CME article

JCU

Journal of Clinical Urology
1–7

DOI: 10.1177/2051415818781289
journals.sagepub.com/home/uro
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A systematic approach to the investigation and treatment of nocturia

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Date received: 21 March 2018; accepted: 2 May 2018

Level of evidence: 4.

Introduction

Nocturia is defined by the International Continence Society (ICS) as the complaint that causes individuals to have to wake at night once or more in order to void.[1] It is considered to be the most bothersome of all lower urinary tract symptoms (LUTS), and can occur as an isolated symptom or alongside other storage and voiding LUTS. Nocturia is estimated to be equally prevalent in both men and women (11% versus 12%, respectively).[2,3] In a study published in Finland involving 6000 randomly selected subjects identified from the Finnish Population Register Centre, the authors found that one in every eight men and women between the age of 18–79 years old reported at least two voids per night on average.[4] The LUTS with the greatest population-level burden were urgency (7.9% with at least moderate bother), stress urinary incontinence (6.5%) and nocturia (6.0%).[5]

An internet-based cross-sectional survey involving 30,000 men and women who were randomly selected from the USA, UK and Sweden evaluating LUTS[6] has suggested that the prevalence may be much higher. The results from this large study have shown that nocturia ($\geqslant 1$) was commonly observed among 69% of men and 76% of women, with 28% men and 34% women reporting two or more episodes per night.

Old age is significantly associated with nocturia.[7,8] It is more prevalent among the African-American population compared to Caucasians. The Epidemiology of Lower Urinary Tract Symptoms study has revealed that comorbid conditions such as arthritis, asthma, bladder cancer, depression, diabetes, cardiac diseases, hypertension, interstitial cystitis, irritable bowel disease, neurological conditions, recurrent urinary tract infections and sleep disorders were more prevalent in patients with nocturia.[6] It has also shown that high body mass index (BMI) and low physical activity are associated with a greater amount of nocturia episodes.

A population study conducted by Boston Area Community Health[9] investigated the relationship of nocturia with quality of life (QoL) and depressive symptoms among 5503 men and women with LUTS. The overall QoL was assessed using the 12-Item Short-Form Survey, which includes both mental and physical components.[10] The study demonstrated a significant association of nocturia with decreased QoL and interference with daily activities in both men and women. It has also shown a strong association of nocturia with depression in both men and women (Figure 1), which supports the theory that nocturia can negatively affect mood, sleep, increase tiredness and adversely impact on QoL.

Pathophysiology

Nocturia has historically been considered as one of the most bothersome complaints among patients with LUTS and may occur because of reduced bladder capacity, increased fluid intake or increased urine production.[11] By applying the ICS guidelines, initial assessment and screening of symptoms will enable clinicians to further categorize nocturia based on the most likely pathophysiological causes.[12] Using frequency volume charts (FVCs) or bladder diaries (BDs) helps to evaluate the origin of nocturia, by objectively comparing and analysing the numbers and timing of voids as well as voided volumes. This will provide important information regarding the patient's possible underlying diagnosis.[13]

Based on the results of the initial clinical evaluation and FVC/BD, nocturia can be categorized in to four main clinical entities (Figure 2 and Table 1).[14]

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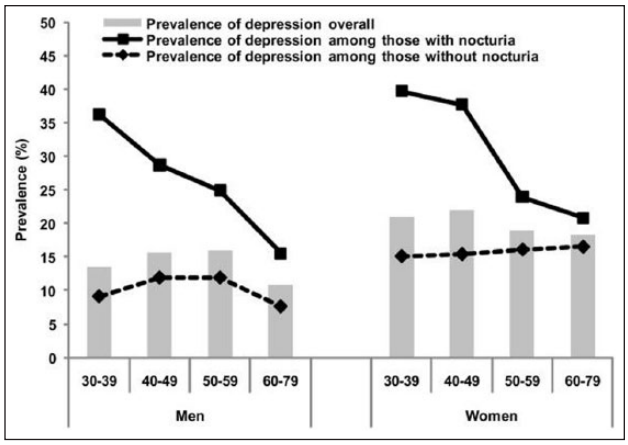

Figure 1. Prevalence of depression (Center for Epidemiological Studies Depression Scale ⩾ 5) by gender, age, and nocturia status (reproduced with permission from[9]).

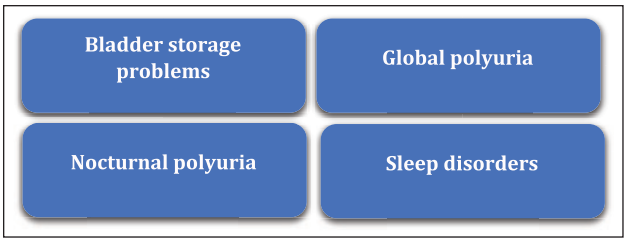

Figure 2. Categorization of nocturia.

Patient evaluation

History

A comprehensive urological history should be taken to fully evaluate all LUTS. This will allow documentation of the baseline level of symptoms and preliminary categorization of any possible underlying abnormality. The ICS subclassifies LUTS into storage, voiding and post-micturition symptoms.[17] The urological history must assess all of these categories; nocturia is a storage symptom. Other points to consider in the history are daily fluid intake including alcohol and caffeine consumption, sleeping pattern, history of comorbidities and treatment including uroselective medications, and any other treatments that may affect urine production such as diuretics. Validated questionnaires such as the International Consultation on Incontinence Modular Questionnaire (ICIQ), the ICIQ-MLUTS, the ICIQ-FLUTS (for males and females, respectively), and the ICIQ-BD, are recommended for patients with LUTS during the initial assessment as they can both quantify symptoms and identify the types of symptoms that predominate.[18]

Physical examination

The basic initial examination should include weight, height and BMI measurement, and cardiovascular, respiratory, abdominal, digital rectal and neurological examinations. Baseline urine analysis and assessment of post-void residual should also be recorded.

Investigations

Additional investigations for the patient with nocturia will depend on the information received in the FVC/BD. This will enable a preliminary categorization according to the pathophysiology of the symptom as defined in Figure 1. As a minimum, clinicians should consider a microbiological urine test (urine analysis in addition to culture and sensitivity if indicated), serum renal function test, blood glucose and prostate specific antigen in carefully selected and counselled men.

The International Consultations on Urological Diseases and the Société Internationale d'Urologie have made recommendations with regards to tools that can be used to investigate the development and progression of symptoms and its impact on QoL on patients with nocturia.[19] Some of these tools can be summarized as follows:

- **International Prostate Symptom questionnaire (IPSS)** is a useful generic tool to assess the nature and severity of symptoms, and determine future treatment options as well a tool for monitoring, especially for any changes in the level of symptoms following treatment.
- **Twenty four-hour urine volume, nocturnal urine volume, nocturnal bladder capacity and length of sleep duration** are clinically useful parameters to determine and analyse factors contributory to nocturia, and should be considered in the evaluation and treatment of most patients.[20,21]
- **FVCs/BDs** are therefore essential to record voiding parameters and allow accurate recording of nocturnal urine production, which can predict the severity and improvement of nocturia.[22,23] Therefore, timing, number of voids and volume of urine voided should be recorded as accurately as possible. The recording of fluid intake that is provided with BDs offers an advantage of BDs over standard FVCs. The information gained from a fully completed BD can often provide guidance toward nocturia therapies.

Management

Strategies to treat and manage nocturia vary and depend on the underlying cause.

Lifestyle and behavioral treatments

Evening fluid intake management has shown to positively affect nocturnal voiding and is recommended for patients

Table 1. Causes of nocturia.

	Definitions	Examples
Bladder storage disorders	Commonly related to lower urinary tract conditions that affect bladder capacity or emptying, or reduce voided volumes	• Bladder outlet obstruction associated with high post-void residual • Reduced functional bladder capacity • Overactive bladder syndrome/detrusor overactivity
Global polyuria	Urine output > 40 mL/kg body weight over a 24-h period is defined as polyuria[15]	• Insulin-dependent and non-insulin-dependent diabetes mellitus • Diabetes insipidus
Nocturnal polyuria	Defined as nocturnal urine output exceeding 20% of the total 24-h urine output in the young, or 33% of urine output in people aged > 65 years[16]	• Heart failure • Renal failure • Sleep apnoea syndrome • Inappropriate secretion of antidiuretic hormone, either primary or secondary
Sleep disorders	Some patients with sleep disturbance feel the need to void for other reasons and it is important to determine whether the sleeping problem is a primary or secondary problem[17]	• Insomnia • Obstructive sleep apnoea syndrome • Restless legs syndrome • Sleep disorders associated with diseases such as chronic obstructive lung disease, cardiac diseases, Alzheimer's or Parkinson's disease, and epilepsy

who suffer from nocturnal polyuria. A previously published study by Griffiths *et al*. aimed to investigate 128 symptomatic elderly patients (median age of 79) who underwent 24-h monitoring of fluid intake, urine loss and voiding pattern.[24] Nocturnal urine loss increased by an average of 28 mL for each 100 mL of evening fluid intake. From this study, nocturnal voiding frequencies were found to be directly related to fluid intake and seen to improve by reducing evening fluid intake. An improvement in urinary incontinence was also observed.

There is some evidence from the literature that demonstrates an association of nocturia with caffeine and alcohol intake. A multivariate logistic regression analysis of data collected from 3048 elderly men aged 55–75 years in 21 general practices in the Netherlands[25] showed that nocturia in elderly men was significantly related to alcohol consumption. Epidemiological evidence suggests that limited caffeine and alcohol intake and has a positive impact on symptoms in patients with nocturia and incontinence.[26]

Increasing physical exercise can also positively impact on nocturia symptoms. Effects on nocturia of daily walking exercise and physical activity for approximately 30 min or more in the evening or at night for 8 weeks proved effective, especially the elderly. This was shown by Sugaya *et al*. when they examined the relationship between nocturia and exercise among 30 patients and found that episodes of nocturia, as well as daytime urine frequency, significantly declined after a programme of regular walking.[27] They also concluded that influence of walking/gentle exercise on nocturia was because the sleep became deeper, which increased the arousal threshold in terms of bladder volume.

Alpha blockers and 5-alpha reductase inhibitors

Several studies have explored the specific pharmacological effect of alpha blockers and 5-alpha reductase inhibitors on nocturia. Most studies have involved men with an underlying diagnosis of nocturia secondary to benign prostatic enlargement (BPE). One-hundred patients with moderate to severe LUTS (IPSS score range from 8–19 or 20–35, respectively) were assessed in a prospective study after using an alpha blocker for at least 3 weeks.[28] Based on the IPSS, nocturnal frequency was reported to have improved by more than 50% in 31 (31%) patients and from 25–49% in 27 (27%) patients. FVC data revealed that the number of nightly voids showed an improvement with an overall reduction of > 25% in objective nocturia ($p = 0.016$).

The Veterans Affairs Cooperative Study Program trial evaluated the benefit of alpha blockers in 1078 men who suffered from nocturia related to benign prostatic hyperplasia (BPH).[29] Baseline nocturia was measured at an average of 2.5 episodes a night. Patients were enrolled into four treatment arms; alpha blockers, 5 alpha reductase inhibitors, combination medical therapy and placebo. After completing 1 year of treatment, overall nocturia decreased from the baseline (2.5) to 1.8 in the alpha blockers group, 2.1 (5-alpha reductase inhibitors), 2.0 (combination treatment) and 2.1 in the placebo group. Treatment

response to alpha blockers was significantly higher than the treatment with combination therapy ($p = 0.03$), 5-alpha reductase inhibitors ($p = 0.0001$) and placebo ($p = 0.0001$).

The effect of alpha blockers and 5-alpha reductase on nocturia was also assessed among 3047 men with LUTS enrolled in the Medical Therapy of Prostatic Symptoms trial.[30] Results from treatment with alpha blockers alone or in a combination therapy were statistically superior to placebo ($p < 0.05$) at 1 and 4 years, with mean nocturia reduction at 1 year by 0.54 and 0.58 in alpha blockers and combination groups, respectively. All of these data suggest that alpha blockers are effective at treating nocturia in men with BPE.

Anticholinergic therapy

Several studies have investigated the effect of anticholinergics on frequency, nocturia and nocturnal enuresis. In one, 3032 patients who presented with overactive bladder (OAB) syndrome were randomized and evaluated for reductions in nocturia episodes after treatment with anticholinergic or placebo as part of a phase 3 trial. Patients reported 35.5 and 36.4% improvement in nocturia episodes after treatment with 5 and 10 mg of solifenacin, respectively, compared to 25.0% for the placebo group.[31]

As well as the direct effect on nocturia, several studies have reported improvements in QoL. A multinational, placebo-controlled, randomized, double-blind 12-week study evaluated the effect of tolterodine extended release (ER) on QoL in 1015 patients with bothersome symptoms of OAB and incontinence.[32] Domains such as physical limitations, sleep, and energy and symptom severity were evaluated. Results showed that tolterodine significantly improved symptoms ($p \leqslant 0.006$) following treatment for 12 weeks.

In another Japanese study, 293 patients with symptoms of OAB were randomized for treatment with tolterodine ER ($n = 114$), oxybutynin ($n = 122$) or a placebo ($n = 57$).[33] Over a 12-week period, treatment efficacy was monitored and resulted in a significant improvement in incontinence and the BD variables ($p < 0.05$) for patients receiving both tolterodine and oxybutynin compared with placebo, as well as overall QoL improvement.

The efficacy and safety of another anticholinergic agent, trospium chloride, was examined in treating OAB-related symptoms among 658 patients who were randomized on a 1:1 basis to either placebo or trospium chloride 20 mg twice daily in a 12-week, multicentre, parallel, double-blind, placebo-controlled study.[34] In addition to its good tolerability, trospium chloride significantly improved the average number of daily frequency, urgency and urge frequency at weeks 1, 4 and 12 compared with the placebo group in this study. Nocturnal toilet voids and nocturnal urgency also improved at 12 weeks ($p = 0.0026$ and $p = 0.0005$, respectively).

Beta3-adrenoceptor agonist

The neurological control of bladder function involves both the sympathetic and parasympathetic nervous system. Beta-adrenoceptor subtypes such as beta3 receptors in the human urinary bladder urothelium are responsible for detrusor muscle relaxation.[35] Beta3 agonist drugs such as mirabegron have been evaluated in clinical trials and introduced as alternative agents to the classical antimuscarinic drugs that have traditionally been used for the management of OAB symptoms.[36] In a multicenter, randomized, double-blind trial,[37] 262 patients were randomized to receive either high-dose mirabegron (100 or 150 mg twice daily), 4 mg tolterodine ER once daily or placebo for 4 weeks. Mirabegron in both doses resulted in a statistically significant improvement in overall voiding frequency amounting to 2.2 voids per 24 h compared to a reduction of 1.2 voids per 24 h in the placebo group ($p \leqslant 0.01$). Compared with placebo, mirabegron 100 mg twice daily resulted in statistically significant improvements in incontinence episodes (2.2 episodes/24 h versus 1.0 episodes/24 h, $p \leqslant 0.01$), urgency incontinence episodes (2.1 episodes/24 h versus 1.1 episodes/24 h, $p \leqslant 0.05$), and nocturia episodes (0.6 episodes/24 h versus 0.2 episodes/24 h, $p \leqslant 0.01$).

In another recently published study, the effects of standard dose mirabegron on nocturia, QoL and sleep quality were evaluated in 60 female OAB patients as a part of prospective multicentre study. After 12 weeks of treatment, based on the results recorded in voiding diaries, mirabegron (50 mg/day) significantly improved nocturnal frequency from 2.5 times per night before treatment to 1.9 episodes per night, which was the primary endpoint in this study. Nocturnal urine volume per void and urine volume of the first nocturnal void were seen to increase, and this study also reported increased hours of undisturbed sleep from 160.6 to 203.8 min.[38]

Studies concluded that beta3-adrenoceptor agonist can improve nocturia by enhancing nocturnal bladder capacity and thereby improve the quality of sleep in patients suffering from nocturia.

Desmopressin

Arginine vasopressin (AVP) is the main antidiuretic hormone (ADH) responsible for the regulation of urine formation. The peak blood concentration of ADH occurs normally during sleeping hours in healthy adults. Researchers have concluded that patients with nocturia and nocturnal polyuria were found to have lower plasma AVP.[39–42]

The long-term efficacy of desmopressin was evaluated in multinational phase 3 study among males and females with nocturia over a 12-month period.[43] Overall, 95 males (72%) and 87 females (75%) completed the study. The

numbers of nocturnal voids decreased in males and females throughout the study compared with baseline. The study also confirmed that patients reported an improvement in the number of sleep hours with a positive impact on QoL. At 12 months, the mean duration of the first sleep period was increased from 157 to 288 min in males and from 157 to 310 min in females.

Further work from Wang *et al*. has evaluated the effect of desmopressin (0.1 mg orally at bedtime) in men with LUTS and nocturnal polyuria secondary to BPH in a randomized, double-blind, placebo-controlled study.[44] In tital, 115 patients out of 126 (58 in the placebo group and 57 in the desmopressin group) complained of nocturia (two or more voids per night). Patients were followed up at 1, 3, 6 and 12 months after treatment. BD and QoL questionnaires were part of the evaluation process. A reduction of two or more voids per night was achieved by 35 (61.40%) patients receiving desmopressin compared to 8 (13.80%) on the placebo ($p < 0.001$). Total nocturnal volume was 392 mL on desmopressin compared with 533 mL on the placebo. Time from sleep to first nocturnal void improved from a baseline value of 91.4 min to 120 min, and this was coupled with significant improvements in QoL parameters in those receiving desmopressin. All of these data suggest that desmopressin is an effective treatment for nocturia in patients with nocturnal polyuria.

Surgery

A multicentre prospective study was carried out to assess the effect of transurethral resection of the prostate (TURP) on nocturia and sleep disturbance on patients suffering from LUTS secondary to BPE, using IPSS and QoL questionnaires as outcome measures.[45] Forty-nine patients were evaluated using IPSS questionnaires and the Pittsburgh Sleep Quality Index[46] before and 6 months after TURP. Nocturia significantly decreased after TURP from 3.0 to 1.9 episodes per night. Furthermore, sleep quality (component 1) and habitual sleep efficiency (component 4) significantly improved after surgery in 20 patients with reported sleep disorders beforehand.

Nocturia is considered to be one of the main bothersome symptoms amongst women who suffer from urge and mixed urinary incontinence, with a major impact on QoL.[47] Two-hundred and thirty-seven patients with mixed urinary incontinence (MUI) who underwent transobturator tape (TOT) procedures between January 2007 and May 2012 were reviewed retrospectively in a recent study. Of those, 36.4% had reported pre-operative nocturia.[48] Analysis of the pre-operative and post-operative 3-day FVCs revealed that the procedure significantly reduced the mean nocturnal void number from 1.68 ± 0.80 to 0.90 ± 0.82 ($p < 0.05$). Post-operatively, the TOT procedure significantly improved nocturnal bladder capacity subscale scores affecting patients' quality of sleep using the King's Health Questionnaire[49] OAB questionnaire.

Conclusion

Nocturia is a considerably bothersome LUTS and may be the main driver for help-seeking behaviour from patients. It can adversely affect QoL, mental health and sleep. Nocturia is significantly associated with old age, BMI and certain other comorbidities that can become evident on initial clinical evaluation. The FVC/BD is perhaps the most important baseline tool to evaluate nocturia and is sensitive to change following an intervention. Therefore, it is a mandatory investigation in those with bothersome nocturia. Categorization of nocturia aims to classify causes based on factors including urine production and underlying lower urinary tract disorders. This classification is essential in the initial evaluation of the patient presenting with nocturia and may be helpful in guiding first-line treatments.

Treatment of nocturia varies and usually depends on the underlying cause. Options range between lifestyle modification, controlling associated comorbidities, pharmacotherapy and surgery. Men with associated bladder outlet obstruction may benefit from alpha blockers and/or bladder outlet surgery. On the other hand, patients with associated urge symptoms can benefit from anticholinergics and/or mirbegron. Research priorities include further investigation of these therapies to investigate whether they are capable of achieving clinically meaningful improvements in nocturia in all patients.

Conflicting interests

CH has received speaker fees from Astellas, BBraun, Pfizer, Ferring, Allergan, Medtronic and has participated in advisory boards/consultancy for Pierre Fabre, AMS and Astellas. None of these declarations are relevant to this manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethical approval

Ethical approval was not sought for this article because it is a literature review.

Informed consent

Informed consent was not sought for this article because it involves a review of current literature.

Guarantor

CH.

Contributorship

All authors researched literature and conceived the study. ME wrote the first draft of the manuscript. All authors reviewed and

edited the manuscript and approved the final version of the manuscript.

Acknowledgements

None.

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