available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Voiding Dysfunction

A Contemporary Assessment of Nocturia: Definition, Epidemiology, Pathophysiology, and Management—a Systematic Review and Meta-analysis

Jean-Nicolas Cornu [a,*], *Paul Abrams* [b], *Christopher R. Chapple* [c], *Roger R. Dmochowski* [d], *Gary E. Lemack* [e], *Martin C. Michel* [f], *Andrea Tubaro* [g], *Stephan Madersbacher* [h]

[a] *Department of Urology, Tenon Hospital, University Paris 6, Assistance Publique-Hopitaux de Paris, Paris, France;* [b] *Bristol Urological Institute, Southmead Hospital, Bristol, UK;* [c] *Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield, UK;* [d] *Department of Urology, Vanderbilt University, Medical Center North, Nashville, TN, USA;* [e] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [f] *Department of Pharmacology, Johannes Gutenberg University, Mainz, Germany;* [g] *Department of Urology, Sant'Andrea Hospital, Faculty of Health Sciences, La Sapienza University of Rome, Rome, Italy;* [h] *Department of Urology and Andrology, Donauspital, Vienna, Austria*

Article info

Article history:
Accepted July 6, 2012
Published online ahead of print on July 20, 2012

Keywords:
Nocturia
Nocturnal polyuria
Systematic review
Meta-analysis
α_1-Blockers
Antimuscarinics
Desmopressin

Abstract

Context: Nocturia is a common urologic symptom that has been covered in a variety of reported studies in the literature but is not specifically covered in current guidelines.
Objective: To comprehensively review the literature pertaining to the definition, etiologies, and consequences of nocturia and assess the evidence supporting the use of conservative medical and interventional therapy.
Evidence acquisition: A literature search was conducted using the keyword *nocturia*, restricted to articles in the English language, after 2000 and before April 2012, in PubMed/Medline, Embase, Scopus, Web of Science, and Cochrane Library databases. Regarding treatment modalities, studies were included only if nocturia was a primary end point and if the studies were designed as randomized controlled trials without limit of date. When suitable, a meta-analysis was conducted. Papers covering treatment options for nocturia specifically related to nonurologic conditions were excluded.
Evidence synthesis: *Nocturia* is still defined as the symptom of wakening from sleep once or more often to void. The prevalence is high in both genders and increases with age. Frequency–volume charts, which are the pivotal tool of clinical assessment, detect 24-h polyuria, nocturnal polyuria (NP), or reduced nocturnal bladder capacity and help to target specific nonurologic etiologies. Nocturia is a morbid condition that significantly affects quality of life and increases mortality. Besides behavioral measures, validated treatment options include oral desmopressin, which is superior to placebo in treating NP. While the level of evidence for desmopressin is high, limited data support the use of α_1-blockers and antimuscarinics; however, only rarely has nocturia been a primary end point when studying these drug classes, and studies have not consistently controlled for the effect of NP.
Conclusions: Our knowledge of nocturia, its etiology, and its management has substantially improved in recent years. The evidence available on the management of nocturia remains limited; contributory factors include (1) the complexity of associated conditions, (2) the underuse of objective evaluation tools, and (3) the lack of specific focus on nocturia in clinical trials.

* Corresponding author. Urology Department, Tenon Hospital, 4 rue de la Chine, 75970 Paris Cedex 20, France. Tel. +33 1 56 01 64 95; Fax: +33 1 56 01 73 06.
E-mail address: jeannicolas.cornu@gmail.com (J.-N. Cornu).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2012.07.004

1. Introduction

Nocturia is a well-recognized, highly prevalent symptom in both men and women [1]. The term *nocturia* is defined by the International Continence Society (ICS) as "the complaint that the individual has to wake at night one or more times to void" [2]. In epidemiological studies, nocturia is often associated with a range of other lower urinary tract symptoms (LUTS) and, especially in elderly patients, is often not seen as the principal symptom [3]. Nocturia is even considered by some authors as "normal" and is not considered a major reason for seeking treatment [4,5]. Clearly, nocturia is a symptom, not a disease. Similarly, it is classified as one component of common urologic conditions harbored by community-dwelling individuals, such as LUTS, overactive bladder (OAB), and urinary incontinence. As a matter of fact, despite the high prevalence, diverse etiology, and clinical importance of nocturia, no existing guideline has specifically addressed the subject of nocturia and its management over the last decade since the first landmark ICS document [2].

The last decade has been marked by a growing interest in nocturia as a specific symptom, in particular considering its etiology and consequences. This movement has led a number of groups of experts to provide consensus statements and helpful collaborative documents to summarize the knowledge on nocturia. These publications have emphasized that nocturia is a symptom that has been underreported, understudied, and often not adequately considered [6–8]. The reports follow the introduction [9] and the further development of the concept of LUTS [10], which has heralded a new era for medical research and clinical practice improvement in the field of functional urology.

Given the growing interest in nocturia as an important cornerstone of LUTS, the aim of the present work was to provide a systematic review of the available scientific evidence regarding the definition, physiopathology, epidemiology, and management of nocturia.

2. Evidence acquisition

A systematic review was conducted based on a literature search through the PubMed/Medline, Embase, Scopus, Web of Science, and Cochrane Library databases using the keyword *nocturia*. The literature search was restricted to full-length articles, in the English language (for practical reasons), after 2000 and before April 2012.

A first selection was made based on the titles and abstracts of the papers. After removal of duplicates and the exclusion of conference abstracts, the articles were classified in six categories: definitions, epidemiology and associated conditions, physiopathology, medical treatment, interventional therapy, and reviews. Articles belonging to the medical treatment category were further analyzed based on abstract and full text, if necessary, according to the following criteria: authors, journal and year of publication, patients' gender, number of patients included, study design, baseline evaluation of nocturia, follow-up duration, number of treatment arms, molecules tested, main outcomes, and secondary outcomes. Studies were included in this systematic review only if nocturia was defined as a primary end point of the study and if the study was designed as a randomized controlled trial (RCT). Pooled analysis or post hoc analysis of previous RCTs was also considered if it contributed further information of critical importance. A supplementary literature search based on the words *nocturia* and *randomized OR randomised* with no limit of date was performed to include any RCT with nocturia as a primary outcome published as a full paper even before 2000. The reference lists of all traced articles and general reviews on the topic of nocturia were examined manually. Papers covering treatment options for nocturia specifically related to nonurologic conditions (eg, multiple sclerosis, sleep apnea, or Parkinson disease) were excluded from this review.

A meta-analysis was conducted if two or more studies assessed the efficacy of a given drug compared with placebo or another reference treatment through an RCT with nocturia as a primary outcome. In this case, the articles were evaluated using multiple criteria of internal and external validity, including attrition bias, concealment, comparability of sites, blindness, detection bias, focused question, intent-to-treat analysis, outcome omission, performance bias, randomization, power calculation, comparability of groups at baseline, funding, and inclusion criteria. When possible, the meta-analysis was carried out using the 2011 Review Manager 5.1. (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). For the sections dealing with definition, classification, epidemiology, and morbidity/sequelae assessment, a consensus has been reached by the authors, although formal consensus tactics methods were not applied.

3. Evidence synthesis

The initial search yielded 11 361 potential citations. After removal of duplicates and application of language limits, 1365 articles were considered and reviewed based on title and abstract. At the end of the process, 277 full papers were obtained and considered for inclusion in this review. The flow diagram is given in Figure 1.

3.1. Definitions

Nocturia is currently defined by the ICS as the complaint that the individual has to wake at night one or more times to void, each void being preceded and followed by sleep [2]. This definition has been recently challenged for two reasons [11,12]. First, many studies on nocturia consider only patients with two or more voids per night, based on the observation that a nocturnal frequency of one void per night does not seem to be harmful and/or bothersome [7,13,14] and thus one void per night is a normal condition, particularly in the elderly. Although the definition is still controversial, the consensus is still to stick to the ICS definition [2,11]. The definition should not be modified according to bother or quality of life (QoL). The second controversial aspect is the need for integrating into the

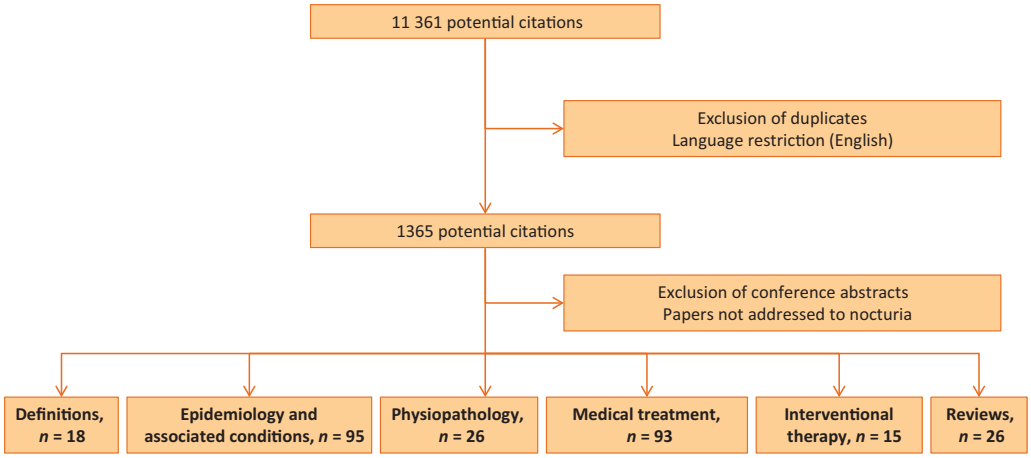

Fig. 1 – Flow diagram of the literature search.

definition the statement that voiding at night must be followed by a period of sleep to be considered as nocturia [12]. This issue mainly affects the last void of the night, which may be followed by an attempt to sleep. The ease of getting back to sleep, in the elderly in particular, has been shown to influence the consequences of nocturia [15]. No consensus has been reached on this point, which is rarely considered in the design of clinical studies. At present, the ICS definition of *nocturia* remains the accepted definition, but for practical purposes the term will be used more loosely in this paper.

