

Desmopressin treatment for nocturia caused by nocturnal polyuria: practical guidelines

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Introduction Desmopressin is an effective and safe therapy for nocturia caused by nocturnal polyuria. However, many physicians are unsure about the proper diagnosis of nocturnal polyuria and the identification of patients who may benefit from desmopressin treatment. Therefore, to support urologists in their routine clinical practice, the aim of this study was to provide a comprehensive paradigm for diagnosing nocturnal polyuria with recommendations for the use of desmopressin.

Material and methods A multidisciplinary group of experts reviewed the available literature. Findings were compiled into a practice-based approach for workup and treatment.

Results We designed the nocturia diagnostic pathway to confirm nocturnal polyuria, identify possible causes of nocturnal polyuria, and classify patients with indications and contraindications for desmopressin therapy. A bladder diary remains a basic diagnostic tool. Underlying conditions that may lead to nocturnal polyuria include mainly cardiac insufficiency, arterial hypertension, chronic kidney failure, obstructive sleep apnea, peripheral edema, and excessive fluid intake at night. Treatment for nocturia caused by nocturnal polyuria is based on conservative management and pharmacotherapy, but pharmacological treatment should not precede a prior attempt at conservative treatment. Before administration of desmopressin, patients should be assessed for serum sodium concentration and carefully educated about the symptoms of hyponatremia. Older individuals or persons with risk factors for the development of hyponatremia should be checked regularly for hyponatremia during desmopressin therapy.

Conclusions People with nocturia due to nocturnal polyuria should be evaluated carefully before initiating desmopressin treatment. Patients treated with desmopressin should be followed for both clinical efficacy and treatment-related adverse effects.

Key Words: desmopressin ↔ nocturnal polyuria ↔ guideline ↔ practice

INTRODUCTION

Nocturia is one of the most frequently reported lower urinary tract symptoms, and it affects a large percentage of adults. Nocturia has a strong effect on quality of life because repeated nocturia-fragmented sleep causes daytime drowsiness, poor concentration, and anxiety that lead to problems in occupa-

tional functioning and impairment of physical and emotional health [1]. Moreover, people with nocturia present a higher mortality rate, not only from an increased incidence of falls and fractures, but also from cardiovascular disease and early death [2].

Nocturia is multifactorial and nocturnal polyuria is one of the mechanisms that leads to nocturia [3]. There are multiple guidelines and recommendations

for diagnosing and treating nocturia [4]. However, for urologists, there is lack of a specific and real-life guideline that discusses desmopressin use for nocturnal polyuria (more specifically, for idiopathic nocturnal polyuria) with a special consideration for a complete diagnostic pathway. Because different, often non-urological conditions, may lead to nocturnal polyuria, urologists are often uncertain about its diagnosis, and they are hindered in confidently identifying people who may benefit from desmopressin treatment [5]. In addition, follow-up of patients who receive desmopressin may be challenging. Therefore, the aim of this study was to compile comprehensive and practical guidelines for diagnosing nocturnal polyuria and idiopathic nocturnal polyuria, and to provide recommendations for desmopressin treatment that will support urologists in their routine clinical practice.

MATERIAL AND METHODS

A comprehensive review of studies on nocturia caused by nocturnal polyuria and studies of low-dose desmopressin for treatment of nocturnal polyuria (the only licensed product for all adults including people aged >65 years, Nocturna[®]/Noqturina[®]/Noqdirna[®], Ferring Pharmaceuticals [6]) was performed using PubMed, MEDLINE, and the Cochrane Library databases. Review data also included the latest consensus of the European Association of Urology, the International Continence Society, and the International Consultation on Incontinence. All pharmacological/non-pharmacological interventions relevant to the scope of this study were reviewed using the evidence-based medicine levels, with the Oxford grading system for recommendations [7]. The focus was on systematic reviews, meta-analyses, and evidence-based recommendations, when available. When the literature was inconsistent or scarce, a consensus multidisciplinary expert opinion was generated to provide appropriate guidelines.

RESULTS

Basic terminology

Nocturnal polyuria (nighttime polyuria) refers to nighttime urine production that exceeds 20% of daily urine production in young people and 33% in older people (aged >65 years), while maintaining proper 24-hour urine production [8, 9, 10]. Idiopathic nocturnal polyuria (idiopathic nighttime polyuria) is nocturnal polyuria without a discernible cause or other disease/pathology entities that may lead to nocturnal polyuria in the course of diagnostics.

