KJU Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2013.54.8.492

Review Article

Current Evaluation and Treatment of Nocturia

Hyoung Keun Park, Hyeong Gon Kim

Department of Urology, Konkuk University School of Medicine, Seoul, Korea

Nocturia is usually considered to be just one of the symptoms included with lower urinary tract symptoms (LUTS) and is treated with therapy based on LUTS. Recent research suggests, however, that nocturia is not merely a simple symptom of LUTS but is a multifactorial condition with many contributing etiological factors. The causes of nocturia can be classified into bladder storage problems, increased urine output, sleep disturbance problems, and other potential diseases. The frequency-volume chart (FVC) is very important in evaluating and diagnosing nocturia. Patients usually record the volume and timing of voids for a period of 1 to 3 days on the FVC. The FVC data can provide information on voiding patterns and clues about the etiology and treatment of nocturia. It is doubtful that alpha-blockers will have clinical significance for treatment because the difference in nocturia episodes between treatment with alpha-blockers and placebo is too small. Antimuscarinics also exert no effect on nocturnal polyuria, and the evidence supporting the efficacy of antimuscarinics for the treatment of nocturia is limited. However, several randomized placebo-controlled trials have shown the efficacy of oral desmopressin in the treatment of adults with nocturia. Short-acting hypnotics may be helpful for patients with sleep disturbances. Although surgical or interventional therapy is not indicated for nocturia, transurethral resection of the prostate appears to confer a greater improvement in benign prostatic hyperplasia symptoms including nocturia. The management of nocturia may require a team approach by making optimal use of multidisciplinary expertise.

Keywords: *Epidemiology; Evaluation; Nocturia; Pathophysiology; Treatment*

Article History:
received 30 April, 2013
accepted 5 June, 2013

Corresponding Author:
Hyeong Gon Kim
Department of Urology, Konkuk University School of Medicine, 263 Achasan-ro, Gwangjin-gu, Seoul 143-701, Korea
TEL: +82-2-2030-7672
FAX: +82-2-2030-7748
E-mail: khgsjh@kuh.ac.kr

INTRODUCTION

Nocturia has usually been considered to be just one of the symptoms that constitute lower urinary tract symptoms (LUTS). As such, except for nocturnal polyuria (NP), nocturia is usually treated with therapy based on LUTS, including alpha-blockers and anticholinergic drugs. Recent research suggests, however, that the etiology of nocturia differs from that of other LUTS and that nocturia should be researched as a condition in its own right and as a part of systemic disease. The objective of this article was to review the current status of nocturia regarding its epidemiology, pathophysiology, evaluation, and treatment.

EPIDEMIOLOGY

The term *nocturia* is defined by the International Continence Society as "the complaint that the individual has to wake at night one or more times to void" [1]. Several reports on the prevalence of nocturia exist in the literature, but prevalence estimates vary and are affected by the population studied, the age range considered, and the definition of nocturia used. Many studies [2-4] on nocturia consider only patients with two or more voids per night on the basis of the observation that a nocturnal frequency of one void per night does not seem to be harmful or bothersome. The BACH study [5] showed that nocturia affected 25% of men and 31% of women. In the Epic study [6], the preva-

lence of nocturia was 49% in men and 55% in women. A recent meta-analysis of 43 articles concluded that although nocturia is common across diverse populations, with the highest prevalence in older people, a significant proportion of younger individuals are also affected [7]. Using the criterion of 2 or more voids per night, this analysis reported the following prevalence rate ranges:

Men aged 20 to 40 years: 2–17%
Women aged 20 to 40 years: 4–18%
Men aged >70 years: 29–59%
Women aged >70 years: 28–62%

Table 1 shows the results of several other representative epidemiological studies on the prevalence of nocturia.

PATHOPHYSIOLOGY

Nocturia is not a simple symptom of LUTS but is a multifactorial condition with many contributing etiological factors. Patients may be affected by one or several of these factors. The cause of nocturia can be classified into bladder storage problems, increased urine output, sleep disturbance problems, and other potential diseases. The possible causes of nocturia are summarized in Table 2.

1. Bladder storage problems

Bladder storage problems include overactive bladder (OAB), benign prostatic hyperplasia (BPH), detrusor overactivity, bladder inflammation, and bladder pain syndrome.

Storage problem, whether functional or anatomic, is related with reduced bladder capacity especially at night. Nocturia occurs when the amount of urine production overwhelm the nocturnal bladder capacity during the night. Therefore, even without exceeding production of urine at night, the bladder cannot store the nocturnal urine volume.

The reasons for the urinary bladder to have this condition are multiple ways: significant following-voiding residual urine due to reduced bladder contractility often seen with associated bladder outlet obstruction caused by benign prostatic obstruction (BPO). OAB or detrusor overactivity may have patients wake up via urgency feeling or bladder filling sense caused by uninhibited contraction. Specific pain of bladder Inflammation or bladder pain syndrome also induce sensory urgency and reduced functional bladder capacity. Lower urinary tract calculi or primary bladder pathology also could cause a reduction in the anatomic capacity.

TABLE 1. Prevalence of nocturia

Author	Country	Demographic	Prevalence (%)
Tikkinen et al. [4]	Finland	Men aged 50–59	12
		Women aged 50–59	16
		Men aged 60–69	40
		Women aged 60–69	25
Fitzgerald et al. [5]	USA	Adults aged 30–79	28
Irwin et al. [6]	USA and Europe	Adults aged >18	24
Hunter et al. [8]	Spain	Men aged >50	34
Rembratt et al. [9]	Sweden	Adults aged >65	29
Bing et al. [10]	Denmark	Adults aged 60–80	36
Lukacz et al. [11]	USA	Women aged 25–84	33

Nocturia was defined as voiding more than once at night.

2. Increased urine output

Increased urine output can be divided into 24-hour polyuria and NP. In particular, NP is an important contributor to nocturia. NP is typically defined as a nocturnal urinary output >20% of the daily total in young adults and >33% in older adults [1]. The currently recognized contributors to NP include increased fluid intake or diuretic intake during the evening (behavioral etiology), return of water of daytime third spacing in the lower extremities, obstructive sleep apnea (OSA), and lack of production of endogenous pituitary arginine vasopressin.

3. Sleep disturbance

Nocturia may be associated with sleep apnea. Community-based elderly populations who have higher levels of sleep disordered breathing (>25 breathing events/h) have nearly double the number of nocturia episodes compared with those with low rates of OSA [12]. Nocturia episodes in these individuals can be at least partially reduced by continuous positive airway pressure treatment for sleep apnea [13]. By contrast, one population-based study reported that there is no relationship between nocturia frequency and OSA pa-

TABLE 2. Causes of nocturia

Bladder storage problem	Increased urine output		Sleep disturbance	Other potential disease
	24-Hour polyuria	Nocturnal polyuria		
Overactive bladder, BPH, detrusor overactivity, bladder inflammation, bladder pain syndrome.	Diabetes mellitus Diabetes insipidus Primary polydipsia	Congestive heart failure Obstructive sleep apnea Peripheral edema excessive fluid drinking in evening Circadian defect in secretion or action of ANP	Insomnia Sleep apnea Periodic leg movement	Cardiopulmonary disease Parkinson disease Dementia Depression Alcohol abuse

BPH, benign prostatic hyperplasia; ANP, atrial natriuretic peptide.

rameters [14]. OSA does not only awaken the patient but also causes NP. OSA results in hypoxia and hypoxia-induced pulmonary vasoconstriction, which in turn leads to elevated atrial natriuretic polypeptide, which increases urine production at night [15].

ASSESSMENT

As previously mentioned, because nocturia has a multifactorial cause, initial assessment involves taking a thorough history to more clearly understand the patient's symptoms and associated underlying diseases. Patients should be evaluated for underlying disease states, cardiovascular conditions, and consumption of liquids (including specifically those containing alcohol and caffeine) [2]. Urine analysis, urine culture, and cytology should also be carried out. If abnormalities are found in any of these, patients should be further evaluated with cystoscopy or urography [2]. The frequency-volume chart (FVC) is very important in evaluating and making a diagnosis of nocturia. Patients usually record the volume and timing of voids for a period of 1 to 3 days on the FVC. The FVC data can provide voiding patterns and clues about the etiology and treatment of nocturia. On the basis of the FVC, nocturia can be categorized into four aspects: 24-hour polyuria, NP, reduced bladder capacity, and mixed disorder [16] (Fig. 1, Table 2). NP is present in up to 83% of the general population with nocturia and, as such, clinicians should be alert to the fact that this overproduction of urine at night may be a key contributory factor in their patients, even among those with an OAB or with a diagnosis of benign prostatic obstruction.

Additional aspects included in a more comprehensive voiding diary are the nature and timing of fluid intake, LUTS such as urgency, potential contributory factors, and sleep pattern. The use of FVCs is additionally recommended because of discrepancies between nocturnal voiding data obtained by using FVCs and data obtained from subjective questionnaires such as the International Prostate Symptom Score (IPSS).

MANAGEMENT

Because it is likely that more than one contributory factor is responsible for nocturia in any group of individuals, it is critically important to revise the FVC. In fact, the multifactorial nature of nocturia with no dominant underlying etiology suggests that in order to achieve clinically significant improvement, multiple treatments with additive effects may be required.

1. Lifestyle modification

Lifestyle modification is often given as a first-line option, but there are limitations to controlling nocturia by lifestyle

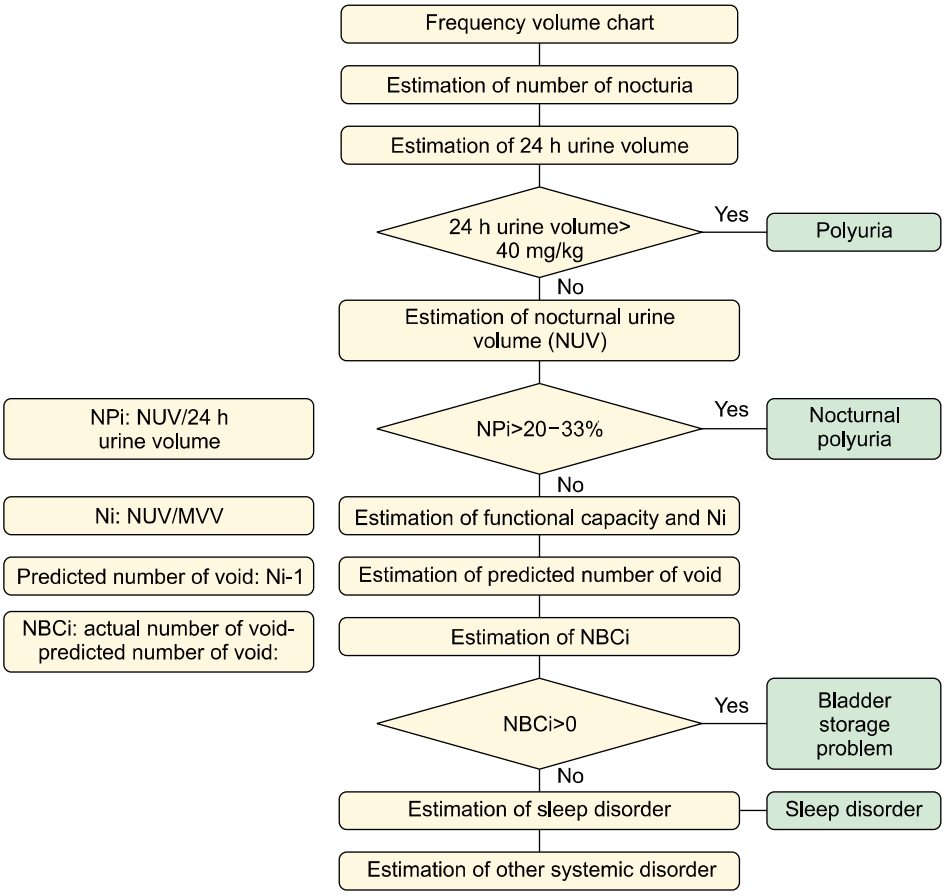

FIG. 1. Etiology of nocturia, classified according to the four definitions based on the frequency volume chart. NPi, nocturnal polyuria index; Ni, nocturia index; MVV, maximum voided volume; NBCi, nocturnal bladder capacity index.

modification only. The information regarding this topic is very scarce compared to its significance and more research should be needed in this topic in the future.

Some modifications include preemptive voiding, nocturnal dehydration, dietary and fluid restrictions (avoidance of caffeinated beverages, alcohol, etc.), medication timing (diuretics in the midafternoon), evening leg elevation to mobilize fluids, use of sleep medications or sleep aides, and use of protective undergarments [2]. Although no randomized controlled trials (RCTs) evaluating the effect of behavioral modification on nocturia as a primary outcome have been found, one study showed that the education about life style modification could reduce nocturia episode and related quality of life [17].

2. Alpha-blockers

Several drugs used in LUTS/BPH medication have shown effects on nocturia and, alpha blocker was thought to reduce residual urine and so increase room for nocturnal urine storage. However, it is doubtful whether alpha-blockers have clinical significance, because the difference in nocturia episodes was too small between treatment with alpha-blockers and placebo. The effect of tamsulosin was assessed in a phase 3B pilot study involving men with LUTS/BPH and at least 2 voids per night [18]. The study concluded that "tamsulosin 0.4 mg was superior to placebo in reducing nocturia." However, this "significant reduction" amounted to a mean change of 3.1 to 2.3 awakenings for placebo and 3.1 to 2.0 for the drug. One RCT compared an α1-blocker with placebo, with a focus on nocturia as a primary outcome. The primary endpoint was the mean variation in the number of nocturnal voids compared with baseline after 8 weeks of treatment with a tamsulosin oral controlled absorption system (OCAS) 0.4 mg/d or placebo. The mean decrease in the number of nocturnal voids was not significantly different between the two groups (0.7 for placebo compared with 1.1 for tamsulosin OCAS) [19]. Another study was a secondary analysis of IPSS nocturia data from the Veterans' Administration Cooperative Study [20]. The data from 1,078 men aged 45–80 years with a diagnosis of BPH and who completed 12 months of the trial were analyzed specifically for reductions in nocturia. There were four arms in the study: terazosin, finasteride, combined terazosin plus finasteride, and placebo. The study presented significant results for α1-blockers and combination over placebo but with a very slight effect. Recently, a few studies have reported the effect of a selective alpha-1D blocker, naftopidil, on nocturia. One study compared the efficacy of two α1-adrenoceptor antagonists, tamsulosin and naftopidil, in the treatment of LUTS with BPH [21]. They concluded that the two drugs had similar efficacy in the treatment of BPH symptoms. However, naftopidil was better than tamsulosin for nocturia. The improvement in the tamsulosin group was from 3.4 to 3.1 voids per night; the improvement in the naftopidil group was from 3.4 to 2.3 voids per night. However, the sample number was small and the study period was too short. We must wait for further long-term, well-designed controlled studies on naftopidil to be convinced of its positive effect on nocturia. In conclusion, most studies on α1-blockers have been conducted in the context of LUTS/BPO management, and the evidence supporting the efficacy of α1-blockers in treating nocturia is low.

3. Antimuscarinic agents

The majority of studies on antimuscarinics have been conducted in the context of OAB management. Because nocturia is commonly seen in OAB, it has been assumed that first-line medications for OAB will exert a clinically significant effect and will show a somewhat positive effect on reducing the number of nocturia episodes for patients without OAB symptoms. However, there is limited evidence showing that antimuscarinics are efficient for the management of nocturia.

1) Solifenacin

There is one interesting study on the efficacy of solifenacin for nocturia and NP [22]. Of 3,032 patients who were randomized, 2,534 reported nocturia at baseline, and 62% of the patients reporting nocturia were classified as having NP. In those without NP, there was a significant reduction in nocturia, but it was only a slight difference (0.18 net advantages over placebo for the 5-mg dose and 0.08 for the 10-mg dose). For those with NP, the reductions were not significantly different between the placebo and drug groups.

2) Trospium chloride

Rudy et al. [23] showed a statistically significant decrease in the mean number of nocturia episodes per night (baseline 2) of 0.57 voids per night for the drug vs. 0.29 voids per night for placebo. However, the difference in nocturia was only 0.28 episodes.

3) Tolterodine and fesoterodine

There is one RCT comparing tolterodine with placebo, with a focus on nocturia as the primary endpoint. The main outcome criterion was the change in the mean number of nocturia episodes from baseline to week 12. Eight hundred fifty men and women with OAB associated with nocturia were recruited and received placebo or tolterodine for 12 weeks. Although tolterodine was associated with improvement in other OAB-specific symptoms, the difference between the two groups for nocturnal frequency was not statistically significant (decreases of 19% and 23% for placebo and tolterodine, respectively, p=0.145) [24]. Herschorn et al. [25] showed no statistically significant decrease in the mean number of nocturia episodes between the placebo group and the fesoterodine group. The mean change in nocturnal voiding was −0.5 in the placebo group and −0.6 in the fesoterodine group.

Whereas antimuscarinics do not reduce the number of nocturia episodes overall, they can reduce urgency episodes, and decreased urgency episodes at night may result in a reduction in overall nocturia episodes. Rackley et al.

[24] reported on the median percentage reduction in nocturnal voiding frequency with tolterodine and divided nocturnal voids into non-OAB voids, OAB voids, and severe OAB voids. Overall, there was no significant effect on nocturia episodes compared with placebo. However, there was a statistically significant improvement in OAB-related nocturnal voids (those associated with urgency). The mean reduction of nocturia episodes was −22% to 43% in the placebo group and −30% to 59% in the tolterodine group.

In conclusion, antimuscarinics exert no effect on NP, one important cause of nocturia, and evidence supporting the efficacy of antimuscarinics for the treatment of nocturia is low. These agents are expected to exert an effect on nocturia only if the episodes of nocturia awakening are associated with urgency.

4. Timed diuretic therapy

Diuretics are often prescribed for peripheral edema with no particular attention to the time of the day at which they would be most effective. In patients with NP owing to reabsorption of third-space lower extremity fluid in the supine position during sleep, diuretics should be administered in the midafternoon to address fluid accumulated over the course of the day, but not so late as to actually exacerbate NP. One trial compared furosemide intake 6 hours before bedtime with placebo. Furosemide 6 hours before bedtime was superior to placebo in reducing the number of nocturnal voids [26]. One preliminary study showed terazosin and thiazide combination therapy could reduce nocturia more than 25% in about half of the study patients [27].

5. Antidiuretic therapy

For patients whose nocturia is related to NP, either alone or combined with OAB or BPH, antidiuretic treatment that reduces nocturnal urine volume is effective. Before antidiuretic treatment, patients should be given advice regarding nighttime fluid intake along with other causes of NP; clinicians should exclude possible causes of NP in these patients. As previously described, NP may occur secondary to any renal tubular dysfunction, third-space fluid sequestration, OSA, circadian impairment, or as a side-effect of drugs (e.g., steroids). For those patients with suspected fluid sequestration (which is a possibility in patients with venous insufficiency, hypoalbuminemia, congestive cardiac failure, etc.), one can consider compression and elevation or the use of a diuretic in the afternoon. Desmopressin is the synthetic analogue of arginine vasopressin. Desmopressin has a more powerful and longer-lasting antidiuretic action than does arginine vasopressin. It increases reabsorption of water in the distal and collecting tubules of the kidney via its action on the V2 receptor and then concentrates the urine, decreasing urine production and postponing the need to void. Given the specific antidiuretic action of desmopressin, it is the pharmacological therapy of choice for patients with nocturia in which NP is present and has a grade A level 1 recommendation from the International Consultation on Incontinence [28].

1) Efficacy of desmopressin

Several randomized placebo-controlled trials have shown the efficacy of oral desmopressin in the treatment of adults with nocturia. A series of 3-week, randomized, double-blind, placebo-controlled trials showed that oral desmopressin (0.1, 0.2, or 0.4 mg tablet) is effective in both men and women aged ≥18 years who are suffering from nocturia [29]. In this study, clinical response was defined as a more than 50% reduction in nocturnal voids from baseline. In a study of men, 34% of patients showed a clinical response with desmopressin, compared with 3% of patients receiving placebo ($p<0.001$). The mean number of nocturnal voids decreased from 3.0 to 1.7 and from 3.2 to 2.7, respectively, reflecting mean decreases of 43% and 12% ($p<0.001$). The mean duration of the first sleep period was increased by 59% (from 2.7 to 4.5 hours) in the desmopressin group. In women, the results were similar [30]. Forty-six percent of desmopressin-treated women showed a clinical response, compared with 7% of those on placebo ($p<0.001$).The mean number of nocturnal voids was reduced from 2.92 to 1.61 and from 2.91 to 2.36, respectively ($p<0.001$). In another RCT, 33% of desmopressin-treated patients had a clinical response vs. 11% with placebo ($p<0.001$), with the mean number of nocturnal voids decreasing from 3.26 to 2.01 with desmopressin and from 2.8 to 2.42 with placebo ($p<0.001$) [31]. A recent meta-analysis [16] also showed the efficacy of desmopressin over placebo. Nocturnal voids per night, nocturnal urine volume, and nocturnal diuresis were significantly reduced in the desmopressin group. The mean difference in nocturnal voids was −0.54 voids per night, and the odds ratio of successful outcome was 3.0 in the desmopressin group. Notably, the duration of the first sleep period was longer in the desmopressin group. A long-term study showed that efficacy was maintained and improved during the 10 to 12 months of treatment. However, a rebound effect was seen when treatment was withdrawn, thus confirming the association between continued treatment and response [32].

2) Adverse effects

The frequently related adverse events described in the studies are headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral edema, and nausea. Hyponatremia, which is recognized as the adverse event of most concern, is most frequent in men older than 65 years of age. Cases are usually not symptomatic and rare. The primary predictor is increasing age. Serum sodium monitoring at baseline and treatment in the early phase in older patients can greatly reduce these patients' risk of developing the condition. Assessment of serum sodium 3 days after starting therapy is recommended in one guideline [33].

6. Sleep disturbance therapy

Sleep disturbance can result from sleep disorders; medical, neurological, or psychiatric diseases; and other influences, which are evaluated when treating nocturia. Patients sus-

pected of having a sleep disorder (e.g., sleep apnea, nocturnal seizures, and excessive daytime sleepiness) should be referred to a sleep specialist. Short-acting hypnotics may be helpful for patients with sleep disturbances. Oxazepam has been associated with a reduction in nocturia (but not nocturnal urine production) [34].

7. Surgical therapy

Although surgical or interventional therapy is not indicated for nocturia, transurethral resection of the prostate (TURP) appears to confer a greater improvement in BPH symptoms including nocturia, and several studies reported a decrease in the mean number of nocturia episodes after TURP [35,36]. The mechanism of improvement in symptoms after TURP is not clear. Possible explanations include a reduction in detrusor overactivity with relief of prostatic obstruction and the effect of adenoma removal on the detrusor muscle.

CONCLUSIONS

The lower urinary tract is not a major cause of nocturia. It is necessary to assess the patient for underlying causes, recognizing that sleep disorders, polyuria, and endocrine disease are the most likely causes. The management of nocturia may require a team approach, by making optimal use of multidisciplinary expertise.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:179-83.
2. Weiss JP, Blaivas JG, Bliwise DL, Dmochowski RR, Dubeau CE, Lowe FC, et al. The evaluation and treatment of nocturia: a consensus statement. BJU Int 2011;108:6-21.
3. Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 2003;92:948-54.
4. Tikkinen KA, Johnson TM 2nd, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010;57:488-96.
5. Fitzgerald MP, Litman HJ, Link CL, McKinlay JB; BACH Survey Investigators. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. J Urol 2007;177:1385-9.
6. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50:1306-14.
7. Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2010;184:440-6.
8. Hunter DJ, Berra-Unamuno A, Martin-Gordo A. Prevalence of urinary symptoms and other urological conditions in Spanish men 50 years old or older. J Urol 1996;155:1965-70.
9. Rembratt A, Norgaard JP, Andersson KE. Differences between nocturics and non-nocturics in voiding patterns: an analysis of frequency-volume charts from community-dwelling elderly. BJU Int 2003;91:45-50.
10. Bing MH, Moller LA, Jennum P, Mortensen S, Skovgaard LT, Lose G. Prevalence and bother of nocturia, and causes of sleep interruption in a Danish population of men and women aged 60-80 years. BJU Int 2006;98:599-604.
11. Lukacz ES, Whitcomb EL, Lawrence JM, Nager CW, Luber KM. Urinary frequency in community-dwelling women: what is normal? Am J Obstet Gynecol 2009;200:552.e1-7.
12. Endeshaw YW, Johnson TM, Kutner MH, Ouslander JG, Bliwise DL. Sleep-disordered breathing and nocturia in older adults. J Am Geriatr Soc 2004;52:957-60.
13. Margel D, Shochat T, Getzler O, Livne PM, Pillar G. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. Urology 2006;67:974-7.
14. Kang SH, Yoon IY, Lee SD, Kim JW. The impact of sleep apnoea syndrome on nocturia according to age in men. BJU Int 2012;110 (11 Pt C):E851-6.
15. Yalkut D, Lee LY, Grider J, Jorgensen M, Jackson B, Ott C. Mechanism of atrial natriuretic peptide release with increased inspiratory resistance. J Lab Clin Med 1996;128:322-8.
16. Cornu JN, Abrams P, Chapple CR, Dmochowski RR, Lemack GE, Michel MC, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management: a systematic review and meta-analysis. Eur Urol 2012;62:877-90.
17. Cho SY, Lee SL, Kim IS, Koo DH, Kim HJ, Oh SJ. Short-term effects of systematized behavioral modification program for nocturia: a prospective study. Neurourol Urodyn 2012;31:64-8.
18. Speakman M. Efficacy and safety of Tamsulosin OCAS. BJU Int 2006;98(Suppl 2):13-7.
19. Djavan B, Milani S, Davies J, Bolodeoku J. The impact of tamsulosin oral controlled absorption system (OCAS) on nocturia and the quality of sleep: preliminary results of a pilot study. Eur Urol Suppl 2005;4:61-8.
20. Johnson TM 2nd, Jones K, Williford WO, Kutner MH, Issa MM, Lepor H. Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial. J Urol 2003;170:145-8.
21. Nishino Y, Masue T, Miwa K, Takahashi Y, Ishihara S, Deguchi T. Comparison of two alpha1-adrenoceptor antagonists, naftopidil and tamsulosin hydrochloride, in the treatment of lower urinary tract symptoms with benign prostatic hyperplasia: a randomized crossover study. BJU Int 2006;97:747-51.
22. Brubaker L, FitzGerald MP. Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:737-41.
23. Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R. Multicenter phase III trial studying trospium chloride in patients with overactive bladder. Urology 2006;67:275-80.
24. Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z; 037 STUDY GROUP. Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. Urology 2006;67:731-6.
25. Herschorn S, Swift S, Guan Z, Carlsson M, Morrow JD, Brodsky M, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU Int 2010;105:58-66.

26. Reynard JM, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. Br J Urol 1998;81:215-8.
27. Cho MC, Ku JH, Paick JS. Alpha-blocker plus diuretic combination therapy as second-line treatment for nocturia in men with LUTS: a pilot study. Urology 2009;73:549-53.
28. Andersson KE, Chapple CR, Cardozo L, Cruz F, Hashim H, Michel MC, et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein AJ, editors. Incontinence. Paris: Health Publication Ltd; 2009. p. 631-99.
29. Mattiasson A, Abrams P, Van Kerrebroeck P, Walter S, Weiss J. Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. BJU Int 2002;89: 855-62.
30. Lose G, Lalos O, Freeman RM, van Kerrebroeck P; Nocturia Study Group. Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. Am J Obstet Gynecol 2003;189:1106-13.
31. van Kerrebroeck P, Rezapour M, Cortesse A, Thuroff J, Riis A, Norgaard JP. Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. Eur Urol 2007;52:221-9.
32. Lose G, Mattiasson A, Walter S, Lalos O, van Kerrebroeck P, Abrams P, et al. Clinical experiences with desmopressin for long-term treatment of nocturia. J Urol 2004;172:1021-5.
33. National Institute for Health and Clinical Excellence. NICE clinical guideline 97. Lower urinary tract symptoms: the management of lower urinary tract symptoms in men [Internet]. London: National Institute for Health and Clinical Excellence; c2010 [cited 2012 Jun 4]. Available from: http://www.nice.org.uk/nicemedia/live/12984/48557/48557.pdf.
34. Kaye M. Nocturia: a blinded, randomized, parallel placebo-controlled self-study of the effect of 5 different sedatives and analgesics. Can Urol Assoc J 2008;2:604-8.
35. Antunes AA, Srougi M, Coelho RF, Leite KR, Freire Gde C. Transurethral resection of the prostate for the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia: how much should be resected? Int Braz J Urol 2009;35:683-9.
36. Yoshimura K, Ohara H, Ichioka K, Terada N, Matsui Y, Terai A, et al. Nocturia and benign prostatic hyperplasia. Urology 2003; 61:786-90.