried lyophilisate, which allows for sublingual use.[17] Desmopressin is the only anti-diuretic hormone that is approved for nocturia.

Many clinical trials have been performed to ensure that this new preparation had demonstrated safety and efficacy in men and women. In trials at the low dose of 25 µgm in women and 50 µgm in men and patients with a baseline serum sodium above 135 mmol/L, no patients had hyponatremia, and the time to first voiding increased and nocturia was reduced.

At these doses, both men and women had reduced nighttime voids, and serum sodium below 125 mmol/L was not observed in any women, nor in any men younger than 65. In women, the initial period of undisturbed sleep was 3 times greater than with placebo, and the effect was durable and sometimes improved with treatment up to 96 weeks.

In men and women, baseline serum sodium measurements were required to ensure that it was in the normal range, and elderly men age 65 and older required additional serum monitoring within 4 to 8 days of treatment initiation and then at 1 month of treatment.[17-20]

Conclusion

Nocturia is very pervasive men or women who present with LUTS. We need to rule out the other medical and non-medical causes of LUTS. We have seen in the past that we can usually manage daytime frequency with prostate and OAB medications, but nocturia often persists. Once we have determined that a patient has nocturnal polyuria based on the frequency-volume chart, now we can safely offer a new, low-dose, effective synthetic oral disintegrating tablet of desmopressin (Nocdurna), which has few side effects.

Disclosure

Dr. Jack Barkin is a speaker and investigator for Glaxo, Actavis, Pfizer, Astellas, Merus Labs, Allergan, Janssen, Ferring, NeoTract and Merck. □

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