Nocturia is defined as a lower urinary tract symptom, from the storage phase, that forces one to wake to pass urine one or more times during the night (provided that sleep precedes and follows passing urine).

Epidemiology of nocturnal polyuria

The main symptom of nocturnal polyuria is nocturia. In population studies that used validated questionnaires, the frequency of nocturia was about 50% in women and men [11]. This frequency increases with age for both sexes. In the EPIC study, the frequency of nocturia was 34.5% and 43.9% in men and women aged 39 or younger, respectively, and, in people aged 60 or older, it reached 71.9% and 70.8% for men and women, respectively [12].

Presently, there is no reliable population data that would determine the prevalence of specific causes of nocturia, including nocturnal polyuria and idiopathic nocturnal polyuria. This lack of data is because of limitations of population studies that use a bladder diary. For some countries, it is possible to estimate the prevalence of idiopathic nocturnal polyuria from international registries of prescription drugs used for treatment (i.e. low dose melt desmopressin with sex-specific doses). Based on that data, for instance, the estimated prevalence of idiopathic nocturnal polyuria in the Polish population is about 35,600 people (9.3 cases per 10,000 inhabitants) [13].

Diagnostics of nocturnal polyuria and idiopathic nocturnal polyuria

The aim of diagnostics is to identify nocturnal polyuria and idiopathic nocturnal polyuria (mainly by finding nocturnal polyuria and eliminating known pathogens/pathologies that may lead to nocturnal polyuria) and to classify individuals with indications and contraindications for pharmacological treatment of idiopathic nocturnal polyuria.

Evaluation of a person with suspected nocturnal polyuria/idiopathic nocturnal polyuria:

1. Medical history
 - a) Detailed evaluation of all symptoms from the lower urinary tract, including storage symptoms (frequency, nocturia, urinary urgency, urinary incontinence), voiding symptoms (hesitancy, straining, slow stream, intermittency, terminal dribble), and post-micturition symptoms (sensation of incomplete bladder emptying, post-micturition dribble);
 - b) Determining the duration, frequency, and severity of individual symptoms;
 - c) Recording concomitant diseases, with a focus on disease/pathology entities that may lead to

- nocturnal polyuria (e.g. cardiac insufficiency/arterial hypertension, renal failure, obstructive sleep apnea, peripheral edema, excessive nighttime fluid supply) or global polyuria (e.g. diabetes insipidus due to vasopressin deficiency, characterized by increased thirst and frequent urination, with large amounts (>4 L/day) of dilute urine (specific gravity <1.005 g/ml);
- d) Verification of drugs taken, principally medications likely to induce polyuria and nocturnal polyuria (diuretics, calcium channel blockers, tetracycline, lithium, selective serotonin reuptake inhibitors) [14] or nocturia in general;
 - e) Verification of previous surgeries or injuries, especially of the urinary tract.
2. Physical examination
 - a) Appearance of the external genital organs;
 - b) Assessment of the prostate in men and statics of the genital system in women;
 - c) Assessment of overweight/obesity;
 - d) Presence of peripheral edema;
 3. Questionnaires: evaluation of severity and bother of nocturia using a validated specific questionnaire (e.g., ICIQ-N, ICIQ-Nqol, N QoL, Tango).
 4. Bladder diary/frequency-volume chart
 - a) Enables confirmation of nocturia and assessment of frequency. The bladder diary is a basic and necessary tool for the diagnosis of nocturnal polyuria;
 - b) The diary should include at least information on the time and volume of urination and the amount and time of fluid intake by the patient;
 - c) The diary should be completed by the patient for 1–7 days (ideally for at least 3 days) [3];
 - d) Interpretation of the micturition diary in case of nocturia (Figure 1) [14]:
 - The amount of urine produced per day exceeds 40 ml per kilogram of body weight – nocturia as a consequence of global polyuria.
 - Possible causes: diabetes mellitus, diabetes insipidus (central, nephrogenic), primary polydipsia, kidney failure in the polyuria phase.
 - Urinary frequency of >8 micturitions per day along with a decrease in the volume of urine passed during a single micturition (usually 100–200 ml) – nocturia resulting from impaired/diminished bladder capacity.
 - Possible causes: overactive bladder (OAB), benign prostatic hyperplasia (BPH), neurogenic bladder, bladder pain syndrome (BPS), interstitial cystitis (IC), cystolithiasis, urinary bladder tu-

mor, urinary bladder infection, anxiety disorders.

