

# NOCTURIA

## Symptom or Disease?

### Musings of a PCP

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# Nocturia

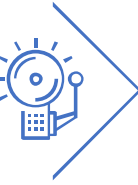
- What is it?
- Why should we care?
- Evaluating the causes?
- How to treat?
- How not to cause harm?
- Who is in charge?

**NOCTURIA** is defined as waking at night to urinate, with each voiding episode preceded and followed by sleep

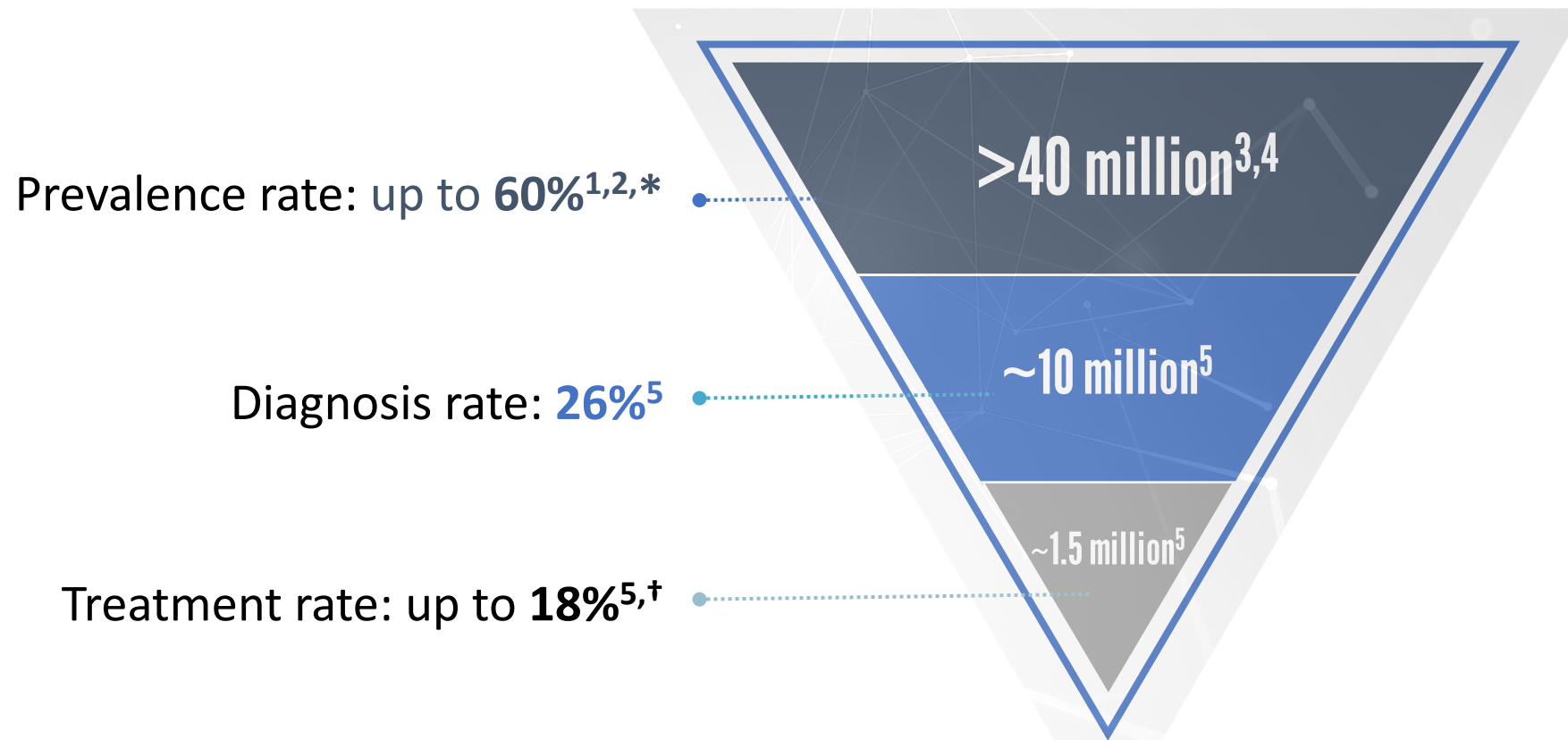
Clinically Meaningful



**NOCTURNAL POLYURIA** is defined as nighttime urine production  $>20\%$  of the total urine output for younger adults and  $>33\%$  for older adults



# Prevalent and Undertreated



\*Prevalence rates of men and women older than 70 years old with  $\geq 2$  nightly voids (range in men, 29-59%; range in women, 28-62%).<sup>1,2</sup>

<sup>†</sup>Desmopressin treatment (melt or tablet) among patients with nocturia only.

1. Bosch JL, Weiss JP. *J Urol.* 2013;189(1 Suppl):S86-92. 2. Weiss JP. *Rev Urol.* 2012;14(3-4):48-55. 3 Fitzgerald MP, et al. *J Urol.* 2007;177(4):1385-1389.

4. KFF. <https://www.kff.org/other/state-indicator/distribution-by-age>. Accessed March 23, 2018. 5. Oelke M, et al. *Int J Clin Pract.* 2016;70(11):940-949.

# The Burden of Nocturia Is Broad and Substantial

## ASSOCIATIONS



Reduced quality of life<sup>1,2</sup>



Poorer overall and mental health<sup>1</sup>



Reduced work productivity<sup>1</sup>



Increased falls and fractures<sup>3-6</sup>



Increased mortality<sup>5</sup>

### Short-Term Consequences<sup>8</sup>

- Increased daytime sleepiness
- Reduced daytime energy
- Longer reaction time
- Reduced psychomotor performance
- Decreased concentration/memory/cognitive function
- Poor mood

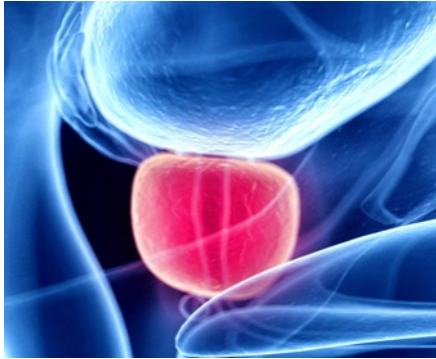
### Long-Term Consequences<sup>8</sup>

- Depression
- Susceptibility to somatic disease
- Risk of cardiovascular disease
- Risk of car accidents

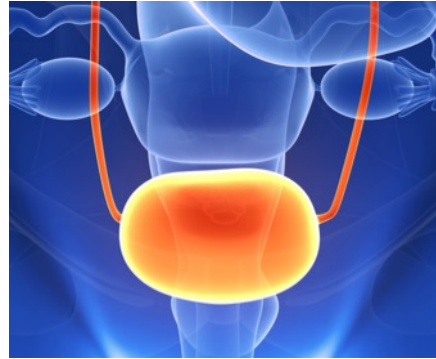
1. Kobelt G, et al. *BJU Int.* 2003;91(3):190-195. 2. van Dijk MM, et al. *BJU Int.* 2010;105(8):1141-1146. 3. Asplund R. *Arch Gerontol Geriatr.* 2006;43(3):319-326. 4. Stewart RB, et al. *J Am Geriatr Soc.* 1992;40(12):1217-1220. 5. Nakagawa H, et al. *J Urol.* 2010;184(4):1413-1418. 6. Temml C, et al. *NeuroUrol Urodyn.* 2009;28(8):949-952. 7. Kupelian et al. *Am Urol Assoc Edu Res.* 2011;185:571-577. 8. Abrams P. *Eur Urol Suppl.* 2005;3(6):1-7.

# NOCTURIA OR NOCTURNAL POLYURIA

**BPH**



**OAB**



**Sleep Disorders**



**Nocturia due to nocturnal polyuria**



# NOCTURNAL POLYURIA: Multiple Etiologies

## OVERCONSUMPTION

*Behavioral*

*Environmental*

*Disogenic diabetes insipidus*

*Diabetes mellitus*

## OVERDIURESIS

*Third-space fluid resorption*

*Fluid shifts*

*Medications (eg, diuretics)*

*Sleep disorders or apnea*

*Congestive heart failure*

*Renal conditions*

*Diabetes mellitus*

## TOO LITTLE ANTIDIURESIS

*Circadian defect in secretion*

*or action of vasopressin*

*Renal conditions*

*Cerebrovascular damage*

*Central diabetes insipidus*

*Nephrogenic diabetes insipidus*

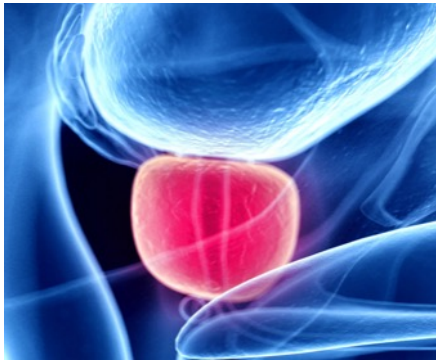
# How much does the etiology matter?

- The etiology of nocturia is multifactorial but >80% of patients with nocturia have nocturnal polyuria (NP)
- Regardless of the frequency or cause, nocturia results from a production of nocturnal urine that exceeds the capacity of the urinary bladder to comfortably store it



# SYMPTOMS DIRECT TREATMENT

**BPH**



**OAB**



**Sleep Disorders**



**Nocturia due to nocturnal polyuria**



Alpha Blockers  
5 ARIs  
PDE 5

Antimuscarinics  
Beta 3

Sleep Clinic

Treat the cause

# WITH NOCTURNAL POLYURIA, IF POSSIBLE, TREAT THE CAUSE

## OVERCONSUMPTION

*Behavioral*

*Environmental*

*Disogenic diabetes insipidus*

*Diabetes mellitus*

## OVERDIURESIS

*Third-space fluid resorption*

*Fluid shifts*

*Medications (eg, diuretics)*

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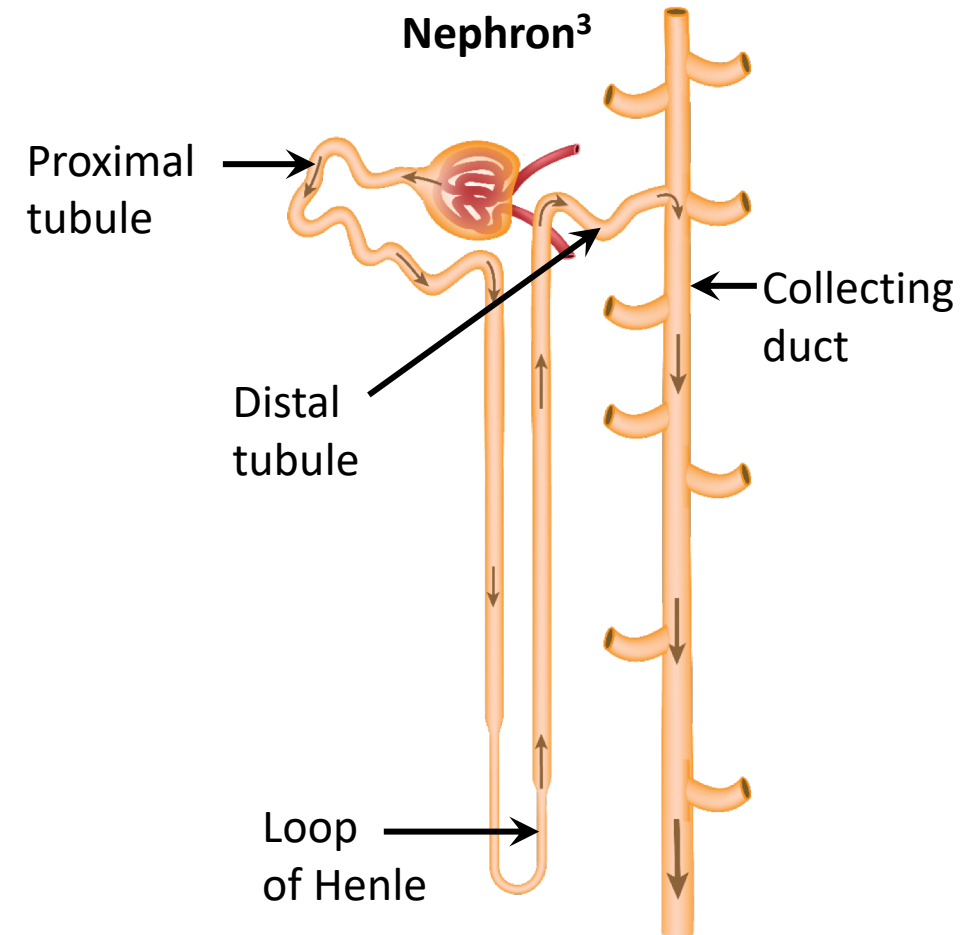
*Nephrogenic diabetes insipidous*



# WHEN TREATMENT CALLS FOR PAUSING URINE PRODUCTION

## Desmopressin

- