CLINICAL INVESTIGATION

EDITORIAL

Clin. Invest. (2013) 3(8), 711–713

Nocturia, of clinical importance

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"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."

Nocturia is a common symptom with multiple potential underlying pathophysiologic 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

Keywords: desmopressin • frequency–volume chart • nocturnal polyuria • nocturnal voiding • quality of life

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ISSN 2041-6792 10.4155/CLI.13.61

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 [15] 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.

Financial & competing interests disclosure

RR Dmochowski works as a consultant to Ferring and Allergan and MR Kaufman works as a consultant to Astellas, Allergan, and Cook. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Cornu JN, Abrams P, Chapple CR *et al.* A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management – a systematic review and meta-analysis. *Eur. Urol.* 62(5), 877–890 (2012).

2 Van Kerrebroeck P. Standardization of terminology in nocturia: commentary on the ICS report. *BJU Int.* 90(Suppl. 3), S16–S17 (2002).

3 van Dijk LL, Kooij DGD, Schellevis FGF, Kaptein AAA, Boon TAT, Wooning MM. Nocturia: impact on quality of life in a Dutch adult population. *BJU Int.* 93(7), 1001–1004 (2004).

4 Asplund R. Nocturia: consequences for sleep and daytime activities and associated risks. *Eur. Urol.* 3(Suppl. 6), S24–S32 (2005).

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).

6 Bosch JLHR, Weiss JP. The prevalence and causes of nocturia. *J. Urol.* 184(2), 440–446 (2010).

7 Weiss JP, Blaivas JG, Bliwise DL *et al.* The evaluation and treatment of nocturia: a consensus statement. *BJU Int.* 108(1), 6–21 (2011).

8 Osman NI, Chapple CR, Wein AJ. Nocturia: current concepts and future perspectives. *Acta Physiol.* 207(1), 53–65 (2012).

9 Yoshimura K. Correlates for nocturia: a review of epidemiological studies. *Int. J. Urol.* 19(4), 317–329 (2012).

10 Klingler HC, Heidler H, Madersbacher H, Primus G. Nocturia: an Austrian study on the multifactorial etiology of this symptom. *Neurourol. Urodyn.* 28(5), 427–431 (2009).

11 Van Kerrebroeck PP, Abrams PP, Chaikin DD *et al.* The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol. Urodyn.* 21(2), 179–183 (2002).

12 Koseoglu H, Aslan G, Ozdemir I, Esen A. Nocturnal polyuria in patients with lower urinary tract symptoms and response to alpha-blocker therapy. *Urology* 67(6), 5 (2006).

13 Abrams P, Andersson KE, Birder L *et al.* Fourth international consultation on incontinence recommendations of the international scientific committee: evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol. Urodyn.* 29(1), 213–240 (2010).

14 Thüroff JW, Abrams P, Andersson KE *et al.* EAU guidelines on urinary incontinence. *Actas Urologicas Espanolas* 35(7), 373–388 (2011).

15 Sand PK, Dmochowski RR, Reddy J, van der Meulen EA. Efficacy and safety of low-dose desmopressin orally disintegrating tablet in women with nocturia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *J. Urol.* 1–26 (2013).

16 Norgaard JPJ, Hashim HH, Malmberg LL, Robinson DD. Antidiuresis therapy: mechanism of action and clinical implications. *Neurourol. Urodyn.* 26(7), 1008–1013 (2007).

17 Weatherall M. The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. *Neurourol. Urodyn.* 23(4), 302–305 (2004).

18 Rembratt AA, Riis AA, Norgaard JPJ. Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia. *Neurourol. Urodyn.* 25(2), 105–109 (2006).

19 Juul KVK, Klein BMB, Sandström RR, Erichsen LL, Norgaard JPJ. Gender difference in antidiuretic response to desmopressin. *Am. J. Renal Physiol.* 300(5), F1116–F1122 (2011).

20 Liu J, Sharma N, Zheng W *et al.* Sex differences in vasopressin V_2 receptor expression and vasopressin-induced antidiuresis. *Am. J. Renal Physiol.* 300(2), F433–F440 (2011).