

## Diagnostic and therapeutic recommendations for patients with nocturia

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**Introduction** Nocturia is defined as the urge to urinate at night when the micturition was directly preceded and followed by sleep. Due to its negative impact on the quality of life of patients, an effective treatment for this disease has become a significant therapeutic challenge. The aim of this article was to explain the main risk factors for the occurrence of nocturia and to present diagnostic and therapeutic schemes in the case of nocturnal polyuria (idiopathic night time polyuria).

**Material and methods** A review of the literature was carried out and the available guidelines of international science societies, which provided the basis for the above recommendations, were analyzed.

**Results** Detailed medical history should include information concerning: lower urinary tract symptoms (including nocturia), underlying illnesses, urogenital disorders, previous surgeries and medications administered. Keeping a bladder diary is recommended. The physical examination, depending on the patient's gender, should include gynecological examination with pelvic organ prolapse assessment or prostate evaluation. In laboratory tests, a urinalysis may be used, in particular cases a cytological analysis of urine sediment may be carried out. In addition, a possible ultrasound and/or cystoscopy may be conducted. Nocturia therapy should begin with modifying dietary habits, including compliance with the fluid regimen, avoiding alcohol, coffee and tea. Moderate physical exercise is also recommended. The pharmacological treatment of nocturia caused by nocturnal polyuria is based on the use of desmopressin at a daily single dose of 25 µg for women and 50 µg for men. The use of desmopressin allows for the reduction in the number of nocturia episodes, as well as improves the overall quality of life and sleep. Treatment with desmopressin can also be considered as a form of therapy added in people with an overactive bladder or benign prostatic hypoplasia, in which nocturia is a significant clinical problem.

**Conclusions** Desmopressin is an effective and safe first-line treatment option in pharmacological therapy of nocturia caused by nocturnal polyuria.

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### What is nocturia?

Lower urinary tract symptoms (LUTS) are a group of signs that may result from impaired:

– urine storage

– voiding

– and post-micturition.

The disability of the storage phase can be associated with symptoms such as: frequency, urgency, nocturia

and urinary incontinence, which significantly decreases the quality of life of patients [1].

According to the International Continence Society (ICS) the term nocturia means the urge to pass urine during nighttime, when the micturition was preceded by sleep and immediately followed by night rest [2]. Nocturia is a serious therapeutic problem due to its great impact on the quality of sleep, which in turn is unfavorably reflected in the physical and mental health of the people affected. For the elderly, nocturia can be a cause of unfortunate accidents (including hard to heal fractures) that increase the mortality rate. Still under discussion are the reference values concerning the number of micturitions during nighttime, which are necessary for the diagnosis of nocturia. Based on the results of population studies, it is assumed that at least 2 micturitions during nighttime become a significant health problem because they substantially reduce the quality of life of the patients [3]. Linear dependence was shown between the increase in the number of nocturia episodes and the subjective feelings of patients regarding their degree of nuisance [4]. It has been observed that the most burdensome, due to the quality of sleep, are awakenings during the first 3–4 hours since falling asleep because they occur during the phase of deep sleep. The disturbance of the deep sleep phase has a significantly more negative impact on patients' health than waking up during the REM (Rapid Eye Movement) phase or during the shallow NREM phase [5].

### The risk factors of nocturia

The results of previous studies on nocturia have made it possible to distinguish factors that increase the risk of this symptom [6]:

Age – numerous studies have unequivocally demonstrated that the risk of nocturia increases with age. For adults aged  $\leq 24$  years the symptoms of clinically relevant nocturia (at least 2 micturitions during nighttime) are observed in less than 5% of the respondents, while that percentage increases to 15% in the 45–54 age group. Among the group of people aged 65–74 years, the symptoms occur in up to 25% of the subjects.

Sex – the symptoms of nocturia are more common among women than men up until about the 6th decade of life. In addition, in women, more frequent occurrences of nocturia are observed during pregnancy and the postpartum period, as well as during the postmenopausal period. In the 6th decade of life there is a reversal of the trend described above; the symptoms of nocturia are more commonly observed

among men, which is probably associated mainly with the onset of prostate diseases.

Obesity – it has been observed that excess weight and obesity may, regardless of gender, increase the risk of nocturia even by 2–3 times. Simultaneously, the protective impact of physical activity has been demonstrated in relation to the occurrence of the previously mentioned symptom.

### Most frequent causes of nocturia

Nocturnal polyuria (NP) – described as a night urinary excretion exceeding 20% of daily urinary collection among young people and 33% in the elderly group ( $>65$  years) [7, 8]. According to some authors, over 90 ml of urine excretion per hour or more at night or more than 6.4 ml/kg of body weight should be considered abnormal [8, 9]. Such a phenomenon is evidence to the existence of nighttime polyuria. Nocturnal polyuria is mainly caused by decreased vasopressin secretion in the evening and during sleep (also referred to as idiopathic nocturnal polyuria). Based on the available literature, it is estimated that nighttime polyuria is responsible for the presence of nocturia in up to 80% of patients; therefore, an effective treatment of NP is essential in the treatment of nighttime urinary disorders [10]. Overactive bladder (OAB) – defined as the presence of urinary urgency, usually accompanied by urinary frequency and nocturia, with or without urge incontinence, when urinary tract infections or other pathologies that explain the occurrence of these symptoms are not found [11].

Population studies have confirmed that half of the patients reporting urinary urgency (a key symptom in overactive bladder) also indicate clinically relevant nocturia ( $\geq 2$  micturitions during nighttime) [12].

Benign prostatic hyperplasia (BPH) – one of the best-known diseases responsible for the occurrence of nocturia. Half of men with benign prostatic hyperplasia report disorders of the nature of clinically significant nocturia ( $\geq 2$  micturitions during nighttime) [12]. The pharmacological or therapeutic treatment of BPH eliminates or alleviates the lower urinary tract symptoms, however, it affects nocturia in a lesser extent. In 38% of patients who underwent transurethral resection of the prostate (TURP) nocturia ( $\geq 2$  micturitions during nighttime) remained 3 years after the procedure [13].

Diabetes – it has been observed that patients with diabetes often report nocturia [12]. Increased urinary excretion (polyuria) may also be related to insufficient glycemic control, therefore before initiating treatment associated with LUTS, the efficacy of diabetic therapy should first be checked.

**Hypertension** – The results of some studies have confirmed the relationship between hypertension and nocturia [14, 15]. It has been found that the use of calcium-channel blockers in hypertension treatment in the population of females and loop diuretics in men affects the occurrence of nocturia [16]. Similar pathophysiological backgrounds for hypertension and night time polyuria are also indicated in the group of elderly [17].

**Depression** – It has been observed that both the presence of depression and the use of antidepressants can lead to increased nocturia [12, 18].

**Demyelinating diseases** – In patients with multiple sclerosis (MS) and Parkinson's disease, the occurrence of nocturia is also common and its severity often depends on the stage of neurological disorders [19].

**Sleep apnea syndrome** – Studies have confirmed the direct correlation between apnea/shortness of breath index (which helps to evaluate the severity of sleep apnea) and the number of nocturia episodes and the amount of urine output at nighttime. In this group of patients, snoring is also considered a risk factor of nocturia [20]. Table 1. Causes of nocturia (modified [21]).

## The diagnostics of nocturia

The correct and effective identification of the cause of nocturia allows the initiation of early treatment [6]. For this purpose, we use:

Patient's medical history with special attention to information on lower urinary tract symptoms, including nocturia (duration, frequency of nocturia episodes, severity) and its possible effect on sleep quality, Patient's history of concurrent conditions (with special attention to cardiovascular, neurological and urogenital diseases, e.g. prevalent urinary tract infections), medications taken and recent surgeries, Bladder diary in which the subject writes information on the amount of fluid intake and the time of intake, time and volume of individual micturitions (including nocturia). Based on the information given in this log you can specify:

- The number of micturitions during the day,
- The number of episodes of nocturia (urination immediately preceded by sleep and then followed by sleep),
- The number of micturitions and the amount of urine produced per day,

## Maximum and average volume of urinary excretion

The existence of nocturnal polyuria, defined by the ICS as a night urinary excretion of greater than 20% diurnal diuresis in young people and greater than

**Table 1. Causes of nocturia (modified [21])**

SLEEP DISORDERS
Primary sleep disorders (insomnia, narcolepsy, sleepwalking)
Secondary sleep disorders (heart failure, chronic obstructive pulmonary disease, hormonal disorders)
Neurological diseases (early phase of Parkinson's disease, dementia disorders, epilepsy)
Psychiatric illnesses (depression, anxiety disorders)
Chronic pain syndromes
Abuse of alcohol and/or drugs
Administered medications (corticosteroids, diuretics, beta- adrenergic receptor antagonists, thyroid hormones, psychotropic drugs, antiepileptic drugs)
POLYURIA (daily urine volume >40 ml/kg body weight)
Diabetes
Diabetes insipidus
Primary polydipsia
Hypercalcemia
Administered medications (diuretics, selective serotonin reuptake inhibitors, calcium-channel blockers, tetracyclines, lithium)
NOCTURNAL POLYURIA
Peripheral edema/ atrial natriuretic factor (ANF) (congestive cardiac failure, sympathetic neuropathy, venous and/or lymphatic insufficiency, hepatic insufficiency, hypoalbuminemia, malnutrition, nephrotic syndrome)
Excessive fluids intake in the evening
Deficiency of daily vasopressin secretion (damage to the central nervous system within the hypothalamic-pituitary axis, Parkinson's disease, multiple sclerosis)
Administered medications (diuretics, steroids)
Alcohol
Damage to renal tubules (diabetes, albuminuria)
Sleep apnea syndrome
REDUCTION OF CAPACITY OF THE BLADDER
Bladder outlet obstruction (benign prostatic hyperplasia, pelvic organ prolapse)
Overactive bladder
Painful bladder syndrome
Neurogenic bladder
Cancer of the lower urinary tract
Urolithiasis
Postoperative disorders
Increased post-void residual
Aging bladder

33% daily diuresis in elderly (>65 years), calculated according to this formula: total volume of nocturia episodes/ total volume of micturition in 24h x 100% [7, 8, 10].

It is believed that maintaining a bladder diary for 3 consecutive days is sufficient to gather and reliably evaluate information about urination. The seven-day

observation period may be too tedious for the subject and is therefore mainly used in clinical trials or diagnostics of patients with an atypical medical history. Physical examination including the gynecological examination (including pelvic organ prolapse assessment) and prostate evaluation, Neurological assessment in case of suspected disorders in the systems mentioned above, Laboratory tests:

- General urinalysis, in case of abnormalities supplemented with urine culture,
- Cytological examination of urine sediment in case of suspected malignancy,
- Ultrasound diagnostics of the urogenital system (with an emphasis on the bladder, including the measurement of urinary volume remaining in the bladder after urination, and the prostate gland),
- If there is a suspicion of malignancy in the bladder it is advisable to perform a cystoscopy, or alternatively electroresection, if the ultrasound image clearly indicates a tumor.

In some clinical situations, urodynamic tests may be justified.

## Treating people reporting nocturia

Regardless of the pharmacological and/or therapeutic treatment, it is advisable to follow a fluid regimen, which involves limiting the intake of fluids in the evening. It is also necessary to avoid alcohol, coffee and tea as these substances increase urination. It is also recommended to drink mainly still water in the afternoon, if possible. The pattern for the amount of evening fluids may be modified based on the information given in the bladder diary by taking into account that chronic constipation can cause a feeling of bowel urgency (also during nighttime) it is considered necessary to modify eating habits among those patients who report symptoms mentioned previously. For this purpose, one can apply both dietary recommendations (high fiber diet) as well as stool softeners. It has also been observed in some patients that the elevation of the lower limbs in the evening led to a reduction in the number of nocturia episodes. In addition, people taking diuretics should be administering them in the afternoon rather than in the evening [21]. It is also advisable to exercise moderately during the day, which may be helpful in reducing the number of nocturia episodes.

## Desmopressin in the treatment of nocturnal polyuria

In the case of nocturnal polyuria, in which the use of the fluid regimen does not improve the symptoms re-

ported, the therapy is based on the use of a synthetic equivalent of vasopressin-desmopressin (dexamethasone-arginine vasopressin – DDAVP), which exhibits antidiuretic activity through vasopressin V2 receptors, influencing water reabsorption in renal tubules. The treatment of nocturia caused by nocturnal polyuria using desmopressin is the only option of pharmacological therapy with the highest recommendation of the European Association of Urology (EAU) [22].

Clinical studies have shown a greater sensitivity in women than in men to the same doses of vasopressin or desmopressin. This phenomenon is explained by larger expression of V2 receptors for vasopressin [23]. For this reason, following the results of numerous clinical studies evaluating therapeutic and adverse effects (in this case especially the risk of hyponatremia), it was found that the recommended daily therapeutic dose for women was 25  $\mu\text{g}$  and for men 50  $\mu\text{g}$  desmopressin lyophilisate, administered sublingually 1 hour before bedtime [24, 25, 26]. In the above studies, subjects receiving desmopressin reported, in comparison to the placebo patients, a significant improvement in the number of nocturia episodes, and also the secondary endpoints, which included an assessment of the overall quality of life and sleep. The response to the treatment usually occurred 7 days after its initiation. In a study carried out among a group of 261 women (19–87 years of age), it had been observed that therapy using 25  $\mu\text{g}$  of desmopressin significantly reduced the number of nocturnal micturitions in comparison to the placebo group ( $-0.22$ ,  $p = 0.028$ ). Analogous correlations were also observed in the quality of life and sleep because a significant improvement was seen in people treated with the vasopressin counterpart. An important part of the study was a point that involved evaluating the elapsed time between falling asleep and the first awakening to urinate. In the group of desmopressin treated patients, the time was 49 minutes longer than in the control group [27]. This parameter had, without a doubt, a positive influence on the quality of sleep. In addition, there is an analysis that shows that the prolongation of the time between falling asleep and the first episode of nocturia, has a beneficial effect on blood glucose levels. The before mentioned relationship was particularly important in patients with impaired glycaemia levels (patients with diabetes type II or with metabolic syndrome). This allows us to say that the treatment of nocturia also has a beneficial effect on the cardio-metabolic syndrome [28].

## The side effects of desmopressin

Among the most commonly reported side effects of desmopressin are: headaches, dry mouth, nausea,

edema, hyponatremia. However, among the side effects listed above we should turn our attention to hyponatremia, even though in most cases it is asymptomatic, in the group of people after 65 years of age. Prior to treatment with desmopressin, people aged  $\geq 65$  years should have their serum  $\text{Na}^+$  levels assessed and the examination should be carried out again at 4-8 days, and at one month after the initiation of therapy. The above pattern reduces the risk of hyponatremia [24].

### Desmopressin in nocturia treatment with a concurrent overactive bladder

It is worth considering the possibility of using desmopressin in patients with an overactive bladder (OAB) where nocturia is a significant clinical problem. A group of female patients with OAB and  $\geq 2$  nocturia episodes was treated with long-acting 4 mg tolterodine and 25  $\mu\text{g}$  ( $n = 45$ ) desmopressin or only long-acting 4 mg tolterodine ( $n = 52$ ). After 12 weeks of treatment, a substantial difference in the nocturnal urine volume had been observed, and an increase in the time between falling asleep and the first nocturia episode in the case of female patients being treated for nocturnal polyuria with underlying OAB. In female patients with nocturia without nocturnal polyuria the differences were statistically insignificant among the groups. There was also no difference in the extent of adverse reactions between the groups. The results of this study clearly indicate that the therapy regimen using desmopressin is superior to mono-therapy in the treatment of nocturia with concurrent overactive bladder, especially with underlying nocturnal polyuria [29]. Therefore, in female patients with clinically significant nocturia with co-existence of an overactive bladder, it is desirable that desmopressin is administered to reduce the number and volume of night time micturitions. The presence of nocturia for a month despite the use of essential pharmacological treatment of patients with OAB suggests the need to implement desmopressin.

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### Desmopressin in nocturia treatment with underlying benign prostatic hyperplasia

Men with benign prostatic hyperplasia often report nocturia. The treatment does not always lead to improving urination at night. As many as 45.4% of treated patients do not achieve a reduction in nocturnal micturition during the pharmacological treatment of BPH. For this reason, a study was conducted in which men with nocturia and benign prostatic hyperplasia were given long-acting 0.4 mg tamsulosin ( $n = 125$ ) or a paired treatment: long-acting 0.4 mg tamsulosin and 60  $\mu\text{g}$  desmopressin ( $n = 123$ ). The results of the study showed an advantage of the paired treatment over the mono-therapy, referring to parameters such as a reduction in the number of nocturia episodes, an increase in the volume of night time urination and a prolongation of time between falling asleep and the first nocturnal micturition. In both groups, patients have noted a significant improvement in their quality of life, with no relevant differences in the treatments used. No serious adverse effects have been observed among the groups. The possibility of the effective use of desmopressin therapy for BPH and nocturia has been confirmed [30]. The above results indicate the appropriateness of the implementation of desmopressin as a therapy added to the pharmacological treatment of patients with benign prostatic hyperplasia. The lack of influence of the significant pharmacological treatment on nocturia during the first month suggests a strong need to implement desmopressin.

### CONCLUSIONS

In view of the clinical data given above, desmopressin is a valuable, effective and safe first-line drug for the treatment of nocturia caused by nocturnal polyuria. Furthermore, the addition of desmopressin should be considered in the treatment of an overactive bladder and benign prostatic hyperplasia with underlying nocturnal polyuria.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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