Nocturia (nocturnal frequency) is distinct from *nocturnal enuresis*, which is defined as a void occurring during sleep [2]. Clearly, when a patient wakes to void and cannot reach a toilet before passing urine, incontinence is associated with nocturia. Another challenging situation is when the patient wakes up for another reason and feels the desire to pass urine once awake [16]; this concept has led some authors to

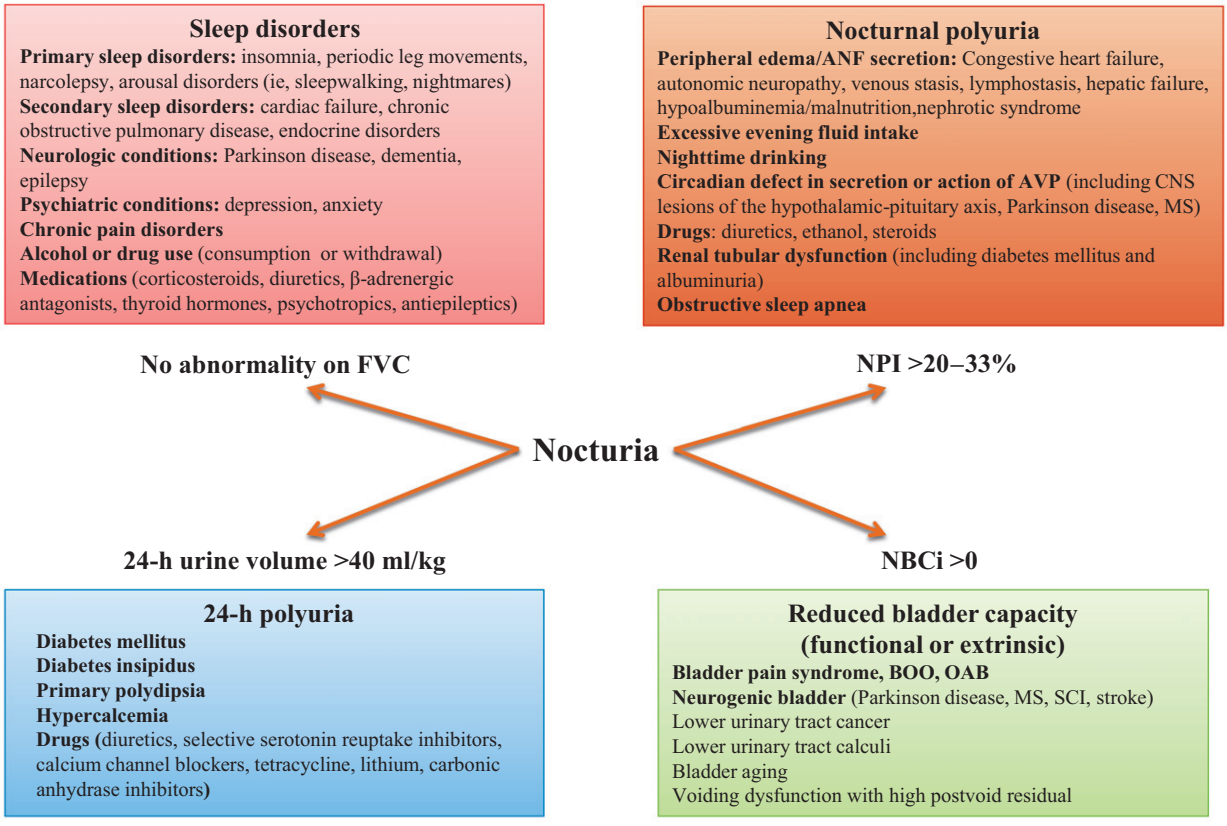

Fig. 2 – Etiologies of nocturia, classified according to the four definitions based on the frequency volume chart (FVC). Sleep disorders have been classified as a cause of nocturia, given the considerations exposed in the International Continence Society document [2].
ANF = atrial natriuretic factor; AVP = arginine vasopressin; BOO = benign outlet obstruction; CNS = central nervous system; MS = multiple sclerosis; NBCi = nocturnal bladder capacity index; NPI = nocturnal polyuria index; OAB = overactive bladder; SCI = spinal cord injury.

introduce the idea of *convenience voids* [12]. However, even if voiding is not the primary cause of awakening, these patients are still considered to have nocturia [2].

Nocturia is a symptom that belongs within the storage component of LUTS and can be an isolated symptom or be associated with other LUTS. Indeed, nocturia is considered part of the definition of the OAB symptom syndrome. It is also included in the evaluation of male LUTS as an item in the International Prostate Symptom Score (IPSS) and therefore, as described below, is often studied as a secondary outcome in LUTS studies.

3.2. Pathophysiology and classification

Nocturia occurs when nocturnal urine volume (NUV) (ie, the total volume of urine passed during the night, including the first morning void) exceeds the maximal voiding volume (MVV) that reflects the functional bladder capacity (which may be different at night compared with during the day). The widely used term *nocturia index (Ni)*, calculated as NUV divided by MVV, is positive if >1.

Nocturia can be further classified according to its underlying pathophysiology [11]. It can be related to four distinct pathophysiologic mechanisms: an overall increase of urine production (24-h polyuria), an increase in urine production only at night (nocturnal polyuria [NP]), a permanent or only nocturnal reduced bladder capacity, or any primary or secondary sleep disorder (Fig. 2).

The term *24-h polyuria* is defined on the basis of measurements using a frequency volume chart (FVC) when the overall urine volume is >40 ml/kg in adults [2]. It is usually seen in individuals with diabetes mellitus, diabetes insipidus, primary polydipsia, voluntary excessive fluid intake, hypercalcemia, or intake of particular drugs [17].

NP is defined by the ICS as NUV >20–33% of total 24-h urine volume (percentage adjusted according to age) [2]. This proportion is called the *NP index (NPI)*. Several cut-off points have been proposed for the NPI, since its normal value varies from 14% in young adults to 34% in people >65 yr [12]. Other definitions have been proposed for NP, such as NUV >6.4 ml/kg, nocturnal urine output >0.9 ml/min, or nocturnal urine production >90 ml/h [18,19]. It depends on not only urine volume but also duration of sleep (which should be 8 h for a valuable evaluation, according to the ICS [2]), which varies among individuals. In contrast to nocturia, the first void after the morning wakeup is included in the NP definition.

NP is one of the most frequent causes of nocturia in adults, especially those in the elderly age group [20]. NP occurs as a possible confluence of factors, including a disturbance of the pattern of endogenous production of arginine vasopressin (AVP) hormone by the posterior pituitary, excess production of atrial natriuretic peptide (notably occurring during sleep apnea and chronic heart failure), a nighttime evacuation of daytime third space fluid sequestration with peripheral edema, and external factors such as medications (diuretics) or fluid intake at night [17]. Mutations of AVP receptors can also contribute to NP [21]. Thus, a variety of common clinical conditions can lead to NP (Fig. 2).

Reduced bladder capacity, whether functional or anatomic, encompasses all the conditions associated with storage symptoms. Nocturia occurs when the nocturnal bladder capacity (NBC) is overwhelmed by the amount of urine entering the bladder during the night. Hence, even without exceeding production of urine at night, the bladder cannot assume the NUV storage. This concept is driven by the NBC index (NBCi), which corresponds to the actual number of voids minus the predicted number of voids. The predicted number of voids is obtained by subtracting 1 from Ni. Hence, NBCi >0 means that voids at night occur below the MVV, indicating that the bladder itself cannot store the amount of urine produced at night.

The reasons for the urinary bladder to behave this way are multiple: significant following-voiding residual urine due to reduced bladder contractility often seen with associated bladder outlet obstruction caused by benign prostatic obstruction (BPO), detrusor overactivity (idiopathic [often concurrent with BPO] or neurogenic), bladder pain syndrome, learned voiding dysfunction, pharmacologic agents, lower urinary tract calculi, primary bladder pathology causing a reduction in the anatomic capacity, or extrinsic compression by pelvis masses or urogenital prolapse [11,17,18]. It is hence logical that some syndrome definitions, such as that of OAB, include nocturia as an important potential component.

Primary or secondary sleep disturbances, for any reason, can lead to nocturnal voids once the patient is awake. Sleep duration in itself has been shown to influence the number of voids per night and thus should be carefully evaluated [22]. A number of clinical conditions or drugs can contribute to nocturia (Fig. 2), especially psychiatric disorders including depression, which have been implicated in sleep disturbance and nocturia itself [23,24].

Various medications can provoke nocturia by way of diverse mechanisms, such as increased urine output (by way of disturbance of AVP secretion, AVP receptor inhibition, aquaporin level modification, atrial natriuretic factor increase, action on proximal tubules, or hypercalcemia), effect on the central nervous system, and sleep disturbance [17,19].

