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Abstract
Nocturia is a common and bothersome symptom that impacts on sleep–quality and quality of life. Nocturia often has a multi-factorial etiology which makes thorough assessment of the complaint indispensable.

This review summarizes the definition of nocturia, its epidemiology, clinical presentation, pathophysiology, diagnostics, and treatment options with special reference to older men.

Nocturia is defined as a nocturnal voiding frequency of two or more, based on impact on quality of life. It is very prevalent in older men. Apart from the negative effects of sleep-disruption, it may be a risk-factor for hip fractures and increased mortality. Most common causes are: nocturnal polyuria, 24-h polyuria, overactive bladder (sometimes due to BPH) and sleep disturbance. A clear understanding of the etiology in the individual patient is indispensable when addressing the various possible causes and comorbidities. Most important tool for this is the frequency–volume chart, but also patient history, physical examination and serum analysis. For treatment, lifestyle adjustments are often helpful. Medical therapy with 5-alpha reductase inhibitors, alpha-blockers, a combination of the two, or anti-muscarinic, has a limited effect. Most important medical option is desmopressin (arginine vasopressin analogue); however, treatment with this drug is limited to men under 65 years mainly due to the risk of hyponatraemia.

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1. Introduction

Nocturia, or waking at night to void, is a common symptom in adult men and women. It is consistently reported as one of the most bothersome lower urinary tract symptoms (LUTS). Nocturia has a variable pathogenesis, potentially involving a wide range of organ systems and environmental influences [1]. This review focuses on older men (aged 50 years and over).

1.1. Definition

The International Continence Society (ICS) defined nocturia as ‘the complaint that the individual has to wake at night one or more times to void’ [2,3]. Each void must be preceded and followed by sleep. This definition does not include waking for other reasons at night (e.g. noise) followed by voiding for convenience, which is proposed to be termed ‘night-time frequency’ [4]. Therefore, the current definition of nocturia (one time waking at night to void is nocturia), is very strict and based on number of voids rather than patient complaints and therefore still subject to debate [4,5].

The ICS standardisation report also defines nocturnal polyuria (NP) and 24-h (or global) polyuria. Since these two types of polyuria are associated with nocturia in a significant number of cases, it is appropriate to recapitulate these definitions as well: 24-h polyuria is defined as a urine output exceeding 40 ml/kg bodyweight per 24 h; NP is defined as a nocturnal urine output (including the first morning void) of >33% of the total 24-h voided volume in the elderly [3].

Despite the strict ICS definition of nocturia, only two or more nocturnal seem to negatively affect quality of life (QoL) [6]. This is mostly attributed to sleep fragmentation and decline in sleep quality [7,8], but another serious problem is an increased risk of falls and (hip) fractures [9,10], (co-)morbidities, and even an increased mortality-rate [8,11,12]. The latter association, mainly seems strong in adults aged 65 and under [13].

1.2. Prevalence and incidence

The prevalence of nocturia in older men is high and increases with age: a systematic review on this subject showed that in men in their 70s and 80s, 68.9–93% reported at least 1 void per night, and 29–59% reported at least 2 voids per night [14]. This high prevalence rate is seen in populations of various ethnicity and nationality throughout the world [15–22].

Multiple ways of assessing nocturia have been used to determine the prevalence of nocturia in the open population: questionnaires, such as the international prostate symptom score (IPSS) and the American Urological Association symptom score (AUA-SS), but also frequency–volume charts (FVCs). Although no evidence-based consensus is available, a 3-day FVC seems to be preferable to questionnaires in terms of patient compliance and because of lack of recall-bias [16,23]. Furthermore, different definitions of (clinically relevant) nocturia have been used. This may explain the variability in prevalence rates among different studies.

Hakkinen et al. were the first to report on incidence rates of nocturia, however, they also showed that nocturia, just like all LUTS, is a fluctuating symptom [18]. This was confirmed by van Doorn et al. [24], showing that the fluctuation of nocturia in older men is as high as 21.6–51.2% after 2.1 years. Prevalence estimates therefore seem to be more relevant than incidence-rates when trying to gain insight in the epidemiology of nocturia [18,25,26].