- o Nighttime urine production (nocturnal and first morning micturitions) exceeds 20% of daily urine production in young people or exceeds 33% of daily urine production in people aged >65 years – nocturia resulting from nocturnal polyuria.
 - Possible causes: cardiac insufficiency/arterial hypertension, chronic renal failure, obstructive sleep apnea, peripheral edema, excessive supply of fluid at night.
- o Note that the mechanisms of nocturia presented above may coexist in some patients.
- e) The diagnosis of idiopathic nocturnal polyuria requires a bladder diary/frequency-volume chart of nocturnal polyuria (discussed above), and elimination of the following disease/pathology entities that may lead to nocturnal polyuria (Figure 2) [15]:
 - o Cardiac insufficiency/arterial hypertension – medical history of reduced physical activity tolerance, dyspnea at rest or during physical activity, orthopnea (dyspnea developing shortly after lying down and subsiding quickly after standing or supine position), paroxysmal nocturnal dyspnea (developing later after lying down, waking the patient up at night and subsiding slowly, sometimes

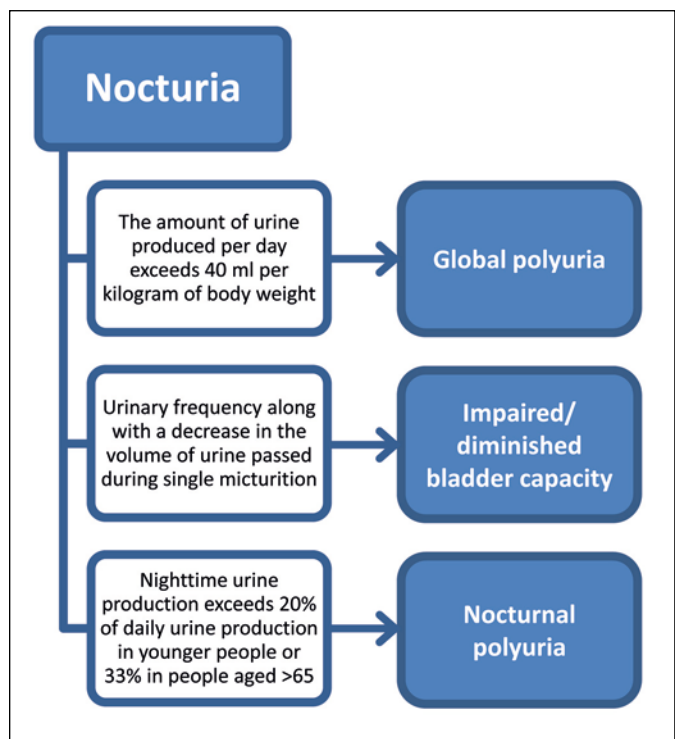


Figure 1. Diagnostic algorithm for nocturia using a bladder diary/frequency-volume chart [30].