This subclassification is relevant for three reasons. First, if systematically used in clinical practice, it leads to a more accurate diagnosis of 24-h polyuria, NP, and associated conditions in all patients, thereby avoiding the previously accepted view that nocturia is usually a secondary consequence of an underlying urologic disease process (BPO or detrusor overactivity). Second, the subclassification helps with diagnosis and treatment of the underlying pathophysiology, which may have multiple causes. Third, and very important, the subclassification facilitates appropriate treatment. It is therefore essential to conduct a complete and structured assessment of the symptom using validated parameters, as noted, in clinical practice (Fig. 3).

3.3. Epidemiology and associated conditions

Several population-based studies have assessed the prevalence of nocturia in the general population [1]. The mean

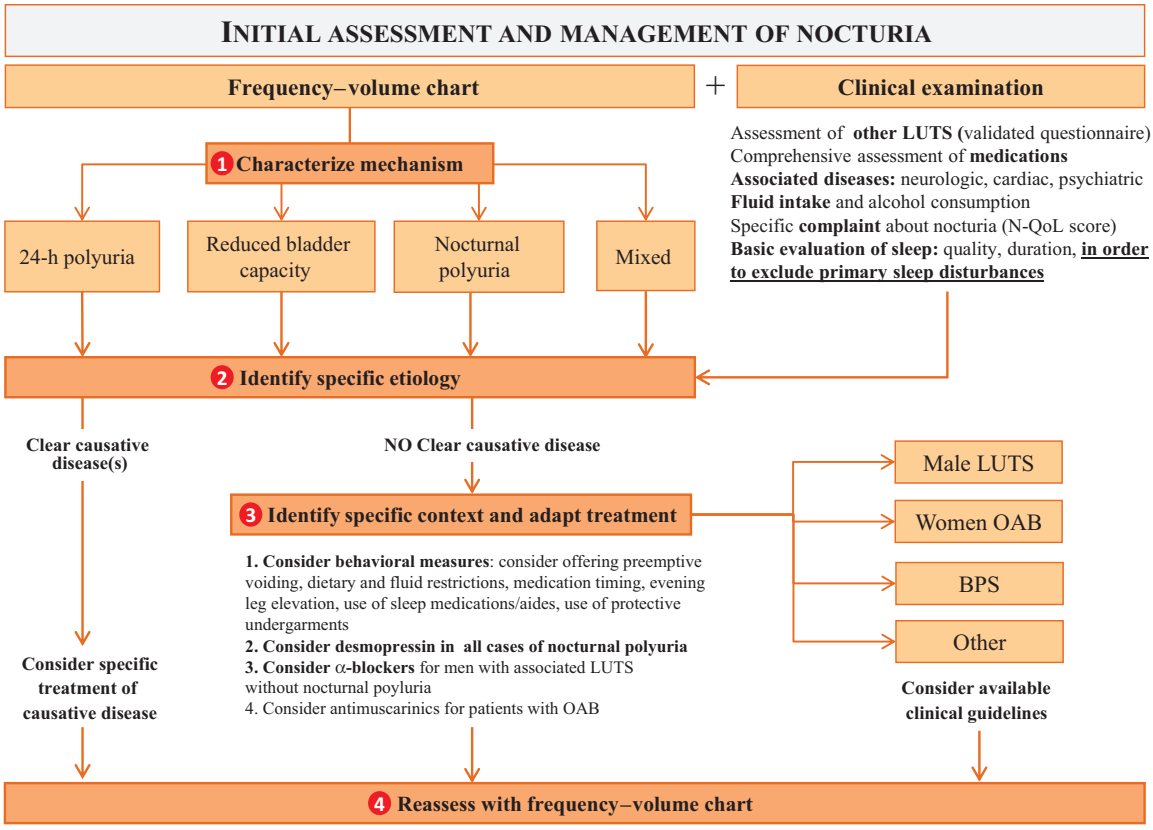

Fig. 3 – Algorithm for evaluation and treatment of nocturia. Primary sleep disorders (responsible for patient's awakening before the desire to pass urine) should be ruled out at clinical examination to avoid in-depth exploration.
BPS = bladder pain syndrome; LUTS = lower urinary tract symptoms; N-QoL = Nocturia Quality of Life; OAB = overactive bladder.

prevalence of nocturia in men and women stratified by decade in contemporary series involving >1000 patients is shown in Figure 4, based on data described in Supplementary Table 1.

In addition to the potential urogenital or systemic etiologies of nocturia that have been described, a myriad of either intrinsic or extrinsic patient characteristics have been correlated with nocturia, mostly in cross-sectional studies [25].

Age is the most important risk factor in both sexes in population-based studies [25,26]. Gender has a significant impact, as evidenced by the observation that the prevalence of nocturia is generally greater in women among young adults and greater in men in elderly population groups [1]. Ethnicity is also important [27,28], with people of African descent being more subject to nocturia; however, several confounding factors and associated conditions may explain this relationship.

Nocturia has also been found to be associated with obesity, metabolic syndrome, hypertension, winter season, increased C-reactive protein levels, lower educational attainment, lifestyle (smoking, alcohol, and drug substances), reproductive history in women, low testosterone levels in men, and/or low vitamin D levels without very clear explanation to date [17,25,29–35]. No clear genetic predisposition has yet been found, although twin studies point toward a possible genetic risk in women [36].

Nocturia is therefore currently considered to be a multifactorial, highly prevalent symptom that increases in prevalence with age in both sexes [37].

3.4. *Sequelae of nocturia*

Nocturia is one of the most bothersome LUTS [8,38]. Nocturia is associated with poor QoL and self-reported insomnia in the elderly [39–41]. Global QoL is substantially affected by nocturia [38], mainly as a consequence of reduced sleep quality [4,8,13,42]. Indeed, reduced sleep due to nocturia has been linked to diurnal fatigue, decreased concentration, lower performance at work, and accidents because of cognitive and motor impairment [40,41]. Nocturia also affects the quality of sleep of the partner [43]. Disturbed sleep related to nocturia has been established as an independent predictor of falls and hip fractures [44–47], especially in the elderly, but has also been associated with cardiovascular morbidity [48]; depression; and endocrine, immune, and metabolic disorders [41]. These consequences lead to a higher risk of institutionalization and dependence [43]. Nocturia has been stressed as being an independent factor in mortality from coronary heart disease [48,49]. It has been associated with increased overall mortality in the frail elderly population [41] but has also been shown to be an independent predictor of mortality in younger patients [50], related to the number

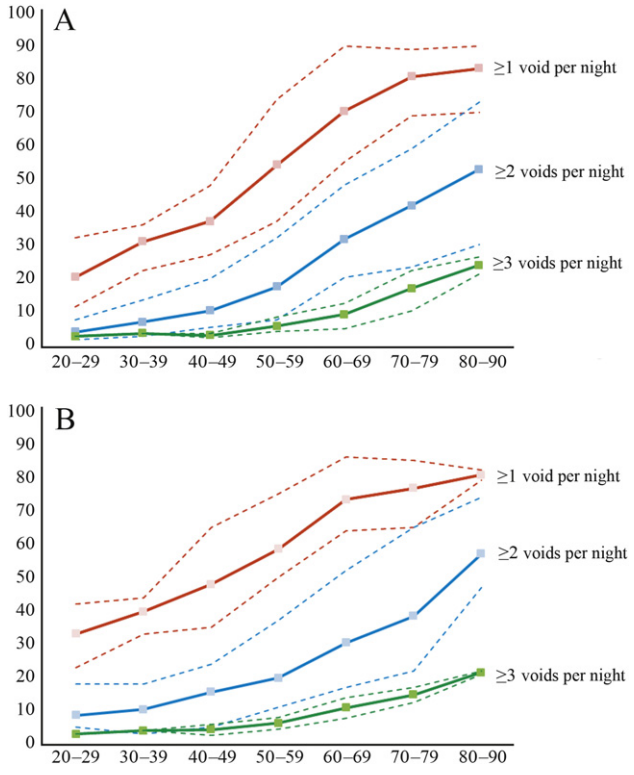

Fig. 4 – Trends in prevalence of nocturia stratified by number of voids per night and age intervals in (A) men and (B) women, represented by continuous lines. Square markers on continuous lines are the mean values of the prevalence for each category in each age interval. Dotted lines represent the minimal and maximal values in the literature for each age interval. The studies included in this evaluation are the studies that were published as a full paper in the English language, that were about cohorts of >1000 patients in each gender group, and that displayed stratified results by age interval. The vertical axis is the percentage of patients with nocturia. The horizontal axis is in 10-yr age intervals.

of voids per night. However, recent data have challenged this hypothesis in a cohort of men aged 50–78 yr [51], and more studies are needed on this point.

These data, in our view, convincingly suggest that nocturia should be fully considered at the time of LUTS assessment, given the severe potential consequences of this symptom.

3.5. Clinical assessment

As nocturia is often not the only symptom mentioned by patients during medical consultations and is rarely the first symptom leading the individual to seek medical care, its evaluation is often limited to the patient-reported numbers of voids per night, for example, as an item of the IPSS in elderly men or noted during a clinical history.

