

HEALTH AND WELLBEING IMPACT AND TREATMENT OF NOCTURIA – A REVIEW OF THE LITERATURE

Nadir I. Osman,¹ Christopher Hillary,¹ *Christopher R. Chapple²

1. Clinical Research Fellow, Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

2. Consultant Urological Surgeon, Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

*Correspondence to c.r.chapple@sheffield.ac.uk

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ABSTRACT

Nocturia is a prevalent and highly bothersome lower urinary tract symptom (LUTS) affecting men and women of all ages. In waking to void there is disruption to an individual's sleep that can lead to daytime tiredness and a loss of vitality. This may significantly impact upon physical, mental, and social wellbeing. It is recognised that nocturia has a multifactorial aetiopathogenesis that encompasses systemic, psychogenic, as well as lower urinary tract factors, necessitating separate evaluation to other LUTS. In particular, nocturnal polyuria is an under-recognised cause of nocturia that may respond well to anti-diuretic pharmacotherapy.

Keywords: Nocturia, nocturnal polyuria, lower urinary tract symptoms, desmopressin.

INTRODUCTION

Nocturia is one of the most common and pragmatic of all the lower urinary tract symptoms (LUTS). It is defined by the International Continence Society (ICS) as: "The complaint that an individual has to wake one or more times to void...each void preceded and followed by sleep."¹ In waking to void there is fragmentation of the sleep cycle, which can have profound consequences on an individual's wellbeing and quality of life (QoL). Epidemiological studies have consistently demonstrated a high prevalence in both men and women, particularly in the elderly where there is a correlation with falls and fall-related morbidity.^{2,3} The economic costs associated with nocturia are substantial; they are estimated to be over \$60 billion per annum in the US on the basis of lost productivity alone.⁴ In this review, we discuss the evidence relating to the impact of nocturia on health and wellbeing in addition to the contemporary therapeutic approaches, with a focus on the role of antidiuretic pharmacotherapy.

NOCTURIA

Definition

Nocturia is defined by the ICS as: "The complaint that an individual has to wake one or more times to void...each void preceded and followed by sleep."¹ The validity of this definition has been questioned as - for many people - waking up once at night to void is normal and not perceived as bothersome.⁵ Tikkinen and colleagues⁵ demonstrated a correlation between the number of night time voids and the grade of symptoms: up to 1 void per night results in no impact on QoL, 2 voids are followed by little discomfort, and ≥ 3 voids in a night causes moderate-to-severe impact upon sleep. Therefore, clinically relevant nocturia is probably ≥ 2 voids; however, it should be emphasised that it is the impact upon sleep that is likely to be the most critical factor determining bother, rather than the exact number of voids.⁶

Prevalence

The prevalence of nocturia was recently summarised in a meta-analysis including >40

population studies. Using the clinically relevant definition of nocturia as ≥ 2 voids, in young women (in the 2nd or 3rd decade) prevalence was 4.4-18%, whilst in older women (7th or 8th decade) the range was 28.3-61.5%. In men, the corresponding age groups demonstrated a prevalence of 2-16.6%, whereas in the older group this rose to 29-59.3%.⁷

Aetiology

The aetiological factors implicated in nocturia can be classified as affecting urine storage, urine production, and unrelated conditions that impact upon sleep. Lower urinary tract dysfunctions that lead to a failure to store urine may result in nocturia. Most commonly this occurs in the context of overactive bladder syndrome (OAB), which is variably correlated to underlying detrusor overactivity (DOA). Urinary urgency, the pivotal symptom of OAB, is correlated with nocturia (OR=1.70), as is urinary incontinence.⁸ OAB is present in one-third of individuals with nocturia,^{9,10} whilst approximately 50% of those with OAB have nocturia.^{10,11} Benign prostatic hyperplasia (BPH) is also associated with nocturia; however, this association may be age related.¹² BPH may lead to a reduction in the functional bladder capacity at night by impairing bladder emptying, leading to a raised post-voiding residual. DOA may also occur due to bladder outlet obstruction as a consequence of BPH. In the past, nocturia was considered by many to result primarily as a consequence of BPH, however it often failed to resolve after outlet surgery, suggesting that other factors were implicated.^{13,14}

It is now recognised that the volume of nocturnal urine produced is a critical aetiological factor in many individuals with nocturia. Global polyuria (GPu) is the overproduction of urine occurring over 24 hours (>2.8 litres of urine/24 hr or >40 ml/kg). A common cause is diabetes mellitus, where high circulating glucose levels lead to an osmotic diuresis. In diabetes insipidus (DI) the kidneys are unable to sufficiently concentrate the urine due to a lack of arginine vasopressin (AVP) (or anti-diuretic hormone) production in the posterior pituitary gland (cranial DI), or loss of renal sensitivity to the hormone (renal DI). Other causes include excessive drinking (either habitual or due to psychiatric causes) and an excessive intake of protein drinks, causing an osmotic diuresis.

Nocturnal Polyuria (NPu) is relative overproduction of urine during the night, defined by the ICS as a

night time volume of $>20\%$ of the daily total in younger patients (<65 years) and $>33\%$ in the elderly (>65 years).¹⁵ Using these definitions it is highly prevalent in patients with nocturia: 66-83% of patients <65 years and in 90-93% ≥ 65 years.¹⁶ However, recently published results from the Krimpen study¹⁷ challenge the clinical utility of the ICS definitions; 70.1% of men without clinically significant nocturia (defined as ≥ 2 voids) had NPu according to the ICS definitions compared to 91.9% of men with nocturia. NPu is thought to occur due to age-related alterations in renal function and a loss of the normal diurnal variation in the release of AVP, albeit this is incompletely understood.¹⁸⁻²⁰ Obstructive sleep apnoea can cause NPu²¹ due to the release of atrial natriuretic peptide from the atrial walls as a secondary effect of a more negative intrathoracic pressure, generated by upper airway obstruction.²² Conditions that cause the third spacing of fluid peripherally (e.g. cardiac failure or venous insufficiency) may also contribute to NPu due to the redistribution of this fluid into the circulation when the patient becomes recumbent.

Certain conditions that cause disturbance of sleep are associated with nocturia, including: insomnia,²³ depression and anxiety,²⁴ pruritus,²⁵ snoring,²⁶ burning mouth syndrome,²⁷ and chronic pain.²⁸ In such situations it can be difficult to determine whether nocturia is a primary or a secondary phenomenon (convenience voids).

IMPACT OF NOCTURIA

Quality of Sleep

Nocturia is commonly unrecognised as a reason for poor sleep.²³ Although there is a positive correlation between the actual number of night time voids and the degree of bother,²⁹ it is probably more useful to consider bother as a product of the relative sleep deficit. The timing of voids is likely to be important. Restorative slow wave pattern sleep occurs during the first half of the night's sleep, hence awakening during this period is more likely to lead to negative consequences.³⁰ Individuals who find it easier to fall asleep and return to sleep after awakening are less likely to incur a significant degree of bother.³¹

QoL

Sleep deficit leads to daytime tiredness and may impair physical and mental functioning,

impacting on QoL. The Boston Area Community Health (BACH) study (USA) demonstrated that significant reductions in QoL scores independently correlated with nocturia, with an inverse correlation between score and number of night time voids.³² Similarly, data from Finland showed that nocturia (≥ 2 voids) was associated with reductions in 14 out of 15 domains of health-related QoL (all except eating).⁵

Greater nocturnal urinary frequency is associated with a greater degree of bother.²⁹ However, it is likely that the relationship between nocturia and sleep disturbance is more complex and a product of the relative deficit in sleep. Shorter interval to initiation of sleep is associated with less bother from nocturia,³³ whilst those with difficulty initiating sleep and returning to sleep after waking up are more likely to be bothered.³¹

Morbidity and Mortality

Older people with nocturia have an increased risk of falling.³⁴⁻³⁶ This risk appears to increase with greater episodes of nocturia (>2 , OR=1.84 and >3 , OR 2.15).³⁷ Unsurprisingly, an increased risk of fracture is also correlated with nocturia.^{3,34,38} An age-independent relationship between the number of nocturia episodes and risk of hip fracture was found in men: nocturia ≥ 2 and ≥ 3 (OR=1.36 and 1.80, respectively).³⁸ Nocturia has also been correlated to an increased risk of mortality in several studies,^{3,39} however, this may potentially be explained by confounding factors, particularly age.⁴⁰ Chung et al.,⁴¹ however, found that severe nocturia had a significant association with mortality (6.1% versus 2.4% in those without severe nocturia, $p=0.001$), which was independent of age or disease duration in patients with diabetes mellitus.

ASSESSMENT AND TREATMENT

Contemporary clinical assessment of nocturia entails an evaluation of the severity of symptoms, impact upon QoL, and the identification of contributory/causative factors. The frequency volume chart is a fundamental part of assessment, providing an objective measure of number of voids and volumes passed, allowing the estimation of nocturnal bladder capacity and the identification of NPu. Current treatment for nocturia entails lifestyle modification and pharmacotherapies for OAB, LUTS/BPH, and NPu.

Outcome Measures

A major limitation of most drug trials for LUTS has been the inadequate assessment of nocturia due to a failure to use voiding diaries or to assess the impact of nocturia on sleep and QoL. Nocturia is often assessed in terms of an absolute reduction in number of voids or by the use of 'question 7' of the international prostate symptoms score (IPSS): "How many times did you typically get up to urinate?" These methods do not assess associated bother, impact on quality of sleep, or QoL. Consequently, methods to more comprehensively assess nocturia are being introduced. The hours of undisturbed sleep (HUS) is the time from falling asleep to first waking,⁴² its use being based on the finding that the most restorative hours in a night's sleep are the initial 3-4.⁴³ The Nocturia Quality of Life module (ICIQ-NQoL)⁴⁴ is a validated nocturia-specific QoL questionnaire that assesses three domains: sleep/energy, bother/concern, and overall QoL.

Lifestyle Changes

Lifestyle modification measures include avoidance of caffeine and alcohol, limiting evening fluid, leg elevation, and interventions aimed at improving sleep (e.g. exercise, warm temperature). A combination of these measures has been found to significantly reduce nocturia episodes (from 2.6 to 1.9 [$p<0.001$]) and quality of sleep.³³ The use of sedatives (e.g. hypnotics)⁴⁵ to promote sleep can provide helpful palliation, although side-effect profiles and risk of dependence limit longer term usage.

OAB Pharmacotherapy

Muscarinic antagonists, the mainstay of drug therapy for OAB, have often demonstrated little impact upon nocturia in clinical trials. This may be attributable to the inclusion of a significant number of individuals with NPu. Even when patients with NPu are excluded, improvements in nocturia are modest. A post-hoc analysis of four Phase III trials of solifenacin in men and women with OAB⁴⁶ found a statistically significant reduction in night time voids of 35.5% in subjects randomised to solifenacin 5 mg and of 36.4% in subjects taking solifenacin 10 mg. By comparison, those receiving placebo experienced a 25.0% reduction in night time voids. In numerical terms, this equated to a 0.18 and 0.08 advantage over placebo for the 5 mg and 10 mg doses, respectively. Similar findings were found in other studies.^{47,48}

LUTS/BPH Pharmacotherapy

Alpha-blockers are the most commonly used first-line drug treatment of LUTS associated with BPH. Where voiding diaries have been used, statistically significant reductions in nocturnal voids are commonly reported. Johnson et al.⁵⁰ performed a subset analysis in the medical therapy of prostate symptoms study (MTOPS). Doxazosin led to a mean reduction of 0.77 voids compared to placebo, 0.61, at 1 year, a statistically significant advantage ($p < 0.05$). Similar findings were seen in trials of Alfuzosin⁴⁹ and Terazosin.⁵⁰ The clinical significance of such reductions is doubtful. Furthermore, given recall bias and the subjective quantification of the level of bother, the IPSS questionnaire is unlikely to be a sensitive measure of nocturia.

Desmopressin Therapy

Desmopressin acetate, a synthetic analogue of AVP, causes the production of smaller volumes of more concentrated urine.⁵¹ It acts as a selective V2 receptor inhibitor (i.e. in the renal collecting system) and thus avoids vasopressor effects associated with V1 receptor agonism. It has Grade A recommendation for use in patients with NPu.⁵² Currently available preparations include an oral tablet, an oral disintegrating tablet, a sublingual spray, and an intranasal spray.

The safety and efficacy of desmopressin therapy is supported by level I evidence.^{51,53,54} A recent meta-analysis by Cornu et al.⁵⁵ demonstrated significant reductions in night time voids and an increase in HUS in five trials (lasting several weeks), primarily assessing the efficacy of desmopressin in non-neurogenic patients. The mean difference in night time voids between desmopressin and placebo across the studies was -0.54 (-0.8 to -0.28). In terms of HUS, desmopressin had a 53.56 (31.67-75.45) minutes mean advantage compared to placebo. open label extension studies up to 1 year showed a durable effect.⁵⁶⁻⁵⁸ Moreover, randomisation periods were short (up to 4 weeks) and most studies included a dose titration period, which excluded non-responders and subjects who had adverse effects.

A dose finding study by Weiss and colleagues⁵⁴ investigated four doses of the oral disintegrating preparation of desmopressin (from 10 to 100 µg) in 757 men and women. An increasing dosage was associated with increased effect in terms of reduction in night time voids and length of HUS, and

voided volume, greater proportions of subjects with >33% reduction in nocturnal voids, and increased duration of first sleep period. The minimal dosage required to attain a significant advantage over placebo in both night time voids and HUS was 25 µg in women and 100 µg in men, suggesting that women are more sensitive to desmopressin therapy.

Desmopressin therapy was well tolerated in most studies and did not indicate any safety concerns other than the expected potential for hyponatraemia. An overall incidence of clinically significant hyponatraemia (Na <130 mmol/L) of 3% has been reported.⁵⁴ Hyponatraemia is most likely to occur in women, the elderly, and at higher doses. When hyponatraemia occurs, it is usually on initiation of treatment and within the first week. Subsequently, the risk of hyponatraemia does not appear to increase with time (up to 1 year).⁵⁶ Current guidance advises checking sodium levels on days 3 and 7^{59,60} in order to identify those patients at risk of developing symptomatic hyponatraemia. Desmopressin is an effective treatment for nocturnal polyuria. It prolongs the first sleep period and thereby improves patient quality of life.

When NPu is due to obstructive sleep apnoea, continuous positive airway pressure (CPAP) treatment overnight is the treatment of choice; Margel et al.⁶¹ demonstrated mean nocturnal voids were reduced from 2.6-0.7 with CPAP ($p < 0.001$).

CONCLUSION

Nocturia is a highly prevalent problem that is under-appreciated in clinical practice. It has a multifactorial aetiology necessitating a comprehensive evaluation not confined to LUTS. The voiding diary is fundamental to the identification of the underlying pathophysiological mechanism, particularly NPu. There has been a failure to use adequate measures of the impact of nocturia in most clinical studies for LUTS pharmacotherapies. The available evidence suggests statistically significant reductions in night time voids with traditional agents used in the treatment of OAB and LUTS due to BPH unlikely to translate into meaningful clinical improvements. There is a growing body of evidence to support the safety and efficacy of desmopressin preparations in patients with underlying NPu; however, optimal dosages and long-term efficacy need to be established.

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