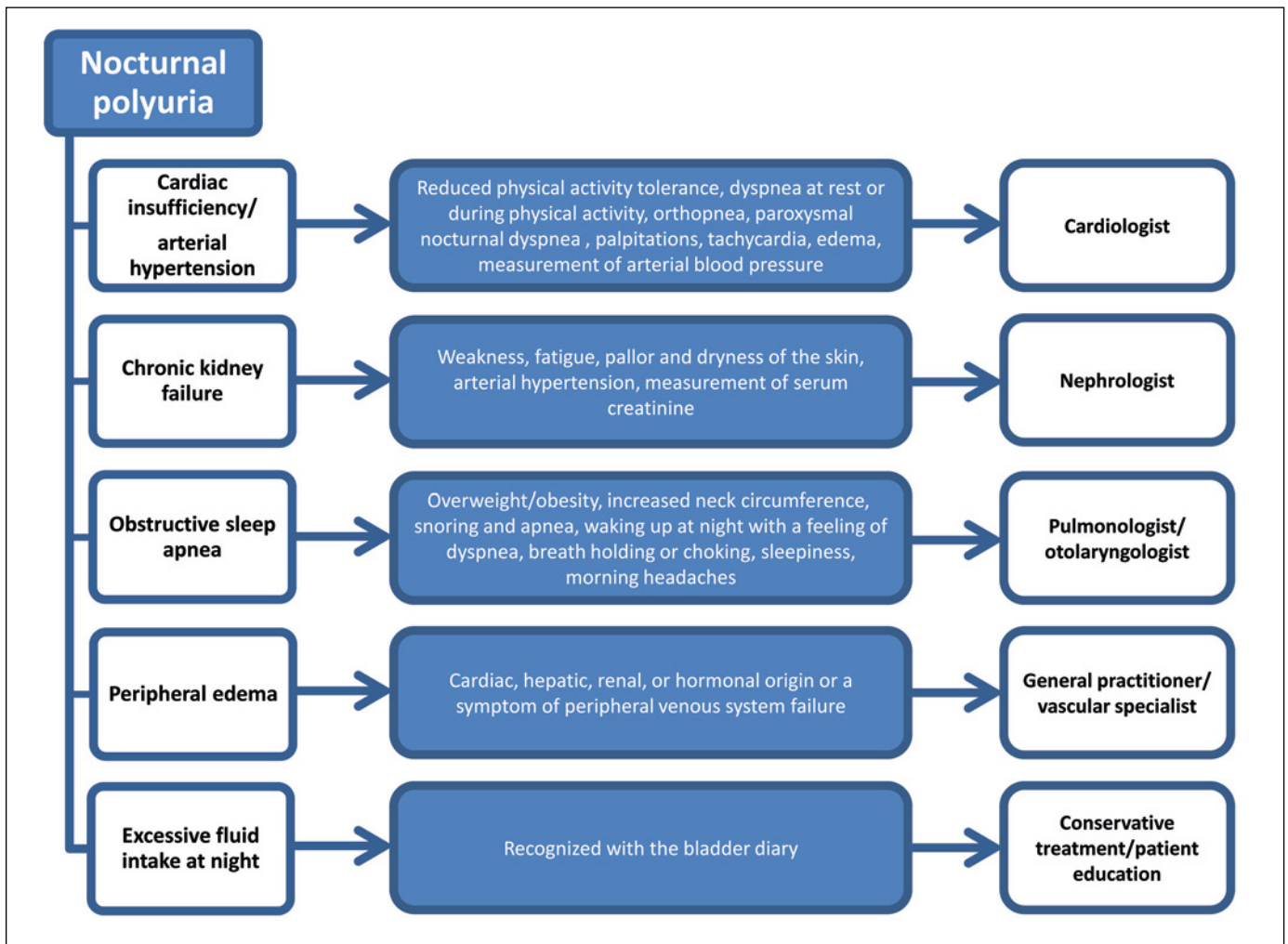


Figure 2. Diagnostics of nocturnal polyuria.

exceeding 30 minutes), palpitation events, tachycardia, edema in the lowest parts of the body (usually around the ankles), undiagnosed arterial hypertension or uncontrolled/unbalanced arterial hypertension. In doubtful cases, it may be helpful to determine the blood serum concentrations of natriuretic peptides BNP and NT-proBNP, which have high negative predictive value for cardiac insufficiency, i.e. enabling elimination of cardiac insufficiency with a high probability, if the measured values are within normal range. Measurement of arterial blood pressure (also measurements taken independently by the patient in the evening/night hours – observation for suspected non-dipping hypertension).

- o Chronic kidney failure – history of weakness, fatigue, pallor, dryness of the skin, and arterial hypertension. Laboratory tests

show abnormal serum creatinine concentration and reduced glomerular filtration rate.

- o Obstructive sleep apnea – likely in overweight/obese persons and with neck circumference >43 cm in men and >40 cm in women; history of snoring and apnea, waking up at night with a feeling of dyspnea, breath holding or choking, sleepiness, morning headaches.
 - o Peripheral edema – may be of cardiac, hepatic (hypoalbuminemia), renal, or hormonal origin, or may be a symptom of peripheral venous system failure.
 - o Excessive supply of fluids during the night hours – recognized from the bladder diary.
5. Laboratory tests:
- a) General urine test – not required for the diagnosis of idiopathic nocturnal polyuria, although it may be useful in doubtful cases. Re-

duced specific gravity (<1.010 g/ml) of the first morning urine may indicate idiopathic nocturnal polyuria.

