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REVIEW

Nocturia: an overview of evaluation and treatment

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ABSTRACT

OBJECTIVE: Nocturia is a highly prevalent and bothersome condition. It is associated with multiple medical comorbidities and an increased mortality. Recent investigations have improved understanding of nocturia and its evaluation and treatment. This paper aims to review the classification, etiology, associated medical conditions, evaluation, and treatment of nocturia.

MATERIALS AND METHODS: A review was conducted surveying published clinical trials, meta-analyses and current clinical practice guidelines on nocturia available as of July 2014. Epidemiology, presentation, evaluation, and treatment recommendations are presented.

RESULTS: Nocturia is a multifactorial condition. Evaluation should include thorough medical history documenting fluid intake, quantified and timed urine output, as well as signs and symptoms of other comorbid conditions. Thorough physical Exam should focus upon detection of conditions contributing to nocturia. Treatment should consist of optimization of underlying medical conditions, behavioral modifications, followed by medications if conservative management fails. Antimuscarinics and alpha blockers have not demonstrated to be effective. Recent studies indicate a possible role of desmopressin in the treatment of nocturia, but concerns about hyponatremia in older patients remain.

CONCLUSIONS: Nocturia is a bothersome condition. Treatment of associated co-morbidities is central to treatment. Currently available treatments are available, but efficacy is limited.

Keywords: nocturia, nocturnal polyuria, lower urinary tract symptoms

INTRODUCTION

Nocturia is defined by the International Continence Society (ICS) as waking from sleep one or more times to void [1]. It is a highly prevalent and bothersome condition, however patients often do not report symptoms or seek treatment. Patients may believe nocturia to be an untreatable condition or a benign consequence of aging. Evidence suggests nocturia becomes bothersome to patients at 2 or more voids per night [2]. At this severity, nocturia negatively impacts patient-reported quality of life (QoL) and may adversely impact patient mortality [3]. This review aims to discuss the epidemiology, etiology, associated medical conditions, diagnosis, and treatment of nocturia.

EPIDEMIOLOGY

Estimates of the prevalence of nocturia vary due to variations in definitions, symptom assessment, and data collection. The population-based Finnish National Nocturia and Overactive Bladder (FINNO) Study collected data on men and women aged 18 to 79. Approximately 40% of subjects reported ≥ 1 void per night, and about one in eight participants reported ≥ 2 voids per night [4]. Overall, nocturia was equally prevalent in both sexes; however, the age distribution differs between the sexes. One third of young women (18–29 years) participating in the study reported nocturia at least once per night, compared to 1 in 9 of young men. The prevalence of nocturia increases with age twice as rapidly in men when compared to women. By the sixth decade of life, the percentage of nocturia reported in both sexes is the same: half of both men and women 50–59 years reported nocturia. In older cohorts, the prevalence was high in both sexes but slightly higher among men, with 45% of men and 37% of women reporting nocturia [5].

Other population studies confirm that nocturia increases with age and is common in the elderly. A questionnaire-based study found the prevalence of nocturia increased from 56% in men > 45 years to nearly 90% of men ≥ 70 years [6]. In a recent meta-analysis, it was found that the majority of elderly men and women experience clinically significant nocturia: 29% to 59.3% in men and 28.3 to 61.5% in women aged ≥ 70 years experienced 2 or more voids per night.

Evidence indicates variability between ethnic groups. The Boston Area Community Health study, a survey of 5,506 adults 30–79 years, found a higher prevalence of nocturia in minorities when compared to non-Hispanic whites: 38.6% of African Americans compared to 23.3% of whites reported ≥ 1 episodes of nighttime voiding ($P < 0.001$) [8].

