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REVIEW ARTICLE

Nocturia in men

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SUMMARY

Nocturia is a common source of sleep disturbance in men and can result from many different causes. A patient-generated frequency/volume chart, along with several simple mathematical formulas, is used to classify nocturia according to its principal aetiology. The categories are nocturnal polyuria (NP), reduced voided volumes, 24-h polyuria and a combination of the aforementioned factors. Identification of the precise type of nocturia can help direct treatment in the cause-specific manner. In particular, use of the antidiuretic desmopressin can be of benefit in those with NP and may also be useful as part of a combination treatment approach in nocturia of mixed aetiology.

Review Criteria

PubMed and Medline search, review of recent guidelines and expert opinion.

Message for the Clinic

Identification of the cause(s) of nocturia is fundamental to the selection of appropriate treatment for this bothersome condition. The frequency/volume chart is an essential tool for the proper characterisation of nocturia allowing cause-specific intervention.

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Introduction

Nocturia, or waking at least once during the night to urinate, is one of the most common reasons for interrupted sleep in the general adult population. In a population-based survey involving 19,165 participants in five countries, nocturia was the most prevalent lower urinary tract symptom, reported by 48.6% of men (1). Both quality and quantity of sleep are necessary for mental and physical well-being. Interrupted sleep can cause fatigue during waking hours, decreased ability to concentrate and impaired memory. It has also been linked to poor job performance and motivation, and mood disturbances (2). Rising at night to urinate can also lead to traumatic falling accidents, especially in the elderly people (3). Nocturia has been directly linked to an increased risk of hip fractures in this population.

Furthermore, nocturia almost inevitably leads to decreased sleep for nocturia patients' sleep partners. It is worth bearing in mind that they can suffer the same effects of sleep deprivation as their partners with nocturia. This is a relatively unique medical situation, perhaps analogous to that of second-hand smoke, and the treatment is especially compelling as it can often benefit multiple people at once.

Men who wake at night to urinate frequently may also have other lower urinary tract symptoms such as urgency, frequency, weak stream and incontinence. This constellation of symptoms may be related to but is not necessarily because of, bladder outlet obstruction (BOO). Despite this, nocturia is often presumed to be secondary to detrusor instability or BOO and empirical treatment is often initiated for these conditions. While either or both of these conditions may contribute to symptoms, other recognised causes of nocturia should first be considered. These include medical conditions such as diabetes mellitus and insipidus, nephrotic syndrome and cardiovascular disease. Behavioural factors include excessive fluid intake, especially of caffeine or alcohol, shortly before retiring. Nocturia may also result from anxiety or sleep disorders, or from a reduction in the nocturnal secretion of antidiuretic hormone (ADH), which is frequently seen with advancing age (4).

There has been increased interest recently in providing treatment options directed at the specific underlying cause(s) of nocturia. The 24-h frequency/volume chart, in conjunction with several simple mathematical formulas, has emerged over the past few years as a tool for distinguishing among four main aetiologies associated with nocturia (5–7). The categories of conditions that cause nocturia are: (i) nocturnal polyuria (NP) (nocturnal urine overproduction), (ii) reduced voided volumes, (iii) mixed, a combination of NP and reduced voided volumes and (iv) 24-h polyuria (or an overproduction of urine during a 24-h period).

Evaluation of nocturia

Patients tend to present to the clinician with either nocturia or indirect symptoms of nocturia, such as insomnia, daytime fatigue or related somatic disease. Evaluation of nocturia includes a focused history of sleep patterns, cardiac problems, other voiding symptoms, previous urological surgery, fluid intake including alcohol and caffeine consumption, and other comorbidities that can account for excessive output of urine at night or bladder overactivity. A review of medications may reveal one or more drugs known to contribute to nocturia, such as diuretics, cardiac glycosides, lithium and phenytoin.

Physical examination should include evaluation of the lower extremities for oedema to help rule out cardiac or renal disease as contributory factors, and digital rectal exam to assess for an enlarged prostate. Obesity should be noted because it confers increased risk for sleep apnoea. Patients with sleep apnoea have transient periods of decreased serum oxygen levels. Hypoxaemia leads to increased pulmonary vascular resistance, which causes secretion of atrial natriuretic peptide (ANP) by the heart. ANP, in turn, is a diuretic, nocturnal secretion of which directly causes nocturia (see Nocturnal polyuria section, below) (8).