2. Clinical presentation, bother and impact of nocturia

Bladder storage symptoms like nocturia are more bothersome than voiding symptoms such as incomplete emptying [27]. Furthermore, nocturia has been shown to be associated with a significant decline in health related QoL (HRQoL) as measured on the 15D HRQoL instrument. The decline was seen in almost all of the 15 dimensions measured, among which were: sleeping, sexual activity, comfort, depression, mental function, and vitality [6]. The degree of bother seems to be related to sleep quality as it would interfere with slow-wave (deep) sleep [7,8,28]. However, a recent study by Bal et al. showed that most nocturia episodes occur during superficial sleep and therefore had no significant impact on sleep quality [29]. Furthermore, despite the significance of these complaints, not many men seek help from a healthcare professional for an isolated complaint of nocturia. In an analysis of the Krimp study, only 9.5% of the population sought help for LUTS, whereas the prevalence of nocturia was 34.6% [26,30]. So, there is a discrepancy between the presumed negative impact on quality of life and actual healthcare-seeking behaviour in older men with nocturia; possibly an isolated symptom of nocturia is less bothersome than nocturia as a part of a symptom complex, but this needs further study.

3. Pathophysiology

Nocturia is a condition with many possible causes. The causes can generally be categorized in: (1) bladder storage problems: decreased (nocturnal) bladder capacity either caused by benign prostatic hyperplasia (BPH) with detrusor overactivity and/or postvoid residual volume or by an isolated overactive bladder (OAB) syndrome, (2) nocturnal polyuria (NP), (3) 24-h polyuria, and (4) sleep disturbance or a combination of these factors. Not all problems are equally common: the most common causes of nocturia in men found in the population-based FINNO study were: urinary urgency, BPH, and sleep disruption. Other causes were obesity and the use of anti-depressants [31]. Obesity is a common co-morbidity throughout all western countries and is related to LUTS. Asplund found that the number of nocturia events increases with a rising body-mass index [32].

3.1. Overactive bladder

The ICS defines overactive bladder (OAB) as a symptom-defined condition characterised by urinary urgency, with or without urinary incontinence, usually with increased daytime frequency and nocturia (2). The association between nocturia and OAB is not well understood, but in the population-based FINNO-study 17% of all men >60 years old reported OAB, and 31% of men with nocturia reported OAB [25]. Data from the population-based Krimp study suggest that OAB plays a role in the genesis of nocturia based on the
finding that the maximal voided volume, a proxy for the functional bladder capacity, in older men declines with age and over time [33].

3.2. Nocturnal polyuria

NP is another important cause of nocturia. An Austrian study in nocturia patients showed that 50% of all men had NP [34]. NP was defined as a nocturnal voided volume of >33% of the total 24-h voided volume. However, van Doorn et al. pointed out that in a general population of older men the prevalence of NP according to this definition is very high as well: it ranges from 41.8% in 50–55 year-old men to 56.9% in 70–78 year-old men [35]. Therefore, Blanker et al. suggested a nocturnal urine production of >90 ml/h as a more appropriate (albeit only modest) predictor of nocturia in older men [36]. Two important causes of NP are identified: incorrect arginine vasopressin levels which might be present in up to 4% of the elderly [37], and the re-absorption of third space lower extremity fluid during sleep [38].

3.3. 24-h polyuria

24-h polyuria is most commonly caused by diabetes mellitus and diabetes insipidus (DI). Polydipsia can exist concurrently with polyuria to prevent circulatory collapse [39]. Another cause is primary (behavioural) polydipsia. An overnight water deprivation test can distinguish between DI and primary polydipsia.

3.4. Sleep disturbance

In the FINNO-study, sleep disruption (defined by snoring, as an indicator for obstructive sleep apnea (OSA)) was an important cause of nocturia [31]. However, there are some limitations to this conclusion: there are no validated nocturia instruments that determine why the patient woke up, why he voided (e.g. convenience, habit or urge), and whether the patient went back to sleep [40]. A recent polysomnographic study suggests that nocturia may indeed not be the major cause of sleep disruption but that OSA negatively interferes with sleep efficacy, total and rapid eye movement (REM) sleep duration [29].

4. Co-morbidity and mortality

Nocturia is an independent risk factor for lowered sleep quality, which, in turn, might be associated with an increased mortality, hypertension, obesity and glucose intolerance [41,42]. Nocturia in itself is also associated with an increased mortality-risk. Four questionnaire-based studies have been reported which showed a significantly higher mortality rate (increased hazard ratio (HR)) in subjects with nocturia [11-13,43]. All studies corrected for age in their multivariable analysis, except the study of Bursztyn et al. in which only 70-year-olds were included; they described an increased HR for nocturia only in men and women who also suffered from congestive heart disease. The largest study, by Kupelian et al., showed that the relation in older men was attenuated, but still significant [13]. The Krimpen-study provides the only FVC-based analysis of the association between nocturia and mortality: in men older than 50 years there was no statistically significant association [26]. It was suggested that future studies should focus on the difference between convenience voids at night and nocturia.

