Neurourology and Urodynamics 27:34–39 (2008)

REVIEW ARTICLE

Nocturia: Etiology, Diagnosis, and Treatment

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Voiding at night, or nocturia, is a common reason for interrupted sleep in the adult population. The condition affects both men and women, with an incidence that increases dramatically with age. Nocturia has a negative impact on quality of life, affecting both morbidity and mortality. Effective diagnosis of the condition is dependent on a clear understanding of its underlying etiology. In general, the causes of nocturia fall into three categories: diurnal polyuria, nocturnal polyuria, and low bladder capacity. In some individuals, however, nocturnal polyuria and low bladder capacity may both contribute to the overall symptomatology of nocturia. Addressing any underlying conditions that contribute to nocturia is the first step in treating the condition. Lifestyle and behavioral changes may provide benefit in some individuals, but for many, the only option is pharmacotherapy. Antimuscarinic agents are first-line therapies for overactive bladder and are often used in the management of nocturia. Pharmacological and physicochemical differences between available antimuscarinic agents, however, translate into different safety and tolerability profiles, which may make some agents more suitable for use in certain populations, including the elderly. Careful selection of the most appropriate antimuscarinic medication is therefore central in optimizing treatment outcomes. *Neurourol. Urodynam. 27:34–39, 2008.* © 2007 Wiley-Liss, Inc.

Key words: antimuscarinics; diagnosis; nocturia

DEFINITION AND PREVALENCE OF NOCTURIA

Voiding at night, or nocturia is not a new problem. However, an aging population and recent innovations in treatment have brought more attention to the disorder, such that it is now being examined as a clinical entity in its own right, as opposed to being viewed as a symptom of another condition. Historically, nocturia has been defined by many authors in different ways, however in 2002, the International Continence Society (ICS) issued a report of terminology standardization in which nocturia was defined as "waking at night to void".[1] The definition covers any number of voids, providing that the person awakens before voiding.[1] Nocturnal enuresis, by contrast, is the term given to voiding at night while asleep.[1]

It is difficult to arrive at a precise figure for the prevalence of nocturia, because epidemiological studies have varied in their definition of the condition, and in addition, there have been relatively few such studies in the United States over the last decade. In a national survey conducted by telephone of 5,204 community-based adults with an average age of 45.8 years, 31% reported at least one void per night and 14.2% reported at least two voids per night.[2] Studies in Japan and Austria, in which nocturia was defined as $\geq$2 voids per night, found rates of 28.5% and 11.3%, respectively.[3,4] In all studies, the prevalence of nocturia was observed to increase dramatically with age.[2–4] Despite a widespread belief that nocturia is more common in men—perhaps because of the association of nocturia with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)—the incidence of nocturia is in fact similar for men and women.[2–4]

IMPACT OF NOCTURIA

Quality of life (QoL) is negatively affected in the majority of individuals who experience nocturia ($\geq$1 void per night); this is perhaps to be expected of a condition that disrupts healthy sleep patterns. Although nocturia is not always defined consistently (generally varying between >1 and >2 voids per night), a number of studies have demonstrated that a high proportion of patients (63–75%) with nocturia perceive it to be troublesome.[5–7] Unfragmented sleep, 7–8 hr for most adults, is necessary for the maintenance of physical, mental, and emotional well-being.[8] Abnormal sleep patterns, as may be observed in patients with nocturia, can result in sleep deprivation, which is a cause of serious health risks in the general population.[9]

Since nocturia disproportionately affects older patients, the potential for it to result in an increased risk of falls and bone fractures is of particular concern. A study of 1,500 older ambulatory patients (average age 80 years) found that individuals voiding $\geq$2 times per night were significantly more likely to fall than those who did not void at night (odds ratio 1.84; $P = 0.03$). The likelihood of falling increased among patients who voided $\geq$3 times per night (odds ratio 2.15;

Karl-Erik Andersson led the review process.
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Received 20 March 2007; Accepted 5 June 2007
Published online 9 October 2007 in Wiley InterScience
(www.interscience.wiley.com)
DOI 10.1002/nau.20484

$P = 0.04$).[10] As fractures among the elderly have a significant effect on patient mortality, it follows that treatment of nocturia could decrease the morbidity and mortality associated with these falls and fractures.

ETIOLOGY OF NOCTURIA

Nocturia is associated with a number of putative conditions or circumstances (Table I) including aging, overactive bladder (OAB), and BPH/LUTS in men. Medication usage (including diuretics, and analgesics), diabetes mellitus, diabetes insipidus, anorexia nervosa, and sleep disturbance can also cause nocturia. The causes of nocturia fall into three categories: diurnal polyuria, nocturnal polyuria, and low nocturnal bladder capacity (Table I). Nocturnal polyuria and low bladder capacity are, however, not mutually exclusive, and both may contribute to the overall symptomatology of nocturia in some patients; this is known as mixed nocturia.[11]

Diurnal Polyuria

Diurnal polyuria is recognized when an individual produces more than 40 mL of urine per kg of body weight over a 24-hr period.[1] Affected individuals experience both increased daytime and nighttime urinary volume. The causes of polyuria include sources of osmotic and free water diuresis, such as diabetes mellitus and diabetes insipidus of both central and nephrogenic origins.[11,12] Central diabetes insipidus results from a dysfunction in the production of the antidiuretic hormone vasopressin, whereas nephrogenic diabetes insipidus occurs when the kidneys fail to respond to antidiuretic hormone (ADH). Treatment with lithium has been shown to cause secondary nephrogenic diabetes insipidus,[11] and electrolyte disturbances, such as hypercalcemia and hypokalemia, can also induce a type of nephrogenic diabetes insipidus.[13] In addition, primary polydipsia can increase total daily urine volume.[11]

Nocturnal Polyuria

Nocturnal polyuria refers to a condition in which the rate of urine production is excessive only at night; the total 24-hr output being within normal limits. Although its precise definition remains somewhat flexible, an approximate description of nocturnal polyuria from the ICS is a nocturnal urine volume (NUV) of at least one-third that of the total daily urine production.[1] As the amount of urine produced at night differs with age—younger people producing less than older people—the actual percentages on which the assessment is based are age dependent.[1]

Abnormality in secretion of arginine vasopressin may, as with diurnal polyuria, play a role in the etiology of nocturnal polyuria.[11,14] Lifestyle and dietary factors, such as increased nighttime liquid, caffeine, and alcohol intake, can also result in increased urinary volume at night and may initiate nocturnal polyuria.[11] The timing of therapy with diuretics, β-blockers, and xanthines may cause some people to void more frequently at night. Congestive heart failure, low blood albumin, venous stasis disease, and high intake of salt may result in third spacing of fluid in the lower extremities, which can contribute to the fluid retention associated with nocturnal polyuria, as can renal insufficiency.[9,11] Respiratory conditions, such as sleep apnea, are also causative of nocturnal polyuria. Hypoxia in the lungs can lead to pulmonary vasoconstriction and raised concentrations of the peptides responsible for elimination of sodium in the urine; this can result in elevated secretion of water while the patient is sleeping.[15]

Reduced Nocturnal Bladder Capacity

Bladder storage problems, such that the amount of urine produced at night exceeds the functional bladder capacity, will result in nocturia. Bladder storage problems may be caused by a reduction in the functional capacity of the bladder, for example as a result of cancer of the bladder, prostate, or urethra.[11] Storage problems may also arise through bladder irritation as a result of infection, interstitial cystitis, calculi, and bladder hypersensitivity.[11] Overactive bladder syndrome (OAB), a condition defined as "urgency, often with frequency and nocturia, with or without urge urinary incontinence" may also be a significant contributor to bladder storage problems. The etiology of OAB is unknown and may involve changes to the bladder smooth musculature, damage to central inhibitory pathways, and sensitization of peripheral afferent terminals.

DIAGNOSIS OF NOCTURIA

The diagnosis of nocturia is often not simple, as patients frequently present with complaints secondary to their

TABLE I. Pathophysiologic Causes of Nocturia and Associated Conditions

Mixed nocturia (a combination of nocturnal polyuria and reduced nocturnal bladder capacity)		
Nocturnal polyuria	**Reduced nocturnal bladder capacity**	**Diurnal polyuria**
Nocturnal urine volume >20–30% of total 24-hr urine volume (age dependent)	Physical or sensory reduction in bladder capacity leading to a situation where nocturnal output is greater than the bladder capacity, even though urine production is within normal limits	24-hr voided volume in >40 mL/kg bodyweight
Altered arginine vasopressin secretiona	Irritation due to infection, interstitial cystitis, calculi, or bladder hypersensitivity	Diabetes mellitus
Congestive heart failure	Overactive bladder	Diabetes insipidus (central and nephrogenic)
Renal insufficiency	Cancer of the bladder, prostate, or urethra	Primary polydipsia
Excessive intake of fluid at night (especially alcohol and caffeine)		Hypercalcemia
Use of long-acting diuretics		
Sleep apnea		
Venous insufficiency		
Edema		
Hypoalbuminemia		

nocturia. Some may complain of daytime tiredness, disturbed sleep patterns, and insomnia, while others may present with a fracture as a result of a nighttime fall. Many patients, although aware that their nocturia is a problem, may believe that the symptom is merely an inevitable part of aging for which no treatment is available.

Differential Diagnosis

In order to diagnose nocturia properly, it is necessary first to establish whether the individual has awoken at night to void, or voids because he or she is already awake. Several medical issues, such as pain and anxiety, may interrupt sleep. A careful review of the etiologies of sleep interruption must include an analysis of sleep-related disorders, such as obstructive sleep apnea, which occurs in about 4% of men and 2% of women in the general population.[16] Upon questioning the patient about what caused them to awaken, it is important that physicians are aware that there may be discrepancies between the actual causes and the reasons given. In a sleep study performed by Pressman et al.,[17] explanations provided by patients as to the cause of their awakenings rarely matched the "objective" findings from polysomnograms.

History and Physical Examination

A thorough patient history and physical examination are central to the diagnosis of nocturia and are the primary means of establishing whether a treatable underlying condition—such as diabetes mellitus, obstructive sleep apnea, diabetes insipidus, OAB, BPH, or congestive heart failure—is present. Other potential causes or contributing factors of nocturia, detrusor dysfunction, or sensory urgency should be evaluated, including prior history of urinary complaints (and related treatment), in addition to descriptions of medication usage and patterns of fluid intake.

Of primary importance in the diagnostic process for nocturia is the voiding diary. Patients must receive clear directions on how to complete a voiding diary in order to procure an accurate portrait of the *typical* daily voiding experience. The diurnal pattern of voids, including any episodes of incontinence, should be documented, as should the volume of urine voided and fluid intake. The diary will provide important data about patterns of micturition, mean and total voided volume, and maximum voided volume (MVV), which is the largest single recorded volume voided during a 24-hr period. For the purposes of analysis, the first void of the morning should be counted toward the NUV, but should not be considered a nocturia event.

Using data from the voiding diary, it is possible to calculate the nocturia index (Ni), the nocturnal polyuria index (NPi), and the nocturnal bladder capacity index (NBCi), which together assist in establishing the etiology of an individual's nocturia.[18] The Ni is the NUV divided by the MVV; an $Ni > 1$ indicates that the nocturnal urine production is greater than the functional bladder capacity. In a study conducted by Rembratt et al.,[19] an Ni of 2.1 was observed in individuals with nocturia while an Ni of 1.0 was observed in individuals without nocturia, suggesting that a mismatch between nocturnal volume of urine excreted and the bladder's capacity to hold adequate urine during sleep is the most significant reason for the condition. The NPi is the NUV divided by the 24-hr urine output; an NPi >33% implies nocturnal polyuria as opposed to diurnal polyuria. The NBCi, is the difference between the actual number of nocturnal voids (ANV) and the predicted number of nocturnal voids (PNV), where the PNV is the Ni minus 1. The greater the NBCi, the more often nocturia is occasioned by nocturnal voided volumes smaller than the MVV. Further details of these indices and their utility can be found in Weiss et al.[18]

TREATMENT OF NOCTURIA

Addressing the underlying condition(s) causative of nocturia is the first step in treatment. Tight control of blood sugar may improve symptoms in patients with diabetes, and treatment of diabetes insipidus requires an accurate evaluation of the etiology. Hypercalcemia and hypokalemia have multiple etiologies and each must be addressed separately. Psychiatric referral and treatment are advised for patients with primary polydipsia. Any infections should be treated and current medications evaluated and possibly altered.

In patients diagnosed with nocturnal polyuria, the first treatment step is lifestyle and behavioral changes. Fluid intake in the evening should be eliminated, if possible, and alcohol and caffeine consumption should be reduced. Advice on diuretics, and in some cases the use of timed-release formulations of these drugs, may be of utility.[20] In addition, compression stockings and afternoon leg elevation may combat fluid retention before retiring at night, while the use of nasal continuous positive airway pressure can be used to treat sleep apnea and, therefore, reduce nocturia associated with this respiratory disease. Any nighttime influences that may awaken the patient should be addressed and removed. These initial measures, however, are rarely effective alone, necessitating pharmacotherapy in many patients.

At present, pharmacotherapeutic options for nocturia largely consist of desmopressin acetate and several different antimuscarinic agents (Table II). The choice of therapy will depend on the type of disorder. Available therapies differ in their efficacy and safety profiles, and should be selected on their individual merits (Table II). When treating elderly patients with comorbid conditions, it is important to consider potential adverse interactions between the nocturia therapy and other medications that they may be receiving.

Desmopressin Acetate

Desmopressin acetate is a synthetic analog of arginine vasopressin that has been used for several decades to treat diabetes insipidus and nocturnal enuresis, and is available in nasal, oral, and parenteral formulations. Arginine vasopressin plays an important role in the homeostatic regulation of the volume and osmolality of body fluids in mammals. It is secreted from the pituitary gland in response to changes in plasma osmotic pressure, and increases water reabsorption from the kidney. As an analog of arginine vasopressin, desmopressin increases urinary osmolality and decreases total urinary volume.[21]

The efficacy of desmopressin in treating nocturia has been examined in various populations, including men, women, and the elderly, in both short- and long-term studies.[21–25] In general, desmopressin increases the length of time until the first nocturnal void and decreases the number of nocturnal voids, the NUV voided, and the percentage of urine voided at night.[21–25] Adverse events associated with desmopressin treatment include headaches, nausea, dizziness, and hyponatremia.

The risk of hyponatremia with desmopressin use appears to increase with age and decreasing baseline sodium concentration.[26] A systematic review of older adults treated with oral or nasal desmopressin showed an incidence of 7.6% for

TABLE II. Pharmacologic Treatment Options

Desmopressin acetate
Synthetic analog of arginine vasopressin
Risk of hyponatremia, especially in the elderly
Avoid in patients with renal failure, CHF, cirrhosis, primary polydipsia
Oxybutynin chloride
Antimuscarinic agent
Tertiary amine
Able to cross BBB
Potential to cause CNS effects
Tolterodine tartrate
Antimuscarinic agent
Tertiary amine
Able to cross BBB
Potential to cause CNS effects
Trospium chloride
Antimuscarinic agent—atropine derivative
Quaternary amine
Does not cross BBB
Unlikely to cause CNS effects
No known metabolic drug–drug interactions
Solifenacin succinate
Antimuscarinic agent
Tertiary amine
Able to cross BBB
CNS side effects unknown
Darifenacin hydrobromide
Antimuscarinic agent
Tertiary amine
Able to cross BBB
Limited effect on cognition
Applicability for nocturia uncertain
Botulinum toxin
Neuromuscular blocking agent
Utility limited by expense, duration of activity, and necessity of repeated injections
Insufficiently studied in nocturia

BBB, blood–brain barrier; CHF, congestive heart failure; CNS, central nervous system.

hyponatremia.[27] It is therefore advised that desmopressin treatment of elderly patients be undertaken only with careful monitoring of sodium concentrations.[22,24,26] Desmopressin should be avoided in patients with primary polydipsia and related polyuria, cirrhosis of the liver, and renal and congestive heart failure.[28]

Antimuscarinic Agents

Antimuscarinic agents, including trospium chloride, oxybutynin chloride, tolterodine tartrate, darifenacin hydrobromide, and solifenacin succinate are first-line drug therapy for OAB and other bladder-related symptoms. These agents are believed to exert their effects by directly inhibiting the muscarinic receptors within the detrusor muscle that, when stimulated by acetylcholine released from activated cholinergic nerves, lead to bladder contraction and voiding.[29] Recent reviews have suggested that in addition to this mechanism, antimuscarinics also work via afferent pathways, mitigating the sensation of urgency.[30,31] Wide distribution of muscarinic receptors throughout the body means that the effects of antimuscarinic agents are not limited to the bladder. Adverse events resulting from antimuscarinic activity at locations outside the bladder include dry mouth, constipation, headache, and dizziness.[32] Despite these adverse effects, antimuscarinic therapy appears to offer a positive benefit:risk ratio for many patients with OAB.[32]

Although not indicated specifically for the treatment of nocturia associated with OAB, antimuscarinic agents are often used to treat this symptom. Clinical trials with some of these agents have indicated improvements in nocturia symptoms associated with OAB providing support for their use in this context.[33–36] For example, in a double-blind trial comparing solifenacin with tolterodine in patients with OAB, both were observed to be effective in reducing nocturia episodes (reduction of -0.71 and -0.63 episodes, respectively),[35] although the absence of a placebo arm in this study greatly limits the extent to which these results can be interpreted in a wider context. However, two pivotal placebo-controlled studies of trospium conducted in the USA showed significant reductions in the number of nocturnal toilet voids for patients with OAB who received trospium compared with those who received placebo ($P < 0.05$ at Week 4 of treatment).[33,36]

The effects of darifenacin on nocturia are less clear cut, with improvements in weekly nocturia episodes observed in one 12-week placebo-controlled trial[37] and no improvement seen in another trial of similar duration.[38] Published data are limited regarding the efficacy of oxybutynin for nocturia. In a placebo-controlled trial investigating the effects of behavioral and drug therapy on nocturia in older incontinent women, oxybutynin was observed to reduce nocturia episodes significantly more than placebo, however, these effects were less than those observed with behavioral modification.[39]

The beneficial effects provided by antimuscarinic agents for the treatment of nocturia may not be limited to patients with nocturia associated with OAB. In a 6-month open-label trial of tolterodine in 43 men with BPH-related LUTS who had failed α-blocker therapy, those treated with tolterodine experienced a reduction in their nocturnal voids from 4.1 episodes per night to 2.9 episodes per night.[40]

Although sharing a central mode of action, the available antimuscarinic agents have different physicochemical and pharmacokinetic properties that may impact their safety and tolerability in certain populations. Oxybutynin, solifenacin, tolterodine, darifenacin, and tolterodine are tertiary amines, which have the potential to cross the blood–brain barrier.[41] Blockade of central muscarinic receptors has the potential to cause adverse central nervous system (CNS) effects, and such effects, including confusion and hallucinations, have been observed with some tertiary anticholinergic agents, for example, oxybutynin and tolterodine.[42–44] Studies with darifenacin suggest that despite being able to cross the blood–brain barrier, this agent is not associated with cognitive adverse events, an effect that may be due to its low affinity for the M_1 muscarinic receptor.[45] No data are available regarding CNS events associated with solifenacin.

As a quaternary amine, trospium is hydrophilic and lipophobic, resulting in a low propensity to cross the blood–brain barrier and cause central adverse effects.[41,46] This assertion is supported by experimental and clinical studies, the lack of incidence of cognitive adverse events in post-marketing monitoring reports, and physician experience.[47–50] In addition, trospium is the only agent not significantly metabolized via the hepatic cytochrome P450 enzyme system, reducing the likelihood of interactions with other drugs metabolized via this pathway.[51] The potential for anticholinergic medication to cause adverse CNS effects or result in adverse metabolic drug–drug interactions may be particularly important considerations when selecting an appropriate therapy for older patients, as they may be more sensitive to the anticholinergic effects of antimuscarinic therapy due to age-related reductions in metabolism and elimination and are also prone to polypharmacy.[52]

Future Treatment—Botulinum Toxin

Botulinum toxin, a presynaptic neuromuscular blocking agent, blocks vesicular release of acetylcholine and induces selective and reversible muscle weakness. It has been extensively studied for bladder-related dysfunction, largely in the area of neurogenic and idiopathic detrusor overactivity; however, most of the studies have been conducted in small patient populations. Botulinum-A toxin has been shown to reduce nocturia in patients with OAB without detrusor overactivity.[53] Botulinum toxin therapy is, at present, limited by its expense and its short duration of efficacy, thus requiring repeated injections to sustain the effect.[53–56] While botulinum toxin has not received an indication for bladder-related symptoms, it may prove useful in patients who are refractory to antimuscarinics. It has also demonstrated promising results in patients with idiopathic and neurogenic detrusor overactivity.[55]

CONCLUSION

Nocturia is a troubling disorder affecting an increasingly aging population. A careful evaluation often provides insight into the etiology of this disease and may provide corresponding remedial actions. Where an underlying cause cannot be identified, behavioral and lifestyle changes may provide some relief, but pharmacologic treatment is often required. Current treatment options include desmopressin, antimuscarinic agents, timed diuretics, compressive lower extremity stockings, and in selected cases, nasal continuous positive airway pressure. While providing benefits for the treatment of nocturia in many patients, the risk of adverse events associated with some of the available medications requires careful selection to optimize the therapeutic index.

AUTHOR DISCLOSURES

Dr. Rodney Appell is a paid consultant for Astellas, Ortho-McNeil, Pfizer, Indevus, Watson, Boston Scientific, American Medical Systems; an investigator for Boston Scientific, American Medical Systems, Allergan, Novartis, Solace; and a stock holder in American Medical Systems and Solace.

Dr. Peter Sand is an advisor for Astellas, Glaxo Smith Kline, Indevus, Esprit, Allergan, Watson, Ortho, and Schwarz Pharma; an investigator for Ortho, Watson, Allergan, Indevus, Astellas, and Medicinova; and a speaker for Ortho, Astellas, Glaxo Smith Kline, Indevus, Esprit and Watson.

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