- b) Assessment of sodium concentration in blood serum – necessary for every patient qualified for pharmacological treatment (desmopressin) of idiopathic nocturnal polyuria.
6. Imaging, endoscopic diagnostics, urodynamic tests: not usually needed to diagnose idiopathic nocturnal polyuria. May be useful or necessary in the case of co-existence of other symptoms from the lower urinary tract other than nocturia, or in the case of nocturia with a background other than idiopathic nocturnal polyuria.

Treatment of idiopathic nocturnal polyuria

Correctly performed analyses for idiopathic nocturnal polyuria enables the clinician to make the foregoing diagnosis and begin appropriate treatment. Treatment is either conservative management and/or pharmacological therapy. It is unacceptable to begin pharmacological treatment without prior diagnosis and without eliminating causes of nocturia other than idiopathic nocturnal polyuria. In addition, pharmacological treatment should not commence without a prior conservative treatment effort.

1. Conservative treatment (level of evidence 3/4, grade of recommendation A – recommendation based on expert consensus) [10, 16]:
 - a) Observation of the fluid regime, which involves limiting the amount of fluid intake in the evening hours (at least 2–3 hours before falling asleep, ideally 4–6 hours);
 - b) Avoiding alcohol, coffee, tea, and liquids that contain artificial sweeteners;
 - c) Emptying the bladder every time possible before bedtime;
 - d) Lower extremity elevation in the evening/during sleep, with the use of elastic stockings/compression stockings;
 - e) In the case of coexisting constipation, modification of dietary habits (increase in the amount of dietary fiber, systematic physical activity, regular attempts at calm defecation) and/or consideration of pharmacological treatment (osmotic or stimulant drugs);
 - f) For patients who take diuretics in the evening, change the time of drug administration (from evening to afternoon, ideally at least 6 hours before bedtime);
 - g) Weight/obesity reduction.

The evaluation of conservative treatment efficacy for idiopathic nocturnal polyuria should take place at least 1–3 months after treatment initiation [17].

2. Pharmacological treatment:

For ineffective conservative idiopathic nocturnal polyuria treatment, the synthetic vasopressin analogue desmopressin (1-deamino-8-D-Arginine vasopressin) is the only available and registered pharmacological treatment option with evidence-based proven efficacy [15]. Desmopressin therapy received a high recommendation from the European Association of Urology, International Continence Society, and the International Consultation on Incontinence [15, 18, 19].

On the basis of randomized clinical trials, investigators found that the recommended daily therapeutic dose of desmopressin lyophilizate was 25 µg for women and 50 µg for men, taken sublingually about 1 hour before bedtime (level of evidence 1, grade of recommendation A/B) [16, 20, 21, 22]. Sex-specific doses result from the observed higher sensitivity of women than men to the same doses of vasopressin or desmopressin, a phenomenon that is likely due to sex differences in expression of vasopressin receptors [23].

In the foregoing studies, compared with people who received a placebo, people who received desmopressin reported a greater reduction in nocturia episodes, an increase in the time between falling asleep and first awakening to urinate, and an increase in sleep quality and the overall quality of life.

- a) Evaluation of treatment effectiveness and monitoring

Although the response to treatment usually occurs 7 days after initiation, the evaluation of desmopressin therapy should be performed after at least another three weeks, ideally after three months (level of evidence 1, grade of recommendation A/B) [21, 24]. The assessment should be made with the appropriate validated questionnaire and/or the bladder diary. For patients with no improvement, assessed by means of a validated questionnaire and/or bladder diary, desmopressin treatment should be discontinued and patients should be reassessed for other causes of reported nocturia. Patients who report improvement should continue treatment, with periodic follow-up and monitoring of effectiveness. For patients who report improvement or subsiding nocturia, it is possible to stop desmopressin use, with a possible repeated therapy in case of recurring ailments. However, there is currently no reliable data to determine in which patients discontinuation of desmopressin therapy would result in nocturia recurrence. The relapse of symptoms after treatment discontinuation, if

present, most often occurs within one month of terminating the medication [25].