A frequency/volume chart is an essential tool in the proper evaluation of nocturia. The frequency/volume chart includes the volume and time of each void, the time of retiring to sleep and the time of arising during a 24- to 72-h period. The patient is instructed to fill in the chart carefully and inform the doctor whether the night measured was typical of a sleep cycle for him (9). Based on data from the chart, the patient can be categorised as having NP, reduced voided volumes, 24-h polyuria or mixed nocturia aetiology (Figure 1).

Using the frequency/volume chart

The International Continence Society's definition of nocturia is the condition of waking to void one or more times during the night (10). A stricter definition of nocturia, however, would be voiding that is preceded by and followed by sleep. This distinction is relevant to shift workers and others who sleep during the day. The essential point in evaluating frequency/volume chart data is measuring urinary activity during sleep hours and not actual nighttime hours. All patients should therefore record on the diary the time they first go to sleep, and awake for the final time so that logical interpretation of the diaries can be carried out. For the sake of convenience, the terms used here assume that the patient sleeps during the night and is awake during the daytime.

Twenty-four hour urine volume is the total volume of urine voided in 24 h. Nocturnal urine volume is the total volume of urine voided during the night. The volume of urine in the first morning void is included in this sum as it represents urine excreted by the kidneys during the hours of sleep. However, the first morning void is considered a normal diurnal voiding episode and should not be included with the tally of actual number of nightly voids (ANV). The nocturnal polyuria index (NPi) is calculated by dividing nocturnal urine volume by the total volume voided over the 24-h period recorded in the chart. If the NPi is > 33% then a diagnosis of NP, or overproduction of urine during sleep hours, can be made (9).

Maximum voided volume (MVV) is defined as the single largest volume of urine voided nocturnal urine volume divided by the MVV is known as the nocturia index (Ni). When Ni > 1, nocturia ensues owing

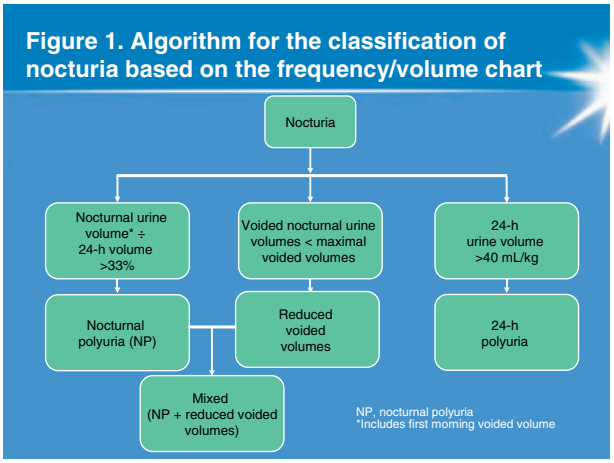

Figure 1 Algorithm for the classification of nocturia based on the frequency/volume chart

to a mismatch between nocturnal urine production and bladder capacity. When Ni−1 (predicted number of nightly voids; PNV), is less than ANV, nocturia occurs because of nighttime voided volumes less than the patients' actual bladder capacity. When MVV is itself low, nocturia is inevitable due to a likely inability to store even a modest nocturnal urine output. If these subjects also have an NPi > 33%, nocturia of mixed aetiology can be identified.

Twenty-four hour polyuria is defined as a 24-h urine output > 40 ml/kg. Polyuric patients have a general increase in urine output resulting in urinary frequency and nocturia despite normal voided volumes. Twenty-four hour polyuria is distinguished from NP, in that the latter is characterised by increased urine production during the night whereas 24-h urine production remains normal.

The frequency/volume chart is an essentially cost-free diagnostic tool that requires only diligence in recording voiding episodes by the patient for a 24-h period and the subsequent use of simple formulas by the physician. Once nocturia is categorised as to aetiology, the management can be directed to the underlying condition. Examples of frequency/volume chart analyses are shown in Table 1.

Nocturnal polyuria

Nocturnal polyuria refers to increased production of urine at night which is offset by lowered daytime urine production resulting in normal 24-h urine volume (10). The diagnosis of NP is a starting point as it may result from multiple underlying causes including diabetes mellitus, peripheral oedema (e.g. nephrotic syndrome hypoalbuminaemia, congestive heart failure), and excessive nighttime fluid or diuretic intake (Table 2). The workup for causes of NP includes history, physical and laboratory examination to look for signs and symptoms of these conditions.