However, according to the ICS, the cornerstone of nocturia evaluation is the FVC [2]. This standardization is underscored by the facts (1) that the FVC is the basis for subclassification of nocturia with the appropriate measurements and calculations (as has been described) and (2) that the FVC is regarded as more accurate than recall-based measures such as the nocturia question of the IPSS [52]. The FVC should hence be added to any other tool that is justified at the first medical evaluation (eg, IPSS, Male-LUTS, Female-LUTS).

Clearly, accurate assessment of nocturia can be based on only the results of an FVC and subsequent investigations to discriminate among the potential underlying causes of nocturia (Fig. 2). A more in-depth evaluation of the impact of nocturia on QoL should be undertaken by validated questionnaires, such as the Nocturia–Quality of Life (N-QoL) questionnaire [19,53]. General QoL questionnaires can also be used. A specific evaluation of sleep is also possible using several other methods (hours of undisturbed sleep [HUS], sleep diaries, even more invasive means such as polysomnography or actigraphy, or specific scales like the Medical Outcomes Study sleep scale in both sexes) [8,54–56].

As described in this paper, the most common way to assess the efficacy of therapeutic intervention in clinical trials is to evaluate the variation in the number of nocturnal voids. As no consensual threshold exists regarding the clinical relevance of a decrease in the number of nocturnal episodes, the best way to estimate the therapeutic effect is probably to evaluate symptoms, QoL, and sleep parameters with dedicated tools.

3.6. Therapeutic intervention

3.6.1. Lifestyle advice

Lifestyle advice is often given as a first-line option [57]. These measures include preemptive voiding immediately before going to bed, nocturnal "dehydration," dietary and fluid restrictions (eg, avoidance of caffeinated beverages and alcohol), medication timing (taking diuretics in the midafternoon), evening leg elevation to mobilize fluids, use of sleep medications/aides, and use of protective undergarments [7]. Pelvic floor exercises to fight urgency at night have been proposed by some authors in cases of OAB with moderate success [58]. No RCTs evaluating behavioral measures focusing on nocturia as a primary outcome were found. One pharmacotherapeutic trial compared furosemide intake 6 h before bedtime with placebo [59]. In this study of 49 men with NP assessed by a 7-d FVC, administration of 40 mg of furosemide 6 h before bedtime was superior to placebo in reducing the numbers of nocturnal voids, but not the nocturnal voided volume. Plants and herbal products, notably *Pygeum africanum* and *Serenoa repens*, have not shown significant efficacy for nocturia management in the RCTs available to date [60,61].

3.6.2. α_1-Blockers

All studies on α_1-blockers have been conducted in the context of LUTS/BPO management. Only five studies designed as RCTs or secondary analyses of an RCT focused on nocturia as a primary outcome [62–66] were identified.

In the only RCT comparing an α_1-blocker with placebo, focusing on nocturia as a primary outcome, Djavan et al. included 117 patients >45 yr with "LUTS/BPH [benign prostatic hyperplasia]" with a total IPSS score ≥13 and two or more voids per night according to a sleep diary [64]. The primary end point was the mean variation of the HUS

compared with baseline after 8 wk of treatment by tamsulosin oral controlled absorption system (OCAS) 0.4 mg/d or placebo. The mean decrease in number of nocturnal voids was no different in the two groups (0.7 for placebo compared with 1.1 for tamsulosin OCAS [$p = 0.099$]). Thus, although secondary end points such as nocturia subscore drawn from IPSS (question 7) were statistically significant, this superiority study failed to demonstrate the superiority of tamsulosin OCAS in improving nocturia.

In another study, Simaioforidis et al. [63] compared transurethral resection of the prostate with administration of tamsulosin 0.4 mg/d in 66 patients followed for 1 yr. Patients were evaluated by 72-h FVC, N-QoL questionnaire, and HUS at each time point. The primary end point was the change in the number of nocturnal awakenings compared with baseline. At 1 yr, the reduction in number of nocturnal awakenings was not significantly different in the two groups.

Zhang et al. [62] compared doxazosin gastrointestinal therapeutic system (GITS) 4 mg/d with tamsulosin 0.2 mg/d given for 8 wk to patients with LUTS/BPO presenting with nocturia in an open RCT. The primary end points were self-reported nocturia rate based on an FVC and self-reported QoL. According to a cut-off of 25% reduction in nocturnal episodes on FVC, doxazosin GITS was presented as superior to tamsulosin; the major problem with this study was its comparison of potentially nonequivalent therapeutic doses of drugs (4 mg doxazosin compared with 0.4 mg tamsulosin).

The two other studies specifically addressing the effect of α_1-blockers on nocturia, both by Johnson et al. [65,66], are post hoc analyses from the Medical Therapy of Prostatic Symptoms and Veterans Affairs cooperative studies. The studies compared α_1-blockers, placebo, finasteride, and combination therapy. Both studies present significant results for α1-blockers and combination over placebo, but with a very slight effect size and based on IPSS question 7.

In summary, it can be concluded that the evidence supporting the efficacy of α_1-blockers in treating nocturia is low. In the majority of studies on LUTS/BPO, nocturia assessment is based on question 7 of the IPSS, hence failing to recognize and exclude patients with coexisting NP and failing to take into account associated OAB in these patients. There is an historical context involved, as no major LUTS/BPO studies used an FVC, instead relying primarily on flow rates and following voiding residual measurements and total IPSS. Clearly, it has to be borne in mind that studies with nocturia as a primary outcome measurement would exclude a large number of studies from this analysis, in which nocturia was a secondary outcome. However, as reported elsewhere [21], these studies have provided only inconsistent evidence that at best accounted for only minor improvements in nocturia.

3.6.3. Antimuscarinics

The vast majority of the studies on antimuscarinics were conducted in the context of OAB management. We identified one RCT that compared tolterodine with placebo, focusing on nocturia as a primary end point [67]. In this study, 850 men and women with OAB associated with nocturia were recruited, and they received placebo or tolterodine for 12 wk after a placebo run-in period. Patients were evaluated by FVC, and the main outcome criterion was the change in the mean number of nighttime micturitions from baseline to week 12. While tolterodine was associated with an improvement in the other OAB-specific symptoms, the difference between the two groups for nocturnal frequency was not statistically significant (decrease of 19% and 23% for placebo and tolterodine, respectively, $p = 0.145$).

All the other studies that primarily focused on nocturia were either pooled analyses or post hoc analyses of previous RCTs [58,68–70]. Two of these studies reported statistically significant reduction of nocturnal voids per night, but the effect size was low and the clinical significance doubtful. A previous meta-analysis on the use of antimuscarinics for OAB did not evaluate nocturia, most probably because of the absence of data [71].

In summary, there is limited evidence that antimuscarinics are efficient for the specific management of nocturia in the context of OAB. It is very likely that at least in part, this finding is also related to the heterogeneous group of patients being treated and a failure to exclude cases with NP. In support of this idea, in the Weiss et al. study [72], the etiology of nocturia in OAB patients was related to age, with reduced bladder capacity in younger patients and increased production of urine at night in the elderly. As has been stated for α_1-blockers, the stringent criteria of the present review led to the exclusion of numerous studies evaluating antimuscarinics in which nocturia was assessed as a secondary end point.

3.6.4. Anti-inflammatory drugs

One study assessed the efficacy of celecoxib compared with placebo for treatment of nocturia [73]. This study included 80 men with LUTS/BPH, with an IPSS >8 and two or more voids per night. Patients received either placebo or celecoxib 100 mg at 9 PM for 1 mo. The primary outcome was focused on nocturia and based on self-assessment, and it was classified as excellent, improved, or unchanged. The results favored the celecoxib group.

Another study comparing diclofenac with placebo was performed in 28 men and women with NP [74]. Patients with more than two voids per night, NPi $>33\%$, and Ni >1 were included in this randomized placebo-controlled crossover study. Patients received placebo or active medication for 2 wk, and the crossover was performed after a 7-d washout period. The main outcome was the change in nocturnal frequency. Diclofenac significantly reduced the nocturnal frequency, as well as the NPi, in these patients. However, although statistically significant, the effect size was very weak (mean decrease of 0.3 void per night for the diclofenac group compared with a mean decrease of 0.1 void per night for the placebo group), and the clinical significance of these data remains doubtful.

In the absence of other reports using anti-inflammatory drugs, the evidence in support of their use in clinical practice for nocturia management remains weak.