5. Diagnostic evaluation

Nocturia has been identified as the most bothersome and prevalent LUTS. Therefore, it is surprising that in clinical practice men do not often present with an isolated complaint of nocturia, but rather as a part of a system of complaints like LUTS. Therefore, clinicians should be alert for the possibility of the existence of nocturia in their patients. Initial assessment should involve a thorough history to clarify the patient’s complaints, possible underlying diseases, such as cardiovascular disease, and fluid intake (including alcoholic beverages and drinks containing caffeine).

Questionnaires such as the 15D HRQoL instrument are useful when quantifying the effect of nocturia on the daily bother [44]. Urinalysis, urine culture and cytology should also be carried out [40]. Next, and most importantly, a 3-day FVC should be completed on which the patient records the volume and timing of each void during the day and night [16,23]. The patterns revealed by the FVC provide valuable information on the etiology and treatment options. The use of FVC should be preferred above the use of questionnaires like the IPSS because of discrepancies in nocturnal voiding frequencies recorded [15].

6. Management of nocturia

A successful treatment of nocturia should result in a clinically, and not just statistically, significant reduction in nocturnal voiding frequency. Furthermore, therapy should have a positive effect on the negative issues associated with nocturia. Unfortunately, there is only limited evidence of the efficacy of available options [40].

6.1. Behavioural

The initial strategy in most patients is to suggest lifestyle changes such as pre-emptive voiding (before going to sleep), nocturnal dehydration and the avoidance of caffeinated beverages and alcohol-intake [40]. Although never officially researched, they seem intuitively correct lifestyle changes to promote in patients with complaints of nocturia.

6.2. Pharmacotherapy

6.2.1. Alpha-blockers and 5-alpha reductase inhibitors (5-ARI), alone or in combination

Data from the Veterans' Administration Cooperative Study Program trial in men aged 45–80 years was secondary analyzed, and showed a significantly greater improvement in nocturia frequency for the terazosin (TER) arm compared to the finasteride (FIN), combination (FIN + TER) and placebo arm (PLA). Men who started on TER improved from 2.5 to 1.8 nocturnal voids, while TER + FIN resulted in a reduction from 2.5 to 2.0 nocturnal voids. The placebo arm showed a reduction from 2.4 to 2.1 voids per night. Although the improvement with TER was significant compared to placebo, it only improved the nocturnal voiding frequency (NVF) by 0.4 over placebo [45]. Yoshimura et al. showed a clinical improvement of NVF (<2 after treatment) in only 13.9% of patients treated with tamsulosin [46].

In an analysis of the Medical Therapy of Prostatic Symptoms trial (MTOPS) nocturia frequency improved significantly compared to placebo after using the combination of finasteride and doxazosin (FIN + DOX) and doxazosin alone (DOX) for one year. However, FIN + DOX and DOX resulted in clinically negligible improvements in mean nocturia frequency of 0.58 and 0.54, respectively [47].

An analysis of the COMBAT-study showed that after 4 years of treatment the mean reductions in the question 7 score of the IPSS [nocturia question] were significantly [p < 0.008] greater with combined therapy than with dutasteride or tamsulosin alone [48]. Unfortunately, the actual change in nocturia frequency was not reported. However, the total IPSS change after 4 years was 1.4, 1.9 and 2.3 points respectively for the tamsulosin, the dutasteride and the combination group; this implies that the nocturia frequency change in the combination group was less than 0.4 and 0.9 lower
than in the tamsulosin and the dutasteride group, respectively. Clinically this is not very relevant.

In summary, 5-ARI, either alone or in combination with an alpha-blocker, or an alpha-blocker alone seem to have a minimal to negligible effect on the NVF in men with BPH.

6.2.2. Anti-muscarinics, alone or as add-on to alpha-blocker treatment

Zinner et al. found in 389 (74.4%) female and 134 (25.6%) male patients with OAB symptoms, that after 12 weeks of treatment with trosipum chloride, the average NVF decreased by 0.47 vs. 0.29 in the placebo group [49].

Fesoterodine, statistically significantly improved NVF in a study-population of 836, including 201 men, by –0.59 for 4 mg daily vs. –0.39 for the placebo group [50]. A head-to-head comparison between fesoterodine and tolterodine showed no significant improvement of NVF for either medication vs. placebo [51].