Urine output normally decreases during the night and appears to be closely related to a corresponding increase in secretion of ADH. As ADH increases the resorption of water from the renal tubule, higher concentrations of ADH occurring at night result in the production of lower volumes of concentrated urine. Exogenous administration of ADH in the form of desmopressin (1-deamino-8-d-arginine-vasopressin; dDAVP) can be an effective approach to the treatment of nocturia associated with NP and is the only International Consultation on Incontinence-recommended therapy for this indication (11). Clinical studies in men have shown that, compared with placebo, desmopressin (taken at bedtime) significantly reduces the rate of nocturnal diuresis and, as a consequence, reduces the frequency of nocturnal voids (12). Desmopressin also increases the duration of the first sleep period in men by an average of 59% compared with 21% with placebo, corresponding to an additional period of uninterrupted sleep of approximately 2 h (12). Desmopressin improves quality of life compared with baseline in long-term treatment in the majority of nocturia patients. Adverse events associated with desmopressin are usually mild (13).

Central nervous system lesions because of cerebral vascular accidents can also disrupt ADH circadian rhythmicity by affecting the hypothalamic-pituitary axis. Exogenous administration of antidiuretic treatment may be appropriate in patients with nocturia secondary to neurologic insults. Desmopressin has been proven effective and well tolerated in the treatment of neurogenic diabetes insipidus (DI) (14,15), multiple sclerosis (16,17), Parkinson's disease (18) and autonomic dysfunction (19).

Obstructive sleep apnoea (OSA) refers to a sudden cessation of respiration because of airway obstruction during sleep. Prospective sleep study trials have shown an increase in the frequency of nocturia in patients with OSA (20,21). The mechanism for nocturia in these patients is an elevation in ANP levels because of increased right atrial transmural pressure resulting from hypoxia-induced pulmonary vasoconstriction (22). Polysomnographic sleep studies can confirm the diagnosis. Treatment of OSA with nasal continuous positive airway pressure has been shown to decrease the number of episodes from a median of three episodes to zero episodes per night. When

Table 1 Frequency/volume chart analysis: practice examples

24-h volume	1900 ml (no polyuria)	5000 ml	2500 ml (no polyuria)
Noctimal urine volume (includes first morning void)	1200 ml	1500 ml	1500 ml
Nocturia episodes	2	2	6
Nocturia urine volume/24-h volume	63% (nocturnal polyuria)	30% (normal)	60% (nocturnal polyuria)
Diagnosis	Nocturnal polyuria	24-h polyuria	Mixed aetiology (nocturnal polyuria and reduced voided volumes)

Table 2 Causes of nocturia

Nocturia category	Causes
Nocturnal polyuria	Congestive heart failure
	Obstructive sleep apnoea
	Peripheral oedema
	Venous stasis
	Nephrotic syndrome
	Hepatic failure
	Hypoalbuminaemia
	Excessive evening fluid intake
	Circadian defect in secretion or action of antidiuretic hormone
	Idiopathic water diuresis
Reduced voided volumes	Bladder outlet obstruction (Boo)
	Nocturnal detrusor overactivity
	Neurogenic bladder
	Cancer of bladder, prostate or urethra
	Learned voiding dysfunction
	Anxiety disorders
	Pharmacological agents
	Bladder calculi
	Ureteral calculi
24-h polyuria	Diabetes mellitus
	Diabetes insipidus
	Primary polydipsia

the uvula or tonsils cause obstruction, surgical removal of these organs can decrease OSA and associated nocturia.

Nocturnal polyuria can also be caused by right-sided congestive heart failure and lower extremity venous stasis disease through third-spacing of fluid in the lower extremities. Compressive stockings may prevent fluid accumulation and diminish nocturnal urinary output. Diuretics can also help decrease third-spacing of fluids, but must be taken with sufficient time before the patient goes to sleep, so that they relieve rather than worsen NP.

Reduced voided volumes

When voided volumes are exceeded by urinary volume during sleep hours the patient is inevitably awakened with the urge to void (otherwise the result is enuresis). Of course if voided volumes are low at all times, even if the patient voids during sleep at maximal capacity, the continued production of urine will likely surpass bladder capacity, resulting in nocturia. As noted above, when PNV < ANV, nocturia occurs because of nighttime voided volumes less than the patients' actual bladder capacity. The significance of this is that the greater the difference between the predicted and actual numbers of nocturnal voids, the more nocturia may be attributed to reduced voided volumes owing to urological as opposed to medical disorders. A significant association has been found between excessively reduced voided volumes and severe nocturia (5). Therefore, the referral to a urologist for evaluation and the treatment for causes of very reduced voided volumes has been recommended. 'Medical' (non-urological) causes of reduced voided volumes are exemplified by factors such as medications, and anxiety disorders, and can usually be discerned from patient history (Table 2).

Urological causes of reduced voided volumes include BOO, idiopathic nocturnal detrusor overactivity, neurogenic bladder, cystitis, bladder stones and neoplasms of the bladder, prostate or urethra. The workup for aetiology of diminished nocturnal bladder capacity (NBC) includes endoscopic and urodynamic techniques for diagnosing these disorders; treatment should be directed at the underlying cause(s).

In practice, however, many men are treated empirically for prostatic obstruction or detrusor instability in the absence of adequate evaluation. In the VA Cooperative Study Program Trial 1078 men with benign prostatic hyperplasia (BPH) had baseline nocturia of 2.5 episodes per night. The patients were randomised to receive treatment with terazosin, finasteride, terasozin and finasteride combined, or placebo. Nocturia episodes decreased to around two per night for all groups (23). No significant difference was found among any of the treatment arms, including placebo, suggesting that nocturia in men with BPH results from factors besides BOO.

Empirical treatment with antimuscarinics is not recommended as reduced voided volumes have not been shown to be related to daytime overactive bladder (OAB) (24). Antimuscarinics are appropriate for patients who demonstrate detrusor instability on urodynamic evaluation especially in the absence of BOO (because of the concern regarding precipitation of urinary retention). In patients with documented OAB, trospium chloride was shown to cause a small but a significant decrease in the number of mean nocturia episodes when compared with placebo (25).

Mixed nocturia

Patients with nocturia may commonly be shown to have both NP and reduced voided volumes. In a study of 194 nocturic patients, nocturia was due to NP in 7%, reduced voided volumes in 57%, 24-h polyuria in 23%, and a mixture of NP and reduced voided volumes in 36% (6). In these patients treatment should be directed at all relevant conditions. A study of patients with mixed nocturia treated by alpha-blockade alone (in which there was no placebo arm) revealed that nocturia decreased

from 3.3 to 2.4 episodes per night (26). Nocturnal urine volumes, however, were unaffected and patients therefore continued to have clinically significant nocturia despite improvement.

The management of patients with mixed aetiology of nocturia can be determined by assessing relative values of NP and reduced voided volumes. For example, if a patient has only slightly reduced nocturnal actual voided volumes compared with MVVs and an NPi of 70%, priority should be given to the treatment of the NP. In contrast, a patient with very reduced voided volumes and an NPi of 33% likely has a predominantly urological aetiology of nocturia. In many cases, there is a rationale for the use of antidiuretics (desmopressin) in combination with other therapies for lower urinary tract symptoms, although further studies are needed to fully evaluate the benefits of this approach.

Twenty-four hour polyuria

Twenty-four hour polyuria is commonly caused by diabetes mellitus and DI. Polydipsia exists concurrently with polyuria to prevent circulatory collapse. In primary polydipsia thirst is the cause, rather than result of, polyuria.

As with other causes of nocturia, the treatment of polyuria is tailored to its underlying aetiology. An overnight water deprivation test (WDT) can distinguish between DI and primary polydipsia (27). If the osmolality of the first morning void is > 800 mOsm/kg H_2O, it can be concluded that there is both normal ADH secretion and renal response. Polyuria with a normal WDT allows for a diagnosis of primary polydipsia. Psychogenic polydipsia is a psychiatric disorder that is treated with behavioural modification; dipsogenic polydipsia results from organic brain disease and is essentially untreatable.

If the WDT is abnormal the patient either has deficient production of ADH (central DI) or inappropriate renal response to ADH (nephrogenic DI). These conditions can be distinguished with a renal concentrating capacity test (RCCT). Following the administration of oral or intranasal desmopressin concurrent with water restriction, a urine osmolality of > 800 mOsm/kg represents normal renal concentrating ability; thus the patient has central DI. Central DI can be treated with dDAVP administration. If the RCCT yields low urinary osmolality (<500 mOsm/kg), polyuria is due to nephrogenic DI. The latter may be due to certain pharmacologic agents (e.g. tetracyclines, lithium) or primary renal disease.

In patients with polyuria owing to diabetes mellitus, treatment of the underlying condition with antiglycaemics or diet significantly decreases urine output as the osmotic effect of glycosuria is corrected.

Conclusions

Nocturia is an important factor in causing fragmented sleep, leading to a variety of health hazards in men. Nocturia can be caused by NP, reduced voided volumes, 24-h polyuria or mixed aetiology. The frequency/volume chart is the principal tool for characterising nocturia according to the cause-specific aetiologies, allowing for cause-specific treatment.

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