

Nocturia due to nocturnal polyuria (NP). A common disorder

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To the Editor,

Nocturia is a significantly underestimated medical problem that affects seriously patients' quality of life, work engagement, productivity, and overall life conditions per se. Nocturia is a common condition, proven to be the most bothersome for patients with *Lower Urinary Tract Symptoms* (LUTS) (1). People with two or more events of micturition per night have a significant increase in mortality rate and an increased risk of fall-related fractures if they visit the toilet two or more times per night (1). The pathophysiology behind nocturia falls into five main categories: Nocturnal polyuria (NP), global polyuria, reduced bladder capacity, sleep disorders, and circadian clock disorders. Urological causes of nocturia are reduced bladder capacity, detrusor overactivity, and other mixed etiologies.

NP refers to increased urine production during nighttime. The *International Continence Society* defines NP as nocturnal urine production above 20% for young patients and 33% for older patients (> 65 yrs) (2).

NP seems to be the most common cause of nocturia. According to the current and most used definition of nocturia by the *International Continence Society* (2), the prevalence of NP, in both genders, is 44% in those under 65 years, and 31.3% in those 65 years or older (3). In a recent study, NP was present in 77% of those with two or more episodes of nocturia per night (4), and in an older study, > 75% of patients with nocturia had NP (5). In a very recent study, 31.5% of men and 38.5% of women had NP (6). Furthermore, it is worth mentioning that in a longitudinal, community-based study, the estimated prevalence of NP in men suffering from nocturia was 80% when the classical definition (NP Index > 33%) was used, but it was reduced to just 15% when was used the definition of Nocturnal Urine Production of > 90 ml/h (7). Moreover, using the Nocturnal Urine Production Index, the aforementioned recent study concluded that 23.8% and 18.1% of men and women respectively presented NP (6). Current definitions of NP are critical for estimating the prevalence and diagnosis of this condition. It seems that more research and evidence are needed to reach a consensus about the most accurate definition for use in everyday clinical practice (8).

NP has a multifactorial pathogenesis. Several non-urological causes are known to provoke this dysfunction. Such causes are untreated diabetes mellitus or insipidus, sleep disorders as obstructive sleep apnea, cardiovascular diseases (hypertension, heart failure) (9), chronic kidney disease, and primary polydipsia. If there is no obvious disorder provoking NP, this is defined as NP Syndrome (10, 11). The interplay among NP and pathological conditions such as hypertension, arteriopathy and arterial stiffness, coronary heart disease, and distribution in the third space of body fluid is thought to be significant and it is a topic of current research (11). This is also the case for the role of brain natriuretic peptide (11).

According to a well-established point of view, a key factor in the decision to consult a physician is the patient's bother because of this condition. The use of the word "disorder" rather than "complaint" would support the medical seriousness of nocturia to the patient's health (12). It is well known that two or more nocturnal voids are considered to be the clinically meaningful threshold associated with significant adverse consequences to health and well-being (13). Furthermore, a strong relationship between NP and nocturia and increased urinary frequency has been demonstrated (14). Commonly associated consequences include increased mortality and morbidity, increased risk of falls and hip fractures, traffic and work accidents, and increased risk of cardiovascular diseases, diabetes mellitus, and depression (13, 15). It also provokes immunological problems and dysfunction of memory and perception, overall deteriorating quality of life, and increase health costs (13, 15). Still, this condition seems to also affect work performance (16). Furthermore, the importance of taking sleep into account should be emphasized when assessing the relationship between nocturia and associated outcomes (16). Another critical element to be highlighted is that despite traditionally regarding nocturia as a pronominally male condition, robust data support the evidence that it is just as prevalent in women as in men and especially in postmenopausal women (12, 17).

The importance of the 'frequency-volume chart,' a very simple exam, has to be underlined as the main tool to guide diagnosis and identify the appropriate treatment of nocturia. Especially for NP, a frequency-volume chart is a cornerstone for the diagnosis of this condition (18).

The treatment rationale for nocturia is that NP, due to inadequate antidiuresis, is a major contributing factor to nocturia.

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Before starting any pharmaceutical treatment, it would be first beneficial to try some lifestyle modifications, as these can offer an improvement of NP. For example, less caffeine, alcohol, and generally fluids intake a couple of hours before bedtime could be of benefit to the patient (18). Furthermore, desmopressin administration offers a significant reduction in nocturia episodes and nocturnal urine production, translating into improvements in sleep and quality of life (19-22). Newer formulations of desmopressin are well tolerated. The risk of hyponatremia is relatively low with appropriate dosing escalation and taking into consideration that a lower minimum effective dose in females is needed compared to males (22-24). Furthermore, sodium monitoring just before treatment initiation and on the first, third, and seventh day of treatment is essential. Research for the treatment of NP is ongoing and includes highly selective arginine vasopressin 2 receptor agonists, non-steroid anti-inflammatory drugs, sex hormone replacement treatment, and short-acting diuretics (22). Improved knowledge regarding nocturia, which is a basic symptom of LUTS, provides insight to understanding that nocturia, and especially NP, can be a pathological entity per se. Further research in the future will shed light concerning the pathophysiology of nocturia. There is evidence that the burden of this symptom is considerable in many aspects, especially for the individual and the society. Therefore, NP should be given the attention it deserves in the medical field, especially by the urological community.

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