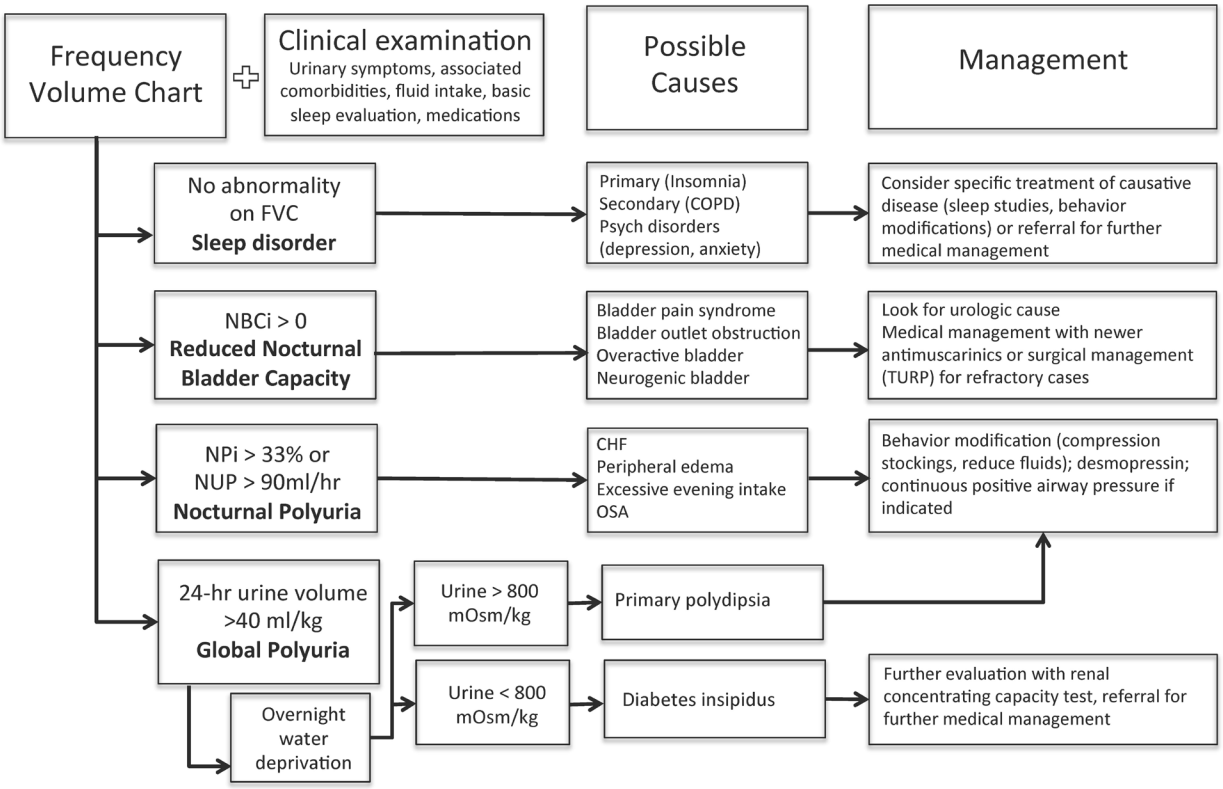

Figure 1. Evaluation and management of nocturia. FVC, frequency volume chart; NBCi, nocturnal bladder capacity index; NPi, nocturnal polyuria index; NUP, nocturnal urine production; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; OSA, obstructive sleep apnea; TURP, transurethral resection of the prostate

ETIOLOGY

Multiple medical conditions are associated with nocturia and result in a complex interplay of cause and effect. The etiology of nocturia is multifaceted and can be clarified using Frequency Volume Charts (FVCs), also known as voiding diaries, to quantify the timing and volume of 24 hour and nocturnal urine output. The data obtained from FVC can classify nocturia into the following subtypes, as shown in **Figure 1**. Reduced bladder capacityacity is defined as a reduced capacity for the bladder to store urine, whether globally or only during sleep. Global Polyuria is excessive production of urine during daytime and night, quantified as a volume of greater than 40 ml/kg in 24 hours. Nocturnal Polyuria is defined as nocturnal urine production > 33% of total 24 hour urine output at any age [9]. The Nocturnal Polyuria Index (NPi) is calculated by dividing nocturnal urine output by the total 24 hour urine output. Another measure that has been proposed to define NP is nocturnal urine production (NUP) in excess of 90 ml/hr. This rate was two standard deviations above the mean in the Krimpen study, a longitudinal study of community dwelling men age 50-78 followed at intervals for 6.5 years using FVCs [10].

Cardiovascular diseases such as congestive health failure (CHF), venous insufficiency, and peripheral artery disease (PAD) can both worsen and be made worse by nocturia. Third spacing caused by venous disease of the legs or CHF may cause nocturnal polyuria resulting from fluid mobilization while recumbent during the hours of sleep. Nocturia in the absence of nocturnal polyuria can be caused by detrusor over activity, a result of chronic pelvic ischemia [11] or white matter disease [12].

Lastly, insomnia compounds nocturnal wakefulness by providing an independent stimulus for awakening. Patients then void once awake. It is difficult for patients to determine if they were awakened by an urge to void, or awoke and then incidentally noticed the urge to void once awake [13].

ASSOCIATED MEDICAL COMORBIDITIES

Nocturia is associated with a myriad of comorbidities, and can signify an undiagnosed or undertreated medical condition. Recent longitudinal data have shown nocturia to be predictive of incident coronary artery disease in men < 60 years. Of the 5,506 participants in the BACH survey, 1,872 (28.4%) reported nocturia > 2 times per night. 45% of respondents who self-reported nocturia also reported cardiac disease, an odds ratio (OR) of 2.28 over the subjects without nocturia. When controlling for age, sex, BMI, and diabetes, this OR remained statistically significant at 1.37 [14].

Epidemiological studies report a relationship between nocturia and hypertension. In an analysis of a data obtained from a Japanese screening program, investigators found the prevalence of hypertension was 34% among subjects reporting nocturia, as compared to 24% for the entire sample of subjects [15].

Diabetes Mellitus contributes to nocturia via several different mechanisms. Poorly controlled serum glucose levels can cause polyuria secondary to osmotic diuresis. Diabetes can cause autonomic dysfunction, leading to either detrusor hypoactivity or overactive bladder. However,

the Fujiwara-kyo study, a cross-sectional questionnaire-based study of 3,685 men, recently questioned the association between diabetes and nocturia. Though an association has been reported in prior studies, Hirayama *et al*. did not find an association between HbA1c and the incidence of nocturia [16].

Patients presenting with nocturia may have undiagnosed obstructive sleep apnea (OSA). A case control study conducted in Israel examined the risk of OSA in men being evaluated for lower urinary tract symptoms. Subjects completed questionnaires to assess OSA risk and symptomatology. OSA was positively correlated with nocturia. The odds ratio for OSA was 1.0 in patients reporting no nocturia, but was 2.44 in subjects reporting 2 episodes of nocturia, 5.75 in patients reporting 2–3 nightly episodes, and 12.3 in patients reporting > 3 voids per night [17]. Patients with symptoms of OSA, including daytime somnolence, obesity, and loud snoring, should undergo overnight polysomnography for diagnosis. Continuous positive airway pressure (CPAP) has been shown to reduce number of nocturnal voids in patients with OSA. A nonrandomized prospective study comparing nocturia severity before and following CPAP treatment found 73 (75%) of 97 patients reporting improvement in their nocturia. The mean number of awakenings in the sleep laboratory was reduced from 1.1 ± 0.9 before CPAP, to 0.5 ± 0.6 awakenings after initiation of CPAP ($P < 0.001$). The number of awakenings at home was reduced to a greater degree, from 2.5 ± 2.4 before CPAP, to 0.7 ± 0.6 times per night ($P < 0.001$) [18].

Nocturia has been associated with major depressive disorder. The Tampere Aging Male Urologic Study was a survey study of men 50 to 70 years old living in or around Tampere, Finland. Baseline surveys were administered in 1994 and follow up surveys were sent in 1999. Nocturia was labeled mild (1 to 2 voids per night), moderate (3 to 4 voids per night), or severe (5 or more voids per night) based on participant survey response. Depressive symptoms were assessed with the Mental Health Inventory 5-Item Version questionnaire. Eight hundred and thirty five subjects had mild nocturia, 53 had moderate or severe nocturia, and 745 were nocturia-free. Men with mild to moderate depressive symptoms were 3 times (95% CI 1.6–5.7 more likely to have nocturia, while men with moderate or severe depression were 6.7 times more likely to have nocturia (95% CI 2.4–18.5). Men with depressive symptoms but without nocturia at baseline were found to have 2.8 higher risk (95% CI 1.5–5.2) of developing moderate or severe nocturia, compared to men without baseline depression. Untreated depression increased the risk development of nocturia over treated depression (RR 3.3, 95% CI 1.7–6.2 vs 1.7, 95% CI 0.4–7.4). Baseline nocturia was not found to have significant effect on depressive symptoms at follow up [19]. These findings would suggest a possible causative effect of depressive symptoms on nocturia and point to the need for further study.

Importantly, nocturia is associated with increased all-cause mortality. In an analysis of data from the National Health and Nutrition Examination Survey (NHANES) III, Kupelian *et al*. assessed the association between nocturia and all-cause mortality. Nocturia was assessed by the question "How many times do you get up at night to urinate?" Possible answers were 0, 1, 2, or 3 or more times. Mortality data was obtained from the National Death Index. Respondents were stratified by age and hazard ratios were constructed for each age group based on their mortality as a function of nighttime voids. Overall, responders' survival decreased with increasing number of nocturia episodes. Men aged 65–90 with 1, 2, and 3 or more nighttime voids had increased risk of death of 1.07, 1.38, and 1.45 respectively when compared to men with no nocturia ($P < 0.001$). The results were more pronounced in younger men. Men aged 20–49 with 1, 2, and 3 or more nighttime voids had increased risk of death, with hazard ratio of 1.40, 2.55 and 3.94 respectively when compared to men with no nocturia ($P < 0.001$). Middle-aged women aged 50–64 with 1, 2 and 3 or more nighttime voids showed a trend toward an increased risk of death of 1.13, 2.25, 1.87 respectively ($P = 0.003$). A less pronounced trend was seen in elderly women, aged 65-90. Increased risk of death in this group was 0.84, 1.04, 1.12 ($P = 0.012$). The differences among women aged 20–49 were not statistically significant ($P = 0.705$) [20].

EVALUATION

The evaluation of nocturia begins with a detailed history. If nocturia is reported, patients should be asked about urinary symptoms, fluid intake, medications, and comorbid medical conditions.

Clinicians should ask about daytime and evening frequency, urinary urgency, and other associated lower urinary tract symptoms. Patients should be asked to quantify the number of times they wake to void at night and complete a voiding diary. Patients should be asked to describe their oral fluid intake. Patients may drink large volumes of fluid throughout the day or in the evening before going to sleep. Patients' caffeine and alcohol intake should be assessed.

Underlying medical conditions such as cardiovascular diseases and diabetes should be sought and optimized. Addressing underlying illness is important for overall patient health, but may also reduce nocturia symptomatology. The treatment of peripheral edema with compression stockings, for example, has been shown to reduce number of nightly voids [21]. Patients should be asked about symptoms of sleep apnea, such as loud snoring, and be referred for sleep study evaluation if present. A review of patients' medications should be performed to identify pharmaceuticals that may cause or exacerbate nocturia. Changing timing of the administration of diuretics from bedtime to afternoon, for example, may alleviate symptoms.

Physical Exam should focus upon detection of conditions contributing to nocturia. Cardiovascular exam should be performed to detect CHF. Abdominal exam should include palpation of the bladder to rule out urinary retention. Digital rectal exam should be performed to evaluate prostate size, but also to assess rectal tone and check for stool impaction. Neurological exam should include evaluation of perineal sensation and presence of anal wink.

Urinalysis should be done in all cases, with urine culture and urine cytology in case of bacteriuria or hematuria, respectively. Upper tract imaging and cystoscopy should be done if only indicated by aforementioned tests.

MANAGEMENT

First-line management involves behavior modification. Such maneuvers are inexpensive and noninvasive, and therefore should be attempted before other interventions. Patients should be counseled against drinking alcoholic or caffeinated beverages. If fluid intake is excessive, it should be reduced to just quench thirst. A study conducted in South Korea showed patients a video explaining the physiology of storing and voiding urine and the regulation of fluid intake. After the training

session, QoL scores, nocturia index (Ni, nocturnal urine volume/functional bladder capacity), and nocturnal bladder capacity index (NBCi, actual number of nightly voids—predicted nightly voids [Ni–1]; the higher the NBCi, the more nocturia is attributable to voided volumes lower than capacity) were significantly improved. Nocturia episodes decreased from 2.6 (CI 2.4–2.8) to 1.1 (CI 0.8–1.3) ($P < 0.001$) [22].

If behavioral maneuvers fail, treatment with pharmacological agents is indicated. 5-alpha reductase inhibitors (5ARIs) are commonly used in men for the treatment of men with prostatic obstruction and lower urinary tract symptoms (LUTS), but their role in the treatment of nocturia is controversial. The Department of Veterans Affairs Cooperative Study Trial randomly assigned 1,229 men with BPH to either terazosin, finasteride, a combination, or placebo. A subgroup analysis looked found that 788 of these subjects had 2 or more nocturia episodes. At twelve months, a 50% reduction in nocturia was seen in 39%, 25%, 32%, and 22% in the terazosin, finasteride, combination, and placebo groups respectively. The percentage of subjects that saw a reduction of nocturia by 50% in the finasteride group was only 3% greater than the placebo group [23]. The Medical Therapy of Prostatic Symptoms (MTOPS) trial is often used to qualify the results of the VA Cooperative Study trial. MTOPS followed more men with BPH for a longer period of time than the VA Cooperative Study and found finasteride and combination finasteride and doxazosin effective at reducing LUTS. A secondary analysis of the MTOPS trial data calculated the mean number of nocturia episodes in each treatment group. At four years, episodes of nocturia were reduced by 0.61, 0.60, 0.77, and 0.80 in the placebo, finasteride, doxasozin, and combination groups respectively [24]. Again, finasteride showed no advantage over placebo in the treatment of nocturia.

Alpha-blockers have been shown to have a measurable, if modest, effect on nocturia. As mentioned above, a subgroup analysis of the VA Cooperative Study trial found a reduction of nocturia episodes of 50% or more 39% of men on terazosin, compared to 22% in the placebo group. Similarly, the subgroup analysis of the MTOPS trial data found the mean reduction of nocturia episodes in men on doxazosin was 0.80, compared to 0.61 in the placebo group. Though these findings are statistically significant, a 0.2 decrease in nocturia episodes is not clinically significant.

Antimuscarinics are useful in the treatment of overactive bladder (OAB) and often used in the treatment of nocturia. Some studies have suggested effectiveness of anticholinergics, but scrutiny of the data questions these conclusions. A study involving 131 women with urge or mixed urinary incontinence and nocturia randomized these women to receive either oxybutynin or placebo. The dosages for those in the treatment group were titrated to effectiveness, with a maximal total daily dose of 15 mg. After eight weeks of treatment, oxybutynin reduced nocturia by 0.30 episodes vs no change in the placebo group ($P = 0.007$). Though statistically significant, a change of 0.30 voids per night cannot be said to be clinically significant [25]. Similarly, a subgroup analysis of a randomized control trial conducted in Japan examined the efficacy of solifenacin, at 5 mg and 10 mg, vs placebo in 962 Japanese subjects with OAB. Nocturia was reduced by 0.42 and 0.46 episodes, by the 5 mg and 10 mg doses, respectively [26]. The change with 10 mg was statistically significant but the small change over placebo is not likely clinically relevant. Finally, a randomized placebo-controlled trial enrolled 850 men with nocturia and randomized them to receive either the anti-muscarinic tolterodine ER or placebo and followed for 12 weeks. Tolterodine reduced overnight urgency, but the median percentage change in nocturia from baseline was only -23% vs -19% in the placebo group ($P = 0.145$), not statistically significant [27]. Promising results were found with fesoterodine. 963 subjects with ≥ 2 nocturia episodes were randomized to receive either fesoterodine or placebo and followed for 12 weeks. Fesoterodine significantly reduced nocturnal urgency episodes over placebo (-1.28 vs -1.07, $P = 0.003$), as were nocturia episodes (-1.02 vs -0.85, $P < 0.01$) [28]. Further study of the newer antimuscarinics' efficacy in nocturia treatment is needed in order to demonstrate clinically significant efficacy.

Recently, there has been much interest in the use of desmopressin, a synthetic analogue of arginine vasopressin, to treat nocturia. Patients with severe nocturia have been found to lack the normal nocturnal increase in vasopressin levels [29]. Van Kerrebroeck and colleagues conducted a double-blind, placebo-controlled trial of the effects desmopressin on nocturia. One hundred and twenty seven people, with ≥ 2 voids nightly, were randomized to receive either an escalating dose of desmopressin or placebo. After 3 weeks, a clinically significant reduction (> 50% reduction in mean number of voids) was found in 33% of the treatment arm, compared to 11% of the placebo arm ($P = 0.0014$) [30].

In a study looking at the durability of the effect of desmopressin, Juul pooled data from three randomized clinical trials. The efficacy of desmopressin was maintained for the duration of long-term treatment. Patients taking varying doses (25 µg, 50 µg, and 100 µg) of desmopressin sublingual "melt" tablets for 52 weeks had a mean decrease in the number of nocturnal voids of 1.4, 1.8, and 2.1 voids, respectively [31].

Serum sodium levels must be monitored as patients on desmopressin are at risk of developing hyponatremia. Therapy should not be inititated in patients with baseline hyponatremia or impaired renal function (eGFR < 60 ml/min). Mild to moderate hyponatremia occurs in approximately 7.6% of adults older than 65 years treated with desmopressin [32]. Therefore, a normal sodium level at baseline and one week and one month after initiation of desmopressin or any dosage increase should be documented. The risk of serious adverse event remains low, however. In a study of 68 elderly patients (aged 66–85 years old) receiving desmopressin, 4.4% developed hyponatremia, but all recovered by discontinuing the medication [33].

Surgical treatment can be considered if symptoms are refractory to medical management. Patients with nocturia and benign prostatic enlargement may benefit from transurethral resection of the prostate (TURP). In a study of 66 men with LUTS and BPH, TURP was compared to oral tamsulosin. Both treatments were found to improve nocturia, but TURP decreased nocturnal awakenings by 34% more than tamsulosin [34].

CONCLUSIONS

Nocturia is a common condition that has considerable impact on quality of life and health outcomes, especially in the elderly. It can be caused by a variety of factors, including nocturnal polyuria resulting from congestive heart failure, detrusor overactivity and insomnia. Evaluation of nocturia should be quantified with FVC. Contributing medical conditions should be sought and optimized. Alpha-blockers, 5-alpha reductase inhibitors, and antimuscarinics are not generally effective. Patients with nocturnal polyuria may benefit from desmopressin but require monitoring for hyponatremia. Prostate reducing surgery such as TURP can be offered for men with evidence of prostatic obstruction refractory to medical treatment.

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