b) Administration

About one hour before bedtime, the tablet should be placed under the tongue to dissolve; there is no need to drink water. Instruct the patient to not take any fluids or to significantly reduce fluid intake after taking the drug for the next 8 hours [25]. Taking the drug with food may reduce the power and duration of the drug's activity. The use of a lyophilizate significantly reduces the frequency of adverse events, including hyponatremia, compared with the oral form (currently not registered for the treatment of nocturnal polyuria) [20, 21, 26, 27].

c) Adverse effects

- The most frequent adverse effects of the lyophilizate form of desmopressin with a sex-specific dose are the following: headaches, dizziness, dry mouth, nausea, edema, and hyponatremia [25].
- Because hyponatremia (including asymptomatic hyponatremia) may occur, each patient should be assessed for serum sodium prior to the start of sex-specific desmopressin therapy. Desmopressin treatment should begin only if the serum sodium concentration is within the normal range (i.e. 135–145 mmol/L). In people aged ≥ 65 years and/or with risk factors for the development of hyponatremia (e.g., past hyponatremia, concomitant heart or kidney disease, diuretic intake, female sex), the serum sodium concentration should be determined again after 4–8 days, one month after the start of therapy, and then every 3–6 months depending on the risk of developing hyponatremia [14, 20, 25, 28]. The foregoing scheme enables a significantly reduced risk of hyponatremia (level of evidence 1, grade of recommendation A/B) [20]. Regular determination of serum sodium concentration should also be performed for all women administered a dose greater than 25 μg and for all men who use a dose greater than 50 μg [29].
- Before starting desmopressin therapy, the patient should be instructed about the symptoms of hyponatremia (nausea, vomiting, severe headache, fatigue, weight gain and, in more severe cases, lower limb muscle spasms, convulsions, confusion, ataxia, reduced awareness) and, if symptoms occur, to urgently consult a doctor and possibly discontinue the medication [25]. It is advisable to consult a doctor again after

3 days of drug withdrawal/first medical consultation.

- If hyponatremia occurs during desmopressin intake (serum sodium concentration < 130 mmol/L, regardless of the hyponatremia symptoms) [15], the drug should be discontinued immediately and a fluid regime (< 1 L of fluids/day) with serum sodium concentration monitoring should be introduced [25]. In case of serum sodium between 130 and 135 mmol/L, the patient should discontinue treatment immediately if hyponatremia symptoms are present [15].
- If the patient resumes treatment, it is necessary to strictly limit fluid intake and to control serum sodium concentration.

d) Contraindications for desmopressin

Desmopressin is indicated for patients with nocturia that results from underlying idiopathic nocturnal polyuria. Desmopressin is contraindicated for patients who present with nocturia exclusively due to global polyuria, reduced bladder capacity, nocturnal polyuria resulting from heart or kidney failure, uncontrolled arterial hypertension, obstructive sleep apnea, or peripheral edema. Desmopressin is also contraindicated for patients with mental disorders (especially in habitual and psychogenic polydipsia), and for patients with chronic cardiac insufficiency, kidney disease (GFR < 50) [15], liver disease, thyroid or adrenal gland disorders, uncontrolled diabetes, uncontrolled hypertension, history of hyponatremia, abnormal antidiuretic hormone secretion syndrome, cancer, or for patients who take psychiatric drugs, diuretics, cytostatics, and other medications that lower serum sodium concentration.

- e) Despite the lack of reliable studies, continuation of conservative treatment is recommended when starting pharmacological treatment [15].

3. Management for cases with no response to treatment

- a) Pharmacological treatment with desmopressin has high clinical efficacy, yet there is a tendency for recurrence after treatment cessation.
- b) The ineffectiveness of desmopressin pharmacotherapy may indicate a mechanism of nocturia different from idiopathic nocturnal polyuria or concomitant idiopathic nocturnal polyuria with another mechanism that leads to nocturia (e.g. impaired bladder capacity resulting from OAB or BPH). The patient then needs to be reassessed, using the micturition diary and other additional tests, to consider a change in treatment or to use combination therapy.

c) If the treatment does not have the desired effect, the patient should undergo additional proceedings in a specialized center with a higher referral level.

CONCLUSIONS

Diagnosis of nocturnal polyuria requires comprehensive and accurate diagnostic evaluation because

many different conditions can lead to nocturnal polyuria. Correct diagnosis entitles the clinician to recommend desmopressin, a valuable, effective, and safe drug for the treatment of nocturia caused by idiopathic nocturnal polyuria.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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