Review – Voiding Dysfunction

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

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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 α1-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.

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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
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

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**Fig. 1 – Flow diagram of the literature search.**

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**Sleep disorders**
- Primary sleep disorders: insomnia, periodic leg movements, narcolepsy, arousal disorders (ie, sleepwalking, nightmares)
- Secondary sleep disorders: cardiac failure, chronic obstructive pulmonary disease, endocrine disorders
- Neurologic conditions: Parkinson disease, dementia, epilepsy
- Psychiatric conditions: depression, anxiety
- Chronic pain disorders
- Alcohol or drug use (consumption or withdrawal)
- Medications (corticosteroids, diuretics, β-adrenergic antagonists, thyroid hormones, psychotropics, antiepileptics)

**Nocturnal polyuria**
- Peripheral edema/ANF secretion: Congestive heart failure, autonomic neuropathy, venous stasis, lymphostasis, hepatic failure, hypoalbuminemia/malnutrition, nephrotic syndrome
- Excessive evening fluid intake
- Nighttime drinking
- Circadian defect in secretion or action of AVP (including CNS lesions of the hypothalamic-pituitary axis, Parkinson disease, MS)
- Drugs: diuretics, ethanol, steroids
- Renal tubular dysfunction (including diabetes mellitus and albuminuria)
- Obstructive sleep apnea

**Nocturia**
- Reduced bladder capacity (functional or extrinsic)
  - Bladder pain syndrome, BOO, OAB
  - Neurogenic bladder (Parkinson disease, MS, SCI, stroke)
  - Lower urinary tract cancer
  - Lower urinary tract calculi
  - Bladder aging
  - Voiding dysfunction with high postvoid residual

**24-h polyuria**
- Diabetes mellitus
- Diabetes insipidus
- Primary polydipsia
- Hypercalcaemia
- Drugs (diuretics, selective serotonin reuptake inhibitors, calcium channel blockers, tetracycline, lithium, carbonic anhydrase inhibitors)

**24-h urine volume >40 ml/kg**

**NPI >20–33%**

**NBCi >0**

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**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) (i.e., 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, hypercalcaemia, 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 pelvic 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...
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
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. α1-Blockers

All studies on α1-blockers have been conducted in the context of LUTS/BPH 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 α1-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 \( \alpha_1 \)-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 \( \alpha_1 \)-blockers, placebo, finasteride, and combination therapy. Both studies present significant results for \( \alpha_1 \)-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 \( \alpha_1 \)-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 (increase 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 \( \alpha_1 \)-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, NP >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 NP, 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients, ITT</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Study design</th>
<th>Primary end point, other efficacy assessments</th>
<th>Main characteristics (study population)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asplund et al. [76]</td>
<td>144 women</td>
<td>Age &gt;18 yr, ≥2 voids per night (3-d FVC), nocturia index &gt;1</td>
<td>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</td>
<td>RCT, 3 wk, 27 centers, tablets, 0.1–0.4 mg according to titration phase</td>
<td>Reduction &gt;50% of mean number of nocturia episodes compared with baseline</td>
<td>Mean age, yr: Treatment 52.4, Placebo 58.7</td>
<td>Exclusion of nonresponders</td>
</tr>
<tr>
<td>Lose et al. [77]</td>
<td>151 men</td>
<td>Age &gt;18 yr, ≥2 voids per night (3-d FVC), nocturia index &gt;1</td>
<td>Diabetes insipidus, polydipsia, uric acidosis, symptoms of diabetes, fluid and/or electrolyte imbalance, low serum sodium levels, uncontrolled hypertension, nonresponder during titration period</td>
<td>RCT, 3 wk, 28 centers, tablets, 0.1–0.4 mg according to titration phase</td>
<td>Reduction &gt;50% of mean number of nocturia episodes compared with baseline</td>
<td>Mean age, yr: Treatment 65.6, Placebo 64.5</td>
<td>Exclusion of nonresponders</td>
</tr>
<tr>
<td>Rezakhanliha et al. [79]</td>
<td>85 men, 41 women</td>
<td>Age &gt;18 yr, ≥2 voids per night (7-d FVC)</td>
<td>Polyuria; uric acidosis; 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</td>
<td>RCT, 3 wk, 18 centers, tablets, 0.1–0.4 mg according to titration phase</td>
<td>Reduction &gt;50% of mean number of nocturia episodes compared with baseline</td>
<td>Mean age, yr: Treatment 60.9, Placebo 64.6</td>
<td>Exclusion of nonresponders</td>
</tr>
<tr>
<td>Johnson et al. [83]</td>
<td>115 men</td>
<td>Age &gt;65 yr, IPSS ≥14, ≥2 voids per night (FVC), nocturnal polyuria</td>
<td>Other voiding dysfunction, infections, any concomitant interacting drugs, cardiac failure, uncontrolled hypertension or diabetes</td>
<td>RCT, 12 mo, 1 center, tablets, 0.1 mg</td>
<td>Reduction by 2 in the mean number of nocturnal voids after long-term treatment compared with baseline</td>
<td>Mean age, yr: Treatment 73.6, Placebo 74.5</td>
<td>Behavioral measures associated</td>
</tr>
<tr>
<td>Hoverd and Fowler [89]</td>
<td>341 women, 416 men</td>
<td>Age &gt;18 yr, ≥2 voids per night (FVC)</td>
<td>PVR &gt;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 &lt;135 mmol/l</td>
<td>RCT, 4 wk, 78 centers, orally disintegrating tablet, 10-25-50-100 μg</td>
<td>Change in mean number of nocturnal voids compared with baseline and reduction &gt;33% in mean number of nocturnal voids from baseline</td>
<td>Mean age, yr: Treatment 62, Placebo 62</td>
<td>Behavioral measures associated</td>
</tr>
</tbody>
</table>

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 nocturias) and patients who failed to return to ≥78% of baseline nocturnal diuresis values after the 1-week 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...
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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Desmopressin</th>
<th>Placebo</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lose et al. [77]</td>
<td>26</td>
<td>25</td>
<td>1.06</td>
</tr>
<tr>
<td>Mattsson et al. [78]</td>
<td>15</td>
<td>16</td>
<td>0.65</td>
</tr>
<tr>
<td>Van Kerrebroeck et al. [80]</td>
<td>15</td>
<td>16</td>
<td>1.11</td>
</tr>
<tr>
<td>Wang et al. [84]</td>
<td>17</td>
<td>19</td>
<td>0.87</td>
</tr>
<tr>
<td>Weiss et al. [80] (10 μg)</td>
<td>99</td>
<td>160</td>
<td>1.79</td>
</tr>
<tr>
<td>Weiss et al. [90] (25 μg)</td>
<td>78</td>
<td>158</td>
<td>1.08</td>
</tr>
<tr>
<td>Weiss et al. [90] (50 μg)</td>
<td>92</td>
<td>158</td>
<td>1.54</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>915</td>
<td>901</td>
<td>1.27</td>
</tr>
</tbody>
</table>

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 include 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.

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Supervision: Madersbacher.

Other (specify): None.

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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.

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**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.eurouro.2012.07.004](http://dx.doi.org/10.1016/j.eurouro.2012.07.004).

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[36] Wennberg AL, Altman D, Lundholm C, et al. Genetic influences are important for most but not all lower urinary tract symptoms:


