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## **Nocturia: A Nighttime Condition With Daytime Consequences**

An expert panel discussion  
regarding the challenges, barriers,  
and opportunities of treating  
this underrecognized condition



## INTRODUCTION

# Nocturia affects more than 40 million adults in the United States.<sup>1,2</sup>



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Nocturia is an under-recognized condition, being diagnosed in only an estimated 26% of patients, with only around 1.5 million of them receiving treatment.<sup>3</sup> Often considered just a normal part of aging or a symptom of common urological illnesses, such as overactive bladder (OAB) or benign prostatic hyperplasia (BPH), nocturia is most often caused by nocturnal polyuria, a distinct condition where urine is overproduced at night.<sup>4</sup> This leads to frequent and ongoing sleep disruptions night after night, resulting in a significant impact on quality of life and potentially serious health consequences. In fact, the impact of nocturia results in an estimated \$62.5 billion dollars of healthcare costs each year, \$61 billion of which is due to lost productivity and sick leave due to patients' inability to properly function during the day.<sup>5</sup> Current treatment options provide limited benefit for patients, highlighting the need for increased awareness and new therapies that help address these limitations.<sup>4</sup>

An expert panel of leading urologists in the area of voiding dysfunction assembled to share the challenges they face in diagnosing and treating nocturia. The following summary of their opinions and perspectives sheds light on the continuing need for effective treatment to address the substantial burden of illness of patients who suffer from nocturia.

## ***Given your knowledge of voiding dysfunction, how do you define nocturia; and at what point does nocturia become bothersome to most patients?***

**DR. WEIN:** The official definition of nocturia from the International Continence Society is “the complaint that the individual has to wake at night one or more times to void.”<sup>6</sup> For most people, however, only getting up once per night isn’t that bothersome. I, therefore, tend to think of nocturia as waking up at least 2 times or more per night to void, because that’s when many patients become bothered by it. Virtually everyone, in my experience, is bothered by getting up 3 times at night because of the need to void.<sup>7</sup>

**DR. ROVNER:** It’s worth keeping in mind that nocturia may mean different things to a patient and to a physician. A patient who goes to the bathroom 4 times while watching the 11 o’clock news and then sleeps for 8 hours would not have nocturia, even though they may complain of frequent urination. I diagnose nocturia only when the patient wakes up 1 or more times specifically to void. Waking up because a patient is a poor sleeper and has nothing better to do than go to the bathroom doesn’t count as a nocturia episode in my practice. From an ICS definition, I suppose it could, but I use the more pragmatic definition of waking up with the purpose of going to the bathroom.

I also include bother in my definition of nocturia. Bother is not defined by me, but by my patients. For example, a patient who wakes up 4 or 5 times a night to urinate but isn’t bothered by it because they go back to sleep may technically have nocturia but may not need treatment. Whereas another individual who wakes up twice but is considerably bothered by it because he’s a poor sleeper or irritated by waking up at night deserves to be treated. Therefore, in my practice, I attach bother to the ICS definition of nocturia. That is, my definition of nocturia is someone who wakes up because of the need to urinate 1 or more times per night and is bothered by it.

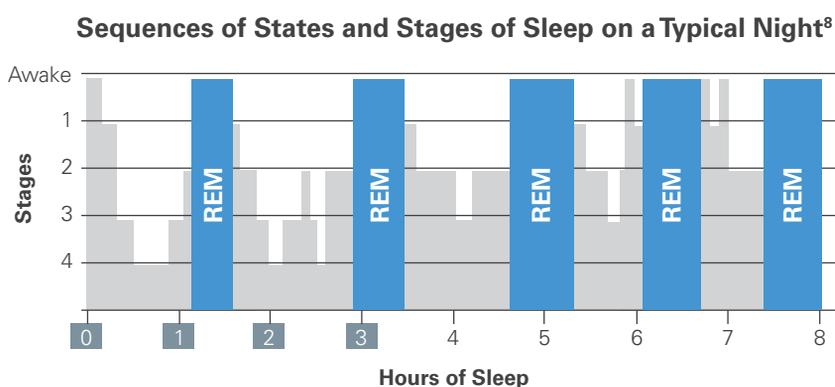
## ***Everyone gets up to urinate occasionally at night. Why is nocturia so important to evaluate and treat?***

**DR. DMOCHOWSKI:** Nocturia can have far-reaching impacts on health and daytime functioning, and many of these effects stem from interruption of sleep. Deep, restorative sleep usually occurs earlier in the night, and interruptions within the first 4 hours of sleep may have a greater impact than interruptions later in the night (**Figure 1**).<sup>8</sup> A lack of stable, deep sleep can leave patients feeling exhausted the next day, affecting concentration, complex memory tasks, and thought processes.<sup>5,8</sup>

**DR. BRUCKER:** Nocturia is a condition that affects both genders and all ages, but it can impact different patients in different ways. For example, its impact on a younger patient in the workforce may be different from its effects on an older, retired patient. Demographic data suggest that the frequency of nocturnal voiding increases with age (**Figure 2**).<sup>9</sup> However, it’s important to remember that not everything that becomes more common with age is considered a normal part of aging that one has to accept. Consider the analogy of cancer. Many types of cancer become more prevalent with age, but that doesn’t mean we don’t treat cancer. So, while nocturia and nocturnal polyuria could be considered a normal part of aging, it’s not something we have to accept as normal in older patients.<sup>10</sup>

**DR. WEIN:** There are data showing strong associations with nocturia and other conditions. Studies have identified associations between nocturia and concentration and complex memory tasks, diminished work productivity, increase in falls and fractures, the number of naps taken during the day, and the number of sick days taken.<sup>5,11,12</sup> Some of the most compelling—and difficult to explain—data show an increase in mortality over time in patients with nocturia, with a clear correlation with the increasing number of nocturic episodes per night.<sup>9</sup>

**Figure 1.** Maintenance of sleep cycle is fundamental for quality of life. The first few hours of undisturbed sleep are the most important for physical and mental functioning as this is the period when deepest sleep typically occurs.<sup>8</sup>





**Not everything that becomes more common with age is considered a normal part of aging that one has to accept. Many types of cancer become more prevalent with age, but that doesn't mean we don't treat cancer."**

**– Dr. Benjamin Brucker**

### ***We've talked about some of the consequences of nocturia, but what are the underlying causes?***

**DR. WEIN:** For a long time we thought of nocturia as a symptom of some other syndrome. It's now clear that nocturia is most often associated with nocturnal polyuria. In many cases, nocturnal polyuria is a result of a hormonal change, namely an abnormality—a decrease—in the production of arginine vasopressin (AVP) from the posterior pituitary at night.<sup>11</sup> Nocturia can have other causes, including peripheral edema due to congestive heart failure and venous or lymphatic stasis; it may also occur from excessive nighttime drinking, obstructive sleep apnea, and renal tubular dysfunction, which occurs with diabetes. Nocturia can also result from 24-hour polyuria, any cause of reduced bladder capacity, and primary or secondary sleep disorders.<sup>4,11</sup>

**DR. DMOCHOWSKI:** AVP works as an antidiuretic by binding to specific receptors in the collecting ducts of the kidneys to help the body reabsorb water, thus concentrating the urine. When blunting of AVP secretion occurs, the ability of the kidneys to reabsorb water during sleep is lost. Therefore, the primary, centralized hypothesis for the cause of nocturnal polyuria is that a reduction in AVP secretion results in the overproduction of urine at night.<sup>4,11</sup> In my practice, around 8 out of 10 patients with nocturia have nocturnal polyuria—the excess production of urine overnight. That number is consistent with studies that have shown up to 88% of nocturia may be caused by nocturnal polyuria.<sup>13</sup>

### ***How do you diagnose nocturnal polyuria in your patients?***

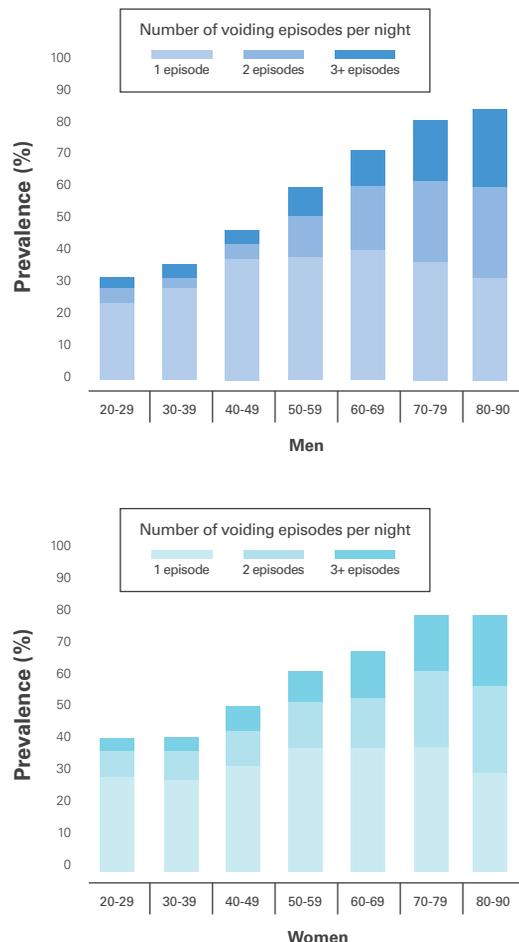
**DR. ROVNER:** My initial evaluation of a patient with a voiding dysfunction involves doing a history, a physical, and a urinalysis. I then roughly divide my patients with a complaint of nocturia into 3 groups: The first includes patients with isolated nocturia without daytime symptoms,

the second group experiences primarily daytime symptoms with some nighttime symptoms, and patients in the third group have both daytime and nighttime symptoms. The third group is the most complicated group, and these patients warrant a more in-depth evaluation. Those with primarily daytime symptoms typically have conditions such as OAB or male lower urinary tract symptoms related to prostatic enlargement, which I then treat appropriately. The group with primarily nighttime symptoms without much in the way of daytime symptoms are the patients whom I suspect of having nocturnal polyuria. My evaluation of all 3 groups involves the use of a voiding diary, which allows me to differentiate patients with nocturnal polyuria from those in the other diagnostic categories.<sup>4</sup>

**DR. DMOCHOWSKI:** Classically, the best way to define nocturnal polyuria is with a voiding diary, which includes a volume metric. Nocturnal polyuria is typically defined as nighttime urine production exceeding 33% of the 24-hour

**Figure 2.** The prevalence of nocturia increases with age in both men and women.<sup>9</sup>

#### **Prevalence of nocturia by gender and age<sup>9</sup>**



urine output. So ideally, a 24-hour collection, with at least a third of the total volume, if not more, being produced at night is necessary to make a diagnosis of nocturnal polyuria.<sup>4</sup>

**DR. WEIN:** Like everyone else, I prefer using voiding diaries to diagnose nocturnal polyuria. However, sometimes it's difficult to have patients give you a reliable diary, and I find that a lot of my patients don't return them. It's not ideal, but occasionally I'll have patients begin an 8-hour urine collection when they retire and I'll look at the amount of urine produced overnight. Most people consume between 2.5 and 3 liters of fluid per day, so if I see that they are excreting over 1000 milliliters of urine during the night, I'm comfortable making a diagnosis of nocturnal polyuria based on the 8-hour urine collection.

### ***Once you diagnose nocturnal polyuria, how do you currently manage it in your practice?***

**DR. DMOCHOWSKI:** I first look for comorbidities that may be contributing to the nocturnal polyuria, because effectively treating these comorbidities can sometimes improve the nocturia. A classic example is sleep apnea: We know that treating sleep apnea has shown a positive effect on nocturnal polyuria.<sup>11</sup> Behavioral modifications, such as fluid restriction, may or may not work, so we often need to get creative with strategies that may or may not be very beneficial, such as improving sleep hygiene. It makes sense that if one improves his or her sleep environment, one might be able to sleep a little bit longer, but the data supporting this are inconclusive, and patients are often left with no real treatments.<sup>13</sup>

**DR. WEIN:** I like to look for quick hits. If someone's diabetes is out of control, I let their diabetologist or endocrinologist know. When I see a 50-year-old overweight patient who has metabolic syndrome and snores all night long, recommending a sleep study to diagnose and treat obstructive sleep apnea may help improve their nocturia. If they have obvious congestive heart failure or uncontrolled hypertension, I send them back to their internist or primary care provider to manage this. If a patient has peripheral edema, I ask him to lay down with his legs raised for about an hour sometime in the late afternoon and I ask him to restrict fluids between around 4:00 PM and bedtime.

Unfortunately, pharmacological treatments for nocturia have been limited. Our available treatment options have largely been relegated to those used to treat OAB. However, OAB medications just don't work that well for nocturia, unless the patient has severe urgency associated with these episodes of awakening. Likewise, if someone has bladder outlet obstructions because of BPH with a complaint of nocturia, I often use alpha blockers or 5-alpha-

reductase inhibitors—sometimes even an OAB drug—but they also just don't work very well for nocturia.<sup>4</sup>

**DR. DMOCHOWSKI:** The bottom line is that medications used to treat OAB and BPH don't attack the physiological reason that people get up at night, which is overproduction of urine. Medications that treat BPH work by improving bladder outlet resistance, so they improve the way the bladder evacuates itself. However, bladder evacuation is not the driving force behind nocturnal polyuria. Similarly, OAB medications affect bladder storage, with no impact on the amount of urine being produced.<sup>4</sup>

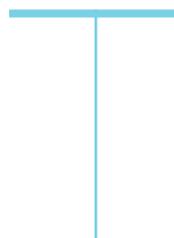


**The bottom line is that medications used to treat OAB and BPH don't attack the physiological reason that people get up at night, which is overproduction of urine."**

**– Dr. Roger Dmochowski**

**DR. BRUCKER:** I would agree. I tend to favor a lot of anticholinergic drugs, but we're doing all these things that are largely ineffective for nocturia because we haven't had therapies that are studied in these populations or FDA-approved to treat nocturnal polyuria. I think it is frustrating for both patients and physicians to cycle through multiple medications without seeing much improvement in their symptoms.<sup>4</sup>

We do have one medication that does directly impact urine production—desmopressin. Until recently, desmopressin wasn't available in a formulation specifically FDA-approved to treat nocturia. Off-label formulations of desmopressin that were used in the past have inconsistent plasma levels. When the bioavailability of a drug is low it may not be effective, yet high bioavailability can lead to the unwanted effect of hyponatremia. A better formulation of desmopressin would be one that provides a small dose that is rapidly absorbed, reaches a predictable therapeutic level, but has a limited duration of action, thus minimizing the risk of hyponatremia. A promising new formulation that meets these criteria recently became the first FDA-approved treatment for adults with nocturia due to nocturnal polyuria.<sup>14</sup>





**A better formulation of desmopressin would be one that provides a small dose that is rapidly absorbed, reaches a predictable therapeutic level, but has a limited duration of action, thus minimizing the risk of hyponatremia.”**

– Dr. Benjamin Brucker

### ***What are the biggest challenges you and your patients face when treating nocturia?***

**DR. ROVNER:** One of the biggest challenges I face is the same one we encounter in virtually all medical conditions when we try to impose behavioral modifications. That is, that a vanishingly small number of individuals tend to adhere to behavioral modifications over the long term. We’re no better at getting patients to be compliant with our behavioral modifications than any others, such as smoking cessation or weight loss.

**DR. DMOCHOWSKI:** There’s a lot of uncertainty about nocturia, and there is a hurdle to overcome to get patients referred who have problematic nocturia. There is also a belief that there isn’t anything that can effectively treat the condition. A lot of people have been told that there is nothing they can do, so they silently suffer while continuing to wake up night after night with no other option than to just live with it. So, they do. Once patients and physicians realize there is an effective therapy available, there will be many more people coming forward for treatment.

***It’s interesting that a condition that is so well-documented to be directly associated with major health implications—not to mention quality of life concerns—still doesn’t seem to be taken seriously by some physicians. Why do you think this is?***

**DR. BRUCKER:** Traditionally in urology and urology training, we haven’t really learned a lot about sleep and its importance, so it is a new subject for many urologists. We deal with a lot of things on a daily basis, but sleep is not something that we talk a lot about. We need to do a better job in training future generations of urologists to understand that sleep is important and the real impact

that interrupted sleep can have on a patient’s health and quality of life. Furthermore, there’s not a great recognition of the fact that there are things you can actually do to decrease the number of times someone gets up at night and, therefore, how much they are affected during the day.

**DR. ROVNER:** Many urological conditions are not viewed as important by our medical colleagues in other fields; they often consider them to be lifestyle conditions. But nocturia can impact a patient’s overall health and quality of life far greater than many other medical conditions that are treated swiftly and earnestly by our medical colleagues. Nocturia should be given this same sense of urgency.<sup>11</sup>



**Nocturia can impact a patient’s overall health and quality of life far greater than many other medical conditions that are treated swiftly and earnestly.”**

– Dr. Eric Scott Rovner

## CONCLUSION

## Nocturia can be caused by nocturnal polyuria in approximately 80% of cases and has been linked to increased mortality, depression, and impairment of overall health.<sup>9,11,13,15</sup>

For the more than 40 million adults in the United States who suffer from nocturia, treatment options for their condition remain limited.<sup>1,2</sup> Adherence to behavior modifications remains a challenge, and medications used for OAB and BPH do not directly target the source of urine overproduction—the root cause of nocturnal polyuria.<sup>4,13</sup> Furthermore, until recently, there has not been an available FDA-approved product indicated to treat nocturia due to nocturnal polyuria, leaving many exhausted patients to suffer night after night in silence.<sup>14</sup>

For the first time, a new option to treat this underrecognized condition has been approved.<sup>14</sup> This milestone marks the first FDA approval of a therapeutic option to help reduce nighttime urine production and decrease the number of times patients wake up to urinate. Because traditional medications used off-label to treat nocturia due to nocturnal polyuria have been limited and are largely ineffective,<sup>4,13</sup> the availability of this new therapeutic option fills an unmet need for urologists and patients alike and brings renewed hope to a condition that has seen little progress despite its widespread impact.

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Figure 2 reprinted from Kupelian V, Fitzgerald MP, Kaplan SA, Nørgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. *J Urol*. 2011;185(2):571-577, with permission from Elsevier.

## Author disclosures

Dr. Brucker, MD, has affiliations with Covance, Inc (investigator), Serenity Pharmaceuticals (advisor), Avadel Specialty Pharmaceuticals, LLC (advisor, speaker), Allergan, PLC (investigator, speaker, advisor), Watkins-Conti Products, Inc (advisor), Medtronic, PLC (investigator), and GTx (consultant).

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Dr. Wein has affiliations with Allergan, Aquinox, Avadel, Axonics, Medtronic, Outpost, Serenity, Urovant, Valencia, and Velicorp (consultant and advisor).



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