Table 1 – Characteristics of the randomized controlled trials about desmopressin

Reference	No. of patients, ITT	Inclusion criteria	Exclusion criteria	Study design	Primary end point, other efficacy assessments	Main characteristics (study population)			Remarks
							Treatment	Placebo	
Asplund et al. [76]	144 women	Age >18 yr, ≥2 voids per night (3-d FVC), nocturia index >1	Polyuria, LUTS, shift work or pregnancy, vaginal or urinary infection, abnormal blood or urine test, multiple sclerosis, treatment with diuretics, psychotropic drugs, nonresponder during titration period*	RCT, 3 wk, 27 centers, tablets, 0.1–0.4 mg according to titration phase	Reduction >50% of mean number of nocturia episodes compared with baseline Changes in the mean number of nocturnal voids, HUS, nocturnal diuresis, night-to-day ratios–BFLUTS	Mean age, yr Nocturnal voids, no., mean Patients with OAB, % Patients with BPH, % Patients with NP, %	52.4 2.92 NA NA NA	58.7 2.91 NA NA NA	Exclusion of nonresponders
Lose et al. [77]	151 men	Age >18 yr, ≥2 voids per night (3-d FVC), nocturia index >1	Diabetes insipidus, polydipsia, urge incontinence, symptomatic BPO, multiple sclerosis, fluid and/or electrolyte imbalance, low serum sodium levels, uncontrolled hypertension, nonresponder during titration period*	RCT, 3 wk, 28 centers, tablets, 0.1–0.4 mg according to titration phase	Reduction >50% of mean number of nocturia episodes compared with baseline Changes in the mean number of nocturnal voids, HUS, nocturnal diuresis, night-to-day ratios–ICS male	Mean age, yr Nocturnal voids, no., mean Patients with OAB, % Patients with BPH, % Patients with NP, %	64.5 3.0 NA NA NA	65.6 3.2 NA NA NA	Exclusion of nonresponders
Rezakhaniha et al. [79]	85 men, 41 women	Age >18 yr, ≥2 voids per night (7-d FVC)	Polyuria; urge incontinence; shift work/pregnancy/lactation; known urologic abnormalities; significant abnormalities of serum potassium, creatinine, or sodium; conditions characterized by fluid or electrolyte imbalance; nonresponder during titration period*	RCT, 3 wk, 18 centers, tablets, 0.1–0.4 mg according to titration phase	Reduction >50% of mean number of nocturia episodes compared with baseline Changes in the mean number of nocturnal voids, HUS, quality of sleep	Mean age, yr Nocturnal voids, no., mean Patients with OAB, % Patients with BPH, % Patients with NP, %	60.9 3.26 NA NA NA	64.6 2.82 NA NA NA	Exclusion of nonresponders
Johnson et al. [83]	115 men	Age >65 yr, IPSS ≥14, ≥2 voids per night (FVC), nocturnal polyuria	Other voiding dysfunction, infections, any concomitant interacting drugs, cardiac failure, uncontrolled hypertension or diabetes	RCT, 12 mo, 1 center, tablets, 0.1 mg	Reduction by 2 in the mean number of nocturnal voids after long-term treatment compared with baseline Number of nocturnal voids, HUS, nocturnal volume, night-to-day ratio, QoL	Mean age, yr Nocturnal voids, no., mean Patients with OAB, % Patients with BPH, % Patients with NP, %	73.6 4.8~ NA 69 100	74.5 4.9~ NA 68 100	Behavioral measures associated
Hoverd and Fowler [89]	341 women, 416 men	Age >18 yr, ≥2 voids per night (FVC)	PVR >150, AUR, history of urologic malignancies, neurogenic DO, current urinary tract pathology that could interfere with voiding, BPO, pregnancy, prolapse or pelvic mass, abnormal renal function, sodium <135 mmol/l	RCT, 4 wk, 78 centers, orally disintegrating tablet, 10-25-50-100 μg	Change in mean number of nocturnal voids compared with baseline *and* reduction >33% in mean number of nocturnal voids from baseline Change in nocturnal and total diuresis, HUS, N-QoL questionnaire	Mean age, yr Nocturnal voids, no., mean Patients with OAB, % Patients with BPH, % Patients with NP, %	62 3.29 29 47 90	62 3.27 27 53 91	Behavioral measures associated

AUR = acute urinary retention; BFLUTS = Bristol-Female Low Urinary Tract Symptoms questionnaire; BPH = benign prostatic hyperplasia; BPO = benign prostatic obstruction; DO = detrusor overactivity; FVC = frequency volume chart; HUS = hours of undisturbed sleep; ICS = International Continence Society; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; NA = not available; NP = nocturnal polyuria; N-QoL = Nocturia-Quality of Life; OAB = overactive bladder; PVR = postvoid residual; QoL = quality of life; RCT = randomized controlled trial; ITT = Intent to treat.

* Patients who did not show a sufficient response during the dose titration period (ie, < 20% reduction in nocturnal diuresis) and patients who failed to return to ≥78% of baseline nocturnal diuresis values after the 1-wk washout period were excluded.

~ Estimated from figure included in the report, since no raw data were available.

3.6.5. Melatonin

One study has compared melatonin with placebo for the treatment of nocturia in men with bladder outlet obstruction who reported nocturia (three or more voids per night) [75]. Twenty men were included in this randomized double-blind crossover study. Patients took 2 mg of melatonin or placebo for 4 wk, and crossover followed a 7-d washout. Patients were assessed by FVC at baseline, 4 wk, and 8 wk. The primary end point was the mean change from baseline on nocturia episodes per night. The mean frequency of nocturia per night changed from 3.1 at baseline to 2.8 with melatonin and 3.0 with placebo ($p = 0.07$). No effect was noted on urine production. These data do not support the use of melatonin for nocturia.

3.6.6. Desmopressin

Desmopressin is the drug that has been the most frequently tested for specific management of nocturia. It is a synthetic analogue of the human hormone vasopressin, aiming at concentrating the urine at night by way of an action on V2 receptors present in the distal collecting tubules. Desmopressin can be administered by intranasal spray, oral tablets, or newly released orally disintegrating tablets. The dosage depends on the pharmaceutical formulation of the drug.

The literature search retrieved 18 studies evaluating the efficacy and safety of desmopressin as a specific treatment of nocturia as compared with placebo [76–93]. Those studies that were RCTs comparing desmopressin with

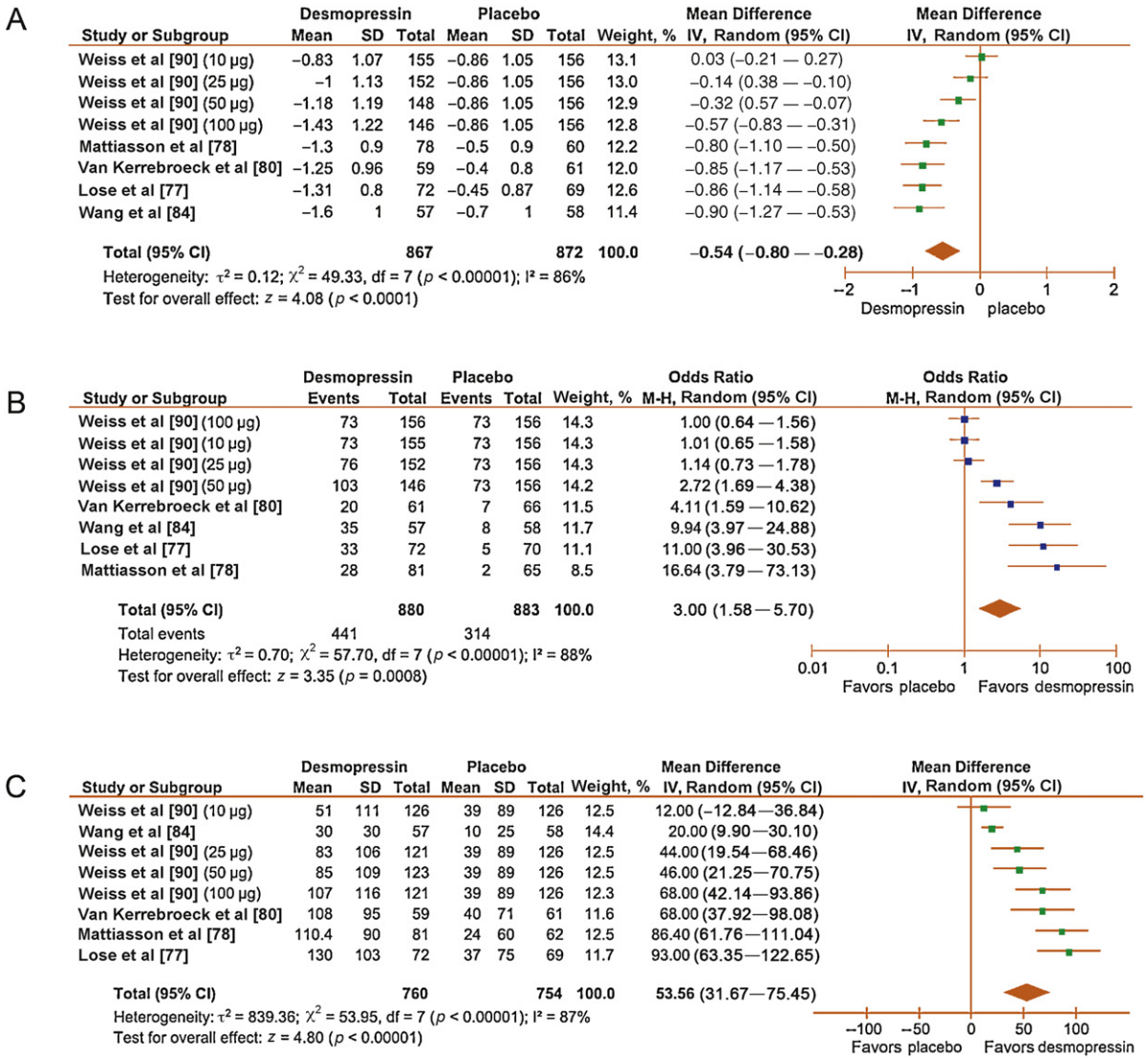

Fig. 5 – Meta-analysis of desmopressin focused on efficacy outcomes. (A) Nocturnal voids: The nocturnal voids were fully available in Weiss et al. [90] but not in other studies. Absolute changes in mean values in the desmopressin and placebo groups could be calculated, but the standard deviation (SD) of the difference was missing and was imputed as the maximal SD of the two groups. (B) Main criterion of successful outcome: The main outcome efficacy criteria of success were different in the five studies considered, but they were comparable: decrease of two or more voids per night [84], reduction of nocturnal voids by >50% [77,78,80], and reduction of nocturnal voids by >33% [90]. The number of events is the number of patients in each group fulfilling the criterion of success. (C) Hours of undisturbed sleep (HUS): HUS figures were estimated from a graph for Wang et al. [84]. Data about mean difference were approximated for the Lose et al. [77] and Mattiasson et al. [78] studies, since SDs of absolute differences were imputed but result in 95% close to the results published in the paper for the 95% confidence interval (CI) of the mean difference.
M-H = Mantel-Haenszel; IV = Inverse Variance.

placebo in patients free of neurologic symptoms were reviewed with a view to inclusion in a meta-analysis. However, of the 18 studies retrieved from the literature, 13 studies were excluded from the meta-analysis because (1) they were dealing with nocturia in patients presenting special conditions such as multiple sclerosis [86–89,91,92], (2) they were crossover-designed studies with <30 included patients [76,81–83,93], (3) they recruited heterogeneous patients with multiple neurologic conditions [79], or (4) they tested desmopressin combined with another pharmaceutical product (ie, furosemide [85]). The characteristics of the five studies included in the meta-analysis are reviewed in Table 1. The quality of studies was heterogeneous. All studies except one were funded by Ferring [84]. The most recent study was conducted as a five-arm RCT evaluating different dosages of a new drug formulation (orally disintegrating tablets). Since the study was sufficiently powered to compare each treatment arm with placebo, this study was separated into four one-to-one comparisons inside the meta-analysis. Given the study heterogeneity, all analyses were conducted under a random-effects model.

3.6.6.1. Efficacy of desmopressin. The primary outcomes varied in the five studies but were always based on the variation of the number of nocturnal voids compared with baseline (Table 1). This analysis demonstrated that desmopressin was superior to placebo in satisfying the primary outcome by reducing the overall number of nocturnal voids. The HUS also increased significantly among patients receiving desmopressin (Fig. 5). The nocturnal diuresis decreased significantly in all studies but could not be integrated into the meta-analysis because it was reported in a nonstandardized fashion (graphically reported by Wang et al. [84], adjusted to the sleep duration [milliliters per minute] by the

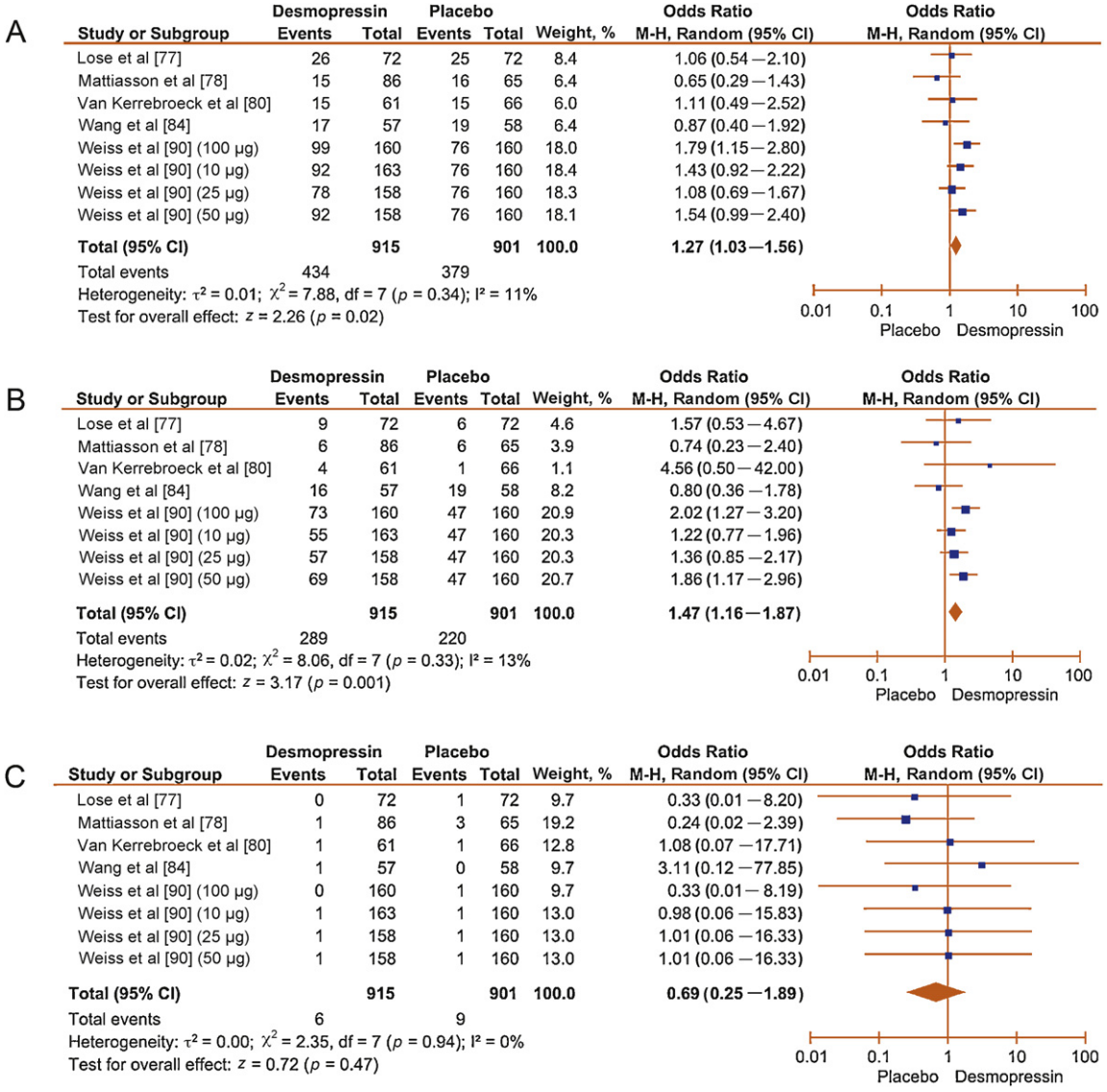

Fig. 6 – Meta-analysis of desmopressin focused on safety outcomes: (A) total adverse events, (B) adverse events related to desmopressin, and (C) serious adverse events. CI = confidence interval.
M-H = Mantel-Haenszel.

Lose et al. [77] and Mattiasson et al. [78] studies, not reported by van Kerrebroeck et al. [80], and reported as a volume per night by Weiss et al. [90]). QoL evaluations, although based on different criteria and questionnaires, have all shown an increase of QoL in patients treated with desmopressin. These data are in line with previous meta-analysis results published by others [94] and overall support the recommendations for the use of desmopressin to treat NP in adults.

However, any conclusion has to be qualified by the recognition that the five RCTs were conducted in extremely heterogeneous populations (Table 1), with variable dosages and distinct primary end points. Three of the pivotal studies [77,78,80] included a titration phase in which patients not responding to desmopressin or presenting notable side effects were excluded. Although it might select the patients presenting NP, this characteristic introduces a major bias in favor of demonstrating efficacy for desmopressin. Even if the open label prolongation of the RCTs were in favor of a sustained efficacy up to 1 yr [95], the follow-up period for the randomized periods of these studies remained limited to a few weeks.

However, the last published study [90] did not included a titration period and clearly demonstrated that desmopressin was superior to placebo, with two important ancillary findings: A dose effect was clearly identified on nocturnal voids and HUS, and females were found to be more sensitive to the drug than males. These results suggesting a different minimal-effect dose in men and women are in line with previous studies [96].

3.6.6.2. Tolerability of desmopressin. Desmopressin is usually well tolerated but is associated with an increased occurrence of adverse events compared with placebo (Fig. 6). The most frequently related adverse events described in the pivotal studies were headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral edema, and nausea. While all these events occurred in <10% of cases, a meta-analysis was not possible, as the documented occurrence of adverse events could be extracted only from the titration phase of the van Kerrebroeck et al. [80], Lose et al. [77], and Mattiasson et al. [78] studies and was not reported in detail in Weiss et al. [90]. Hyponatremia, recognized as the adverse event of most concern, is most frequent in men >65 yr of age. Although most of these cases are not symptomatic, assessment of serum sodium at 3 d after starting therapy is recommended in modern guidelines [97].

3.7. Surgical and interventional options

No surgical or interventional therapy is especially indicated for nocturia. Bladder outlet obstruction surgery has been evaluated in the context of LUTS/BPO, but nocturia has been a primary outcome in only one study [63], as has been described. Botulinum toxin detrusor injections, sacral neuromodulation, or tibial electric nerve stimulation are used in the context of OAB, but nocturia is always regarded as a secondary outcome. Hence, existing interventional studies for the result of nocturia fall outside the scope of this manuscript.

4. Conclusions

Nocturia has been comprehensively studied; it is a highly prevalent symptom with multiple potential underlying pathophysiologic mechanisms, some of which may have life-threatening consequences. In addition to an adequate history and clinical examination, an FVC is the cornerstone of initial assessment of this symptom and is suggested as such in all modern guidelines. The treatment options are largely determined by the clinical context and the etiology of the nocturia (NP, 24-h polyuria, reduced bladder capacity, or other). While desmopressin has been shown to be efficient for treatment of nocturia due to NP, the evidence supporting other therapeutic options remains limited. Most of the trials do not distinguish NP from other causes of nocturia. Undoubtedly, before any more definitive conclusions can be drawn, further research is necessary regarding initial assessment and therapeutic options to do the following: (1) reach a multidisciplinary consensus regarding the role of each evaluation tool and further determine which other diagnostic criteria in addition to an FVC would be helpful in the diagnostic algorithm to provide an accurate diagnosis; (2) further integrate and emphasize the importance of an adequate evaluation of nocturia and its management in guidelines for LUTS; (3) adequately evaluate and characterize the patient population with nocturia through appropriate interpretation of an FVC in clinical trials evaluating nocturia, OAB, and LUTS/BPO; (4) systematically evaluate QoL with validated tools, such as the N-QoL questionnaire, as well as sleep quality and parameters in clinical trials; and (5) refine the role of both behavioral and interventional therapies in the management of nocturia.

Author contributions: Jean-Nicolas Cornu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cornu, Madersbacher, Tubaro, Michel, Chapple, Abrams, Lemack, Dmochowski.
Acquisition of data: Cornu.
Analysis and interpretation of data: Cornu, Madersbacher, Michel, Abrams, Tubaro, Lemack, Chapple, Dmochowski.
Drafting of the manuscript: Cornu.
Critical revision of the manuscript for important intellectual content: Madersbacher, Michel, Abrams, Tubaro, Lemack, Chapple, Dmochowski.
Statistical analysis: Cornu.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Madersbacher.
Other (specify): None.

Financial disclosures: Jean-Nicolas Cornu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Martin C. Michel

received research support, consultancy, and/or lecturer honoraria from Allergan, AltheRX, Astellas, Bayer, and Pfizer and is currently an employee of Boehringer Ingelheim. Gary E. Lemack is part of the Astellas speakers bureau and the Pfizer speakers bureau; is speaker, consultant, and involved in clinical trial of Allergan; and is involved in a clinical trial for NIDDK. Stephan Madersbacher is lecturer for Boehringer, Astellas, Allergan, Bayer, Madaus, Pfizer, and Ferring. Roger R. Dmochowski is consultant for Allergan, Merck, Johnson and Johnson, and Ferring. Christopher R. Chapple is consultant and researcher for Allergan, Astellas, Pfizer, Ono, and Recordati and consultant to Lilley and Schering. Paul Abrams is consultant to Astellas, Eli Lilly, and Allergan and lecturer for Ferring and Astellas. Andrea Tubaro is consultant to Allergan, Astellas, Ferring, and MSD; consultant and speaker for Amgen and GSK; investigator for Ipsen and Takeda-Millenium; and investigator and recipient of a research grant from AMS.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j. eururo.2012.07.004.

References

[1] Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2010;184:440–6.
[2] van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 2002;21:179–83.
[3] Irwin DE, Milsom I, Hunskaar 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;50:1306–15.
[4] van Dijk L, Kooij DG, Schellevis FG, Kaptein AA, Boon TA, Wooning M. Nocturia: impact on quality of life in a Dutch adult population. BJU Int 2004;93:1001–4.
[5] Chen FY, Dai YT, Liu CK, Yu HJ, Liu CY, Chen TH. Perception of nocturia and medical consulting behavior among community-dwelling women. Int Urogynecol J Pelvic Floor Dysfunct 2007;18: 431–6.
[6] Van Kerrebroeck PE, Dmochowski R, FitzGerald MP, et al. Nocturia research: current status and future perspectives. Neurourol Urodyn 2010;29:623–8.
[7] Weiss JP, Blaivas JG, Bliwise DL, et al. The evaluation and treatment of nocturia: a consensus statement. BJU Int 2011;108:6–21.
[8] Chapple CR, Batista JE, Berges R, et al. The impact of nocturia in patients with LUTS/BPH: need for new recommendations. Eur Urol Suppl 2006;5:12–8.
[9] Abrams P. New words for old: lower urinary tract symptoms for ''prostatism.'' BMJ 1994;308:929–30.
[10] Chapple CR. Lower urinary tract symptoms revisited. Eur Urol 2009;56:21–3.
[11] Weiss JP, Wein AJ, van Kerrebroeck P, et al. Nocturia: new directions. Neurourol Urodyn 2011;30:700–3.
[12] Weiss JP, Weinberg AC, Blaivas JG. New aspects of the classification of nocturia. Curr Urol Rep 2008;9:362–7.
[13] 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.
[14] Tikkinen KAO, Johnson II TM, Tammela TLJ, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010;57:488–98.
[15] Endeshaw Y. Correlates of self-reported nocturia among community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2009;64: 142–8.
[16] Bing MH, Moller LA, Jennum P, Mortensen S, Lose G. Validity and reliability of a questionnaire for evaluating nocturia, nocturnal enuresis and sleep-interruptions in an elderly population. Eur Urol 2006;49:710–9.
[17] Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. BJU Int 2011;107:702–13.
[18] Weiss JP. Nocturia: ''do the math.'' J Urol 2006;175:S16–8.
[19] Weiss JP, Bosch JL, Drake M, et al. Nocturia Think Tank: focus on nocturnal polyuria: ICI-RS 2011. Neurourol Urodyn 2012;31:330–9.
[20] Weiss JP, van Kerrebroeck PE, Klein BM, Norgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. J Urol 2011;186:1358–63.
[21] Schneider T, de la Rosette JJ, Michel MC. Nocturia: a non-specific but important symptom of urological disease. Int J Urol 2009;16:249–56.
[22] Udo Y, Nakao M, Honjo H, Ukimura O, Kitakoji H, Miki T. Sleep duration is an independent factor in nocturia: analysis of bladder diaries. BJU Int 2009;104:75–9.
[23] Hakkinen JT, Shiri R, Koskimaki J, Tammela TL, Auvinen A, Hakama M. Depressive symptoms increase the incidence of nocturia: Tampere Aging Male Urologic Study (TAMUS). J Urol 2008;179:1897–901.
[24] Asplund R, Henriksson S, Johansson S, Isacsson G. Nocturia and depression. BJU Int 2004;93:1253–6.
[25] Yoshimura K. Correlates for nocturia: a review of epidemiological studies. Int J Urol 2012;19:317–29.
[26] Hakkinen JT, Hakama M, Shiri R, Auvinen A, Tammela TL, Koskimaki J. Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006;176:2541–5.
[27] Fitzgerald MP, Litman HJ, Link CL, McKinlay JB. 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.
[28] Burgio KL, Johnson II TM, Goode PS, et al. Prevalence and correlates of nocturia in community-dwelling older adults. J Am Geriatr Soc 2010;58:861–6.
[29] Yoshimura K, Kamoto T, Tsukamoto T, Oshiro K, Kinukawa N, Ogawa O. Seasonal alterations in nocturia and other storage symptoms in three Japanese communities. Urology 2007;69:864–70.
[30] Liao CH, Chiang HS, Yu HJ. Serum testosterone levels significantly correlate with nocturia in men aged 40–79 years. Urology 2011;78:631–5.
[31] McKeigue PM, Reynard JM. Relation of nocturnal polyuria of the elderly to essential hypertension. Lancet 2000;355:486–8.
[32] Vaughan CP, Johnson II TM, Goode PS, Redden DT, Burgio KL, Markland AD. Vitamin D and lower urinary tract symptoms among US men: results from the 2005–2006 National Health and Nutrition Examination Survey. Urology 2011;78:1292–7.
[33] Tikkinen KA, Auvinen A, Tiitinen A, Valpas A, Johnson II TM, Tammela TL. Reproductive factors associated with nocturia and urinary urgency in women: a population-based study in Finland. Am J Obstet Gynecol 2008;199: 153 e1-12.
[34] Lu Z, Gao Y, Tan A, et al. Increased high-sensitivity C-reactive protein predicts a high risk of lower urinary tract symptoms in Chinese male: results from the Fangchenggang area male health and examination survey. Prostate 2012;72:193–200.
[35] Kupelian V, McVary KT, Kaplan SA, et al. Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston Area Community Health Survey. J Urol 2009;182:616–24.
[36] Wennberg AL, Altman D, Lundholm C, et al. Genetic influences are important for most but not all lower urinary tract symptoms:

a population-based survey in a cohort of adult Swedish twins. Eur Urol 2011;59:1032–8.
[37] Klingler HC, Heidler H, Madersbacher H, Primus G. Nocturia: an Austrian study on the multifactorial etiology of this symptom. Neurourol Urodyn 2009;28:427–31.
[38] Kupelian V, Wei JT, O'Leary MP, Norgaard JP, Rosen RC, McKinlay JB. Nocturia and quality of life: results from the Boston Area Community Health Survey. Eur Urol 2012;61:78–84.
[39] Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK. Nocturia and disturbed sleep in the elderly. Sleep Med 2009;10:540–8.
[40] Chartier-Kastler E, Chapple CR. LUTS/BPH in clinical practice: the importance of nocturia and quality of sleep. BJU Int 2006;98:3–8.
[41] Asplund R. Nocturia: consequences for sleep and daytime activities and associated risks. Eur Urol Suppl 2005;3:24–32.
[42] Yoshimura K, Oka Y, Kamoto T, et al. Night-time frequency, sleep disturbance and general health-related quality of life: is there a relation? Int J Urol 2009;16:96–100.
[43] Wyndaele JJ. Nocturia and quality of life. Eur Urol 2012;61:85–7.
[44] Asplund R. Hip fractures, nocturia, and nocturnal polyuria in the elderly. Arch Gerontol Geriatr 2006;43:319–26.
[45] Parsons JK, Mougey J, Lambert L, et al. Lower urinary tract symptoms increase the risk of falls in older men. BJU Int 2009;104:63–8.
[46] Temml C, Ponholzer A, Gutjahr G, Berger I, Marszalek M, Madersbacher S. Nocturia is an age-independent risk factor for hip-fractures in men. Neurourol Urodyn 2009;28:949–52.
[47] Nakagawa H, Niu K, Hozawa A, et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol 2010;184:1413–8.
[48] Lightner DJ, Krambeck AE, Jacobson DJ, et al. Nocturia is associated with an increased risk of coronary heart disease and death. BJU Int. In press. http://dx.doi.org/10.1111/j.1464-410X.2011.10806.x.
[49] Bursztyn M, Jacob J, Stessman J. Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921. Am J Cardiol 2006;98:1311–5.
[50] Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol 2011;185:571–7.
[51] van Doorn B, Kok ET, Blanker MH, Westers P, Bosch JL. Mortality in older men with nocturia: a 15-year followup of the Krimpen study. J Urol 2012;187:1727–31.
[52] Yap TL, Cromwell DA, Brown C, van der Meulen J, Emberton M. The relationship between objective frequency-volume chart data and the I-PSS in men with lower urinary tract symptoms. Eur Urol 2007;52:811–8.
[53] Abraham L, Hareendran A, Mills IW, et al. Development and validation of a quality-of-life measure for men with nocturia. Urology 2004;63:481–6.
[54] Chartier-Kastler E, Davidson K. Evaluation of quality of life and quality of sleep in clinical practice. Eur Urol Suppl 2007;6:576–84.
[55] Kim SO, Choi HS, Kim YJ, et al. Impact of nocturia on health-related quality of life and Medical Outcomes Study sleep score in men. Int Neurourol J 2011;15:82–6.
[56] Kim S, Kwon D, Hwang EC, et al. The effect of nocturia on health-related quality of life and MOS sleep score in female. Neurourol Urodyn 2009;28:927–8.
[57] van Kerrebroeck P, Hashim H, Holm-Larsen T, Robinson D, Stanley N. Thinking beyond the bladder: antidiuretic treatment of nocturia. Int J Clin Pract 2010;64:807–16.
[58] Johnson II TM, Burgio KL, Redden DT, Wright KC, Goode PS. Effects of behavioral and drug therapy on nocturia in older incontinent women. J Am Geriatr Soc 2005;53:846–50.
[59] Reynard JM, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: a double-blind randomized trial of furosemide against placebo. Br J Urol 1998;81:215–8.
[60] Macdonald R, Tacklind JW, Rutks I, Wilt TJ. Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review. BJU Int 2012;109:1756–61.
[61] Wilt T, Ishani A, Mac Donald R, Rutks I, Stark G. Pygeum africanum for benign prostatic hyperplasia. Cochrane Database Syst Rev 2002:CD001044.
[62] Zhang K, Yu W, Jin J, et al. Effect of doxazosin gastrointestinal therapeutic system 4 mg vs tamsulosin 0.2 mg on nocturia in Chinese men with lower urinary tract symptoms: a prospective, multicenter, randomized, open, parallel study. Urology 2011;78: 636–40.
[63] Simaioforidis V, Papatsoris AG, Chrisofos M, Chrisafis M, Koritsiadis S, Deliveliotis C. Tamsulosin versus transurethral resection of the prostate: effect on nocturia as a result of benign prostatic hyperplasia. Int J Urol 2011;18:243–8.
[64] 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.
[65] Johnson II TM, Burrows PK, Kusek JW, et al. The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. J Urol 2007;178:2045–50.
[66] Johnson II TM, 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.
[67] Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z. Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. Urology 2006;67:731–6.
[68] Chapple CR, Cardozo L, Steers WD, Govier FE. Solifenacin significantly improves all symptoms of overactive bladder syndrome. Int J Clin Pract 2006;60:959–66.
[69] Yokoyama O, Yamaguchi O, Kakizaki H, et al. Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary. J Urol 2011;186:170–4.
[70] Fitzgerald MP, Lemack G, Wheeler T, Litman HJ. Nocturia, nocturnal incontinence prevalence, and response to anticholinergic and behavioral therapy. Int Urogynecol J Pelvic Floor Dysfunct 2008;19: 1545–50.
[71] Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol 2008;54:543–62.
[72] Weiss JP, Blaivas JG, Jones M, Wang JT, Guan Z. Age related pathogenesis of nocturia in patients with overactive bladder. J Urol 2007;178:548–51, discussion 551.
[73] Falahatkar S, Mokhtari G, Pourreza F, Asgari SA, Kamran AN. Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study. Urology 2008;72:813–6.
[74] Addla SK, Adeyoju AB, Neilson D, O'Reilly P. Diclofenac for treatment of nocturia caused by nocturnal polyuria: a prospective, randomised, double-blind, placebo-controlled crossover study. Eur Urol 2006;49:720–6.
[75] Drake MJ, Noble JG, Mills I. A randomised double blind crossover trial of melatonin to treat nocturia in men with benign prostatic hypertrophy. J Urol 2004;171:1199–202.
[76] Asplund R, Sundberg B, Bengtsson P. Oral desmopressin for nocturnal polyuria in elderly subjects: a double-blind, placebo-controlled randomized exploratory study. BJU Int 1999;83:591–5.

[77] Lose G, Lalos O, Freeman RM, van Kerrebroeck P. 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.
[78] 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.
[79] Rezakhaniha B, Arianpour N, Siroosbakhat S. Efficacy of desmopressin in treatment of nocturia in elderly men. J Res Med Sci 2011;16:516–23.
[80] van Kerrebroeck P, Rezapour M, Cortesse A, Thüroff J, Riis A, Norgaard JP. Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. Eur Urol 2007;52: 221–9.
[81] Cannon A, Carter PG, McConnell AA, Abrams P. Desmopressin in the treatment of nocturnal polyuria in the male. BJU Int 1999;84: 20–4.
[82] Hvistendahl GM, Riis A, Nørgaard JP, Djurhuus JC. The pharmacokinetics of 400 μg of oral desmopressin in elderly patients with nocturia, and the correlation between the absorption of desmopressin and clinical effect. BJU Int 2005;95:804–9.
[83] Johnson TM, Burridge A, Issa MM, Miller M, Tang T, Ouslander JG. The relationship between the action of arginine vasopressin and responsiveness to oral desmopressin in older men: a pilot study. J Am Geriatr Soc 2007;55:562–9.
[84] Wang CJ, Lin YN, Huang SW, Chang CH. Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study. J Urol 2011;185:219–23.
[85] Fu FG, Lavery HJ, Wu DL. Reducing nocturia in the elderly: a randomized placebo-controlled trial of staggered furosemide and desmopressin. Neurourol Urodyn 2011;30:312–6.
[86] Eckford SD, Swami KS, Jackson SR, Abrams PH. Desmopressin in the treatment of nocturia and enuresis in patients with multiple sclerosis. Br J Urol 1994;74:733–5.
[87] Fredrikson S. Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. Acta Neurol Scand 1996;94:31–4.
[88] Valiquette G, Herbert J, Maede-D'Alisera P. Desmopressin in the management of nocturia in patients with multiple sclerosis: a double-blind, crossover trial. Arch Neurol 1996;53:1270–5.
[89] Hoverd PA, Fowler CJ. Desmopressin in the treatment of daytime urinary frequency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 1998;65:778–80.
[90] Weiss JP, Zinner NR, Klein BM, Norgaard JP. Desmopressin orally disintegrating tablet effectively reduces nocturia: results of a randomized, double-blind, placebo-controlled trial. Neurourol Urodyn 2012;31:441–7.
[91] Hilton P, Hertogs K, Stanton SL. The use of desmopressin (DDAVP) for nocturia in women with multiple sclerosis. J Neurol Neurosurg Psychiatry 1983;46:854–5.
[92] Kinn AC, Larsson PO. Desmopressin: a new principle for symptomatic treatment of urgency and incontinence in patients with multiple sclerosis. Scand J Urol Nephrol 1990;24:109–12.
[93] Hilton P, Stanton SL. The use of desmopressin (DDAVP) in nocturnal urinary frequency in the female. Br J Urol 1982;54:252–5.
[94] Zong H, Yang C, Peng X, Zhang Y. Efficacy and safety of desmopressin for treatment of nocturia: a systematic review and meta-analysis of double-blinded trials. Int Urol Nephrol 2012;44:377–84.
[95] Lose G, Mattiasson A, Walter S, et al. Clinical experiences with desmopressin for long-term treatment of nocturia. J Urol 2004;172:1021–5.
[96] Hvistendahl GM, Frokiaer J, Nielsen S, Djurhuus JC. Gender differences in nighttime plasma arginine vasopressin and delayed compensatory urine output in the elderly population after desmopressin. J Urol 2007;178:2671–6.
[97] National Institute for Health and Clinical Excellence. NICE Clinical Guidelines. Lower urinary tract symptoms: the management of lower urinary tract symptoms in men. http://publications.nice.org.uk/lower-urinary-tract-symptoms-cg97. Accessed June 4, 2012.