Current Evaluation and Treatment of Nocturia

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

Keywords: Epidemiology; Evaluation; Nocturia; Pathophysiology; Treatment

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INTRODUCTION

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

EPIDEMIOLOGY

The term nocturia is defined by the International Continence Society as “the complaint that the individual has to wake at night one or more times to void” [1]. Several reports on the prevalence of nocturia exist in the literature, but prevalence estimates vary and are affected by the population studied, the age range considered, and the definition of nocturia used. Many studies [2-4] on nocturia consider only patients with two or more voids per night on the basis of the observation that a nocturnal frequency of one void per night does not seem to be harmful or bothersome. The BACH study [5] showed that nocturia affected 25% of men and 31% of women. In the Epic study [6], the preva-
ience of nocturia was 49% in men and 55% in women. A recent meta-analysis of 43 articles concluded that although nocturia is common across diverse populations, with the highest prevalence in older people, a significant proportion of younger individuals are also affected [7]. Using the criterion of 2 or more voids per night, this analysis reported the following prevalence rate ranges:

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

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

### PATHOPHYSIOLOGY

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

#### 1. Bladder storage problems

Bladder storage problems include overactive bladder and detrusor overactivity, bladder inflammation, bladder pain syndrome.

#### TABLE 1. Prevalence of nocturia

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

Nocturia was defined as voiding more than once at night.

#### TABLE 2. Causes of nocturia

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

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

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

**ASSESSMENT**

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

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

**MANAGEMENT**

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

1. **Lifestyle modification**

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

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**FIG. 1.** Etiology of nocturia, classified according to the four definitions based on the frequency volume chart. NPi, nocturnal polyuria index; Ni, nocturia index; MVV, maximum voided volume; NBCi, nocturnal bladder capacity index.
modification only. The information regarding this topic is very scarce compared to its significance and more research should be needed in this topic in the future.

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

2. Alpha-blockers

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

3. Antimuscarinic agents

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

1) Solifenacin

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

2) Trosiptium chloride

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

3) Tolterodine and fesoterodine

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

Whereas antimuscarinics do not reduce the number of nocturia episodes overall, they can reduce urgency episodes, and decreased urgency episodes at night may result in a reduction in overall nocturia episodes. Rackley et al.
[24] reported on the median percentage reduction in nocturnal voiding frequency with tolterodine and divided nocturnal voids into non-OAB voids, OAB voids, and severe OAB voids. Overall, there was no significant effect on nocturia episodes compared with placebo. However, there was a statistically significant improvement in OAB-related nocturnal voids (those associated with urgency). The mean reduction of nocturia episodes was −22% to 43% in the placebo group and −30% to 59% in the tolterodine group.

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

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

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

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

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

6. Sleep disturbance therapy
Sleep disturbance can result from sleep disorders; medical, neurological, or psychiatric diseases; and other influences, which are evaluated when treating nocturia. Patients sus-
pected of having a sleep disorder (e.g., sleep apnea, nocturnal seizures, and excessive daytime sleepiness) should be referred to a sleep specialist. Short-acting hypnotics may be helpful for patients with sleep disturbances. Oxazepam has been associated with a reduction in nocturia (but not nocturnal urine production) [34].

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

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

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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