Several studies in men have reported the effect of an anti-muscarinic drug used as an add-on after an unsatisfactory response to an alpha-blocker alone. Tolterodine-ER 4 mg was added to an [unspecified] alphablocker and compared to placebo added to the alpha-blocker: there were no significant differences in change in nocturnal micturitions or nocturnal urgency episodes [52].

The ASSIST study group reported that among three treatment arms (tamsulosin 0.4 mg + placebo vs. tamsulosin 0.4 mg + solifenacin 2.5 mg vs. tamsulosin 0.4 mg + solifenacin 5 mg) there were neither significant difference in change in bladder diary recorded nocturia episodes per 24 h nor in the night-time frequency score [53]. In summary, anti-muscarinics either alone or as an add-on to alpha-blocker treatment seems to have a minimal to negligible effect on NVF in men with BPH.

6.2.3. Timed diuretic therapy

Diuretics are often prescribed for peripheral oedema without attention to the time of day at which they would be most effective [40]. In patients with NP due to re-absorption of third space lower extremity fluid at night, mis-timing actually could lead to exacerbation of NP. Therefore it is recommended to administer diuretics during the mid-to-late afternoon, when diuresis before going to bed is the goal.

6.2.4. Anti-diuretic therapy

Anti-diuretic therapy may be appropriate in patients whose nocturia is caused by NP, but who do not have a high nightly fluid intake, and in whom other causes of NP have been excluded. In some countries, anti-diuretic therapy with the synthetic analogue of arginine vasopressin, desmopressin, is the only pharmacological therapy which is indicated specifically for nocturia [40]. Because of the evidence-base of its specific anti-diuretic action, desmopressin has a grade A recommendation from the International Consultation on Incontinence [54]. Several randomized placebo-controlled trials have proven its efficacy: compared to placebo, Cannon et al. [58] showed a decrease of 0.8 voids per night in men treated with 40 µg desmopressin. Mattiaison et al. [59] showed an identical result [51,52]. Although the results from both studies were statistically significant, patients still had a rounded average NVF of 2 or more.

And important adverse event found in both studies was hyponatraemia. The primary predictor for hyponatraemia is age; therefore, desmopressin use is currently not indicated in patients >65 years. Serum sodium monitoring at baseline and early in treatment in older patients can greatly reduce the risk of developing hyponatraemia.

6.2.5. Alternative pharmacotherapy

Patients often initially try herbal supplements. In the USA, 50–90% of men have tried supplements before seeking medical treatment for their LUTS/BPH [55]. The most often used supplement for complaints of nocturia is Serenoa repens, a saw palmetto berry extract. However, a placebo-controlled trial showed no improvement in LUTS measured by the AUA-SS [56]. Therefore, we feel that natural supplements are not helpful in the treatment of nocturia.

6.3. Surgical options

Procedures such as transurethral resection of the prostate (TURP) are offered to patients with BPH [40]. However, nocturia is the least responsive symptom to treatment of BPH, both medically and surgically [57]. In a study by Yoshimura et al. a prevalence reduction of only 19.6% in nocturia was found after TURP [46]. BPH-patients should be counselled on the effects of TURP on nocturia: specifically, a reduction should not be expected when NP is a part of the problem.

7. Conclusions and recommendations

Nocturia is a highly bothersome symptom with a prevalence that increases with age. Especially a NVF of two or more gives rise to a diminished QoL, which seems to be attributable to sleep deprivation and decline in sleep quality. Furthermore, it might increase the risk of hip-fractures due to nightly falls and can possibly even result in a higher mortality-risk. Therefore, nocturia might be regarded as a condition rather than a symptom. It is surprising that, although it is highly bothersome, it is not an initial complaint in many patients. Therefore, physicians should be alert when patients come in with complaints of LUTS or sleep-related complaints.

As nocturia has many possible causes, a thorough history, serum analysis and, most importantly, a frequency–volume chart, play a key role in its analysis. Treatment should be tailored to the causes of the nocturia in the individual patient.

Although many (pharmacological) options exist, none of these single-handedly seems to have a clinically significant effect on the NVF and QoL of the patient. Future studies should focus on a validated means to objectively an increase in QoL with the combination of lifestyle advices and medication to restore the proper balance between nocturnal urine production and the nocturnal bladder capacity. The combination of an anti-diuretic and an anti-muscarinic drug is an interesting subject for future clinical trials.

Contributors

B. van Doorn, MD was responsible for designing the review, J.L.H.R. Bosch, MD, PhD critically revised the manuscript.

Competing interests

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