Nocturia, of clinical importance

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Nocturia is a common symptom with multiple potential underlying pathophysiological mechanisms, some of which may be associated with life-threatening consequences [1]. As defined by the International Continence Society, nocturia is the “complaint that the individual has to wake at night one or more times to void” [2]. Nocturia has high prevalence, diverse etiology and is of clinical importance.

The detrimental impact of nocturia is thought to be associated with sleep fragmentation and is related to sleep status rather than nocturnal voiding [3]. Interestingly, the sleep fragmentation coupled with nocturia can lead to other sequelae such as reduced quality of life (QoL), mood disturbance, reduced productivity at work, diminished overall health and increased falls and fractures [4]. Nocturia has also been linked to coronary heart disease and mortality [5]. In addition, nocturia has been associated with depression, endocrine, immune and metabolic disorders, as well as increased overall mortality in the frail, elderly population [4]. Given the severe potential consequences, the complaint of nocturia should be a critical part of the clinical evaluation of a patient’s lower urinary tract symptoms.

Current evidence acknowledges that nocturia, in many cases, may be a clinical entity of its own, whether or not this condition is associated with another disorder [2]. Nocturia is highly prevalent, occurs in both genders [6] and presents to generalists and specialists. Although patients may present with lower urinary tract symptoms to their urologists, they may also present to the gynecologist, geriatrician, neurologist, sleep expert, endocrinologist and/or general practitioner [2]. For this reason, practitioners across all disciplines should follow a clinical algorithm, as described in the literature [1,7,8], to aid in making an accurate diagnosis and initiate an appropriate course of action. Recognizing the burden of the problem has been fundamental in this shift in understanding nocturia and the development of the multifactorial theory of causation [8].

Associated risk factors of nocturia include bladder storage problems, nocturnal polyuria (NP; congestive heart failure, obstructive sleep apnea), 24-h polyuria (diabetes mellitus, diabetes insipidus, primary polydipsia), sleep disturbance, medical disorders (cardiac failure, chronic obstructive pulmonary disease), neurologic conditions (Parkinson’s disease, dementia), psychiatric conditions (depression, anxiety), chronic pain disorders, alcohol or drug abuse (consumption or withdrawal) and medications (corticosteroids, diuretics, β-adrenergic antagonists) [7]. In addition to these medical conditions, factors such as age, sex and ethnicity may additionally contribute to nocturia as well [9].

If no primary problem is immediately identified, then the possibility that nocturia is the first manifestation of a significant underlying disease should be investigated [8]. Early in the diagnostic process, a clinical examination and frequency–volume chart may aid in the daily monitoring and assessment. From the frequency–volume chart may aid in the daily monitoring and assessment.

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chart, nocturia can be further classified into four distinct pathophysiological mechanisms: 24-h polyuria (24-h urine volume of >40 ml/kg body weight), NP, bladder storage problems or sleep disorders [1,2]. If polyuria and NP can be excluded as the cause of nocturia, then it is probable that the patient has either a bladder storage problem or a sleep disorder [2].

NP has a high prevalence, as much as 82.9% in patients with nocturia [10]. NP is age related and has been defined as >20% of total 24-h urine volume in the young (<65 years of age) and >33% in the elderly (>65 years of age) [11]. It can be due either to an increased night-time solute diuresis, reduced reabsorption of free water, or a combination the two [8]. NP can be present in isolation or as part of another etiology, but if it is not diagnosed or treated, the patients symptoms will persist. For example, in a study of patients with complaints of nocturia and benign prostatic hyperplasia, α-blocker therapy did not improve patients’ symptoms and subsequent analysis revealed that 95% had NP as well as benign prostatic hyperplasia [12]. Therefore, treatment with α-blockers and/or anticholinergics alone is not generally effective in patients with NP [7]. Greater recognition of NP and improved diagnosis by clinicians can broaden treatment options to patients with nocturia.

If, after first addressing the underlying problems and improving lifestyle influences, the patient with NP still remains symptomatic, a trial of antidiuretic therapy may be initiated [8]. Some clinicians also use this therapy for symptomatic nocturia, not just specifically NP. Desmopressin acetate is a synthetic analog of arginine vasopressin and is approved for the treatment of nocturia in >80 countries outside the USA and is recommended by the International Consultation on Incontinence and European Association of Urology for the treatment of nocturia associated with polyuria [13–15]. Desmopressin acetate acts at the distal convoluted tubules and collecting duct to increase water reabsorption, resulting in smaller volumes of more concentrated urine [16]. The adverse event of most concern is hyponatremia (sodium <130 mM) and is more likely in the older age group [17]. Therefore, desmopressin is not currently recommended in men >65 years of age [18]. Although most cases are not symptomatic, assessment of serum sodium 3 days after starting therapy is recommended in modern guidelines [1].

Evidence supports the fact that women have a larger diuretic response to desmopressin than men at a given dose, in addition to having a fivefold-higher risk of developing hyponatremia than men [19]. Animal and human data suggest that the desmopressin sensitivity and/or the expression of the V2 receptor is different in males and females and that these differences are likely regulated by both hormonal and genetic differences [19,20]. Studies suggest that in women, a dose of 25 µg is shown to be equally efficacious and safer than a dose of 50–100 µg in men, supporting the evidence that there may be an increased sensitivity to desmopressin in women [19]. Recently, a Phase III trial demonstrated the efficacy and safety of 25-µg desmopressin orally disintegrating tablets in women with nocturia [15].

When patients present with the chief complaint of nocturia, in addition to providing counseling for symptom control, other possible etiologies may need to be investigated. Symptomatic relief with anticholinergics, α-blockers or desmopressin may lead to favorable outcomes in regards to the number of voids per night [18] and even if the overall reduction in nocturia episodes is minimal, the QoL improvement may be remarkable. However, providing symptomatic relief without full consideration of its diverse etiology may result in long-term loss of QoL not specifically related to their nocturia. After ruling out any underlying factors, the use of combined therapy to address the multiple factors underlying the patients’ symptoms in addition to their nocturia is an accepted and rational treatment strategy [7]. Following a step-wise approach will aid in providing quality care with a broad stroke while tailoring it to the specific needs of the patient, the ultimate goal being not only improved symptoms, but also an improved QoL, well-being and longevity.

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References
Nocturia is associated with an increased risk of coronary heart disease and death. BJU Int. 110(6), 848–853 (2012).

5 Lightner DJ, Krambeck AE, Jacobson DJ et al. Nocturia is associated with an increased risk of coronary heart disease and death. BJU Int. 110(6), 848–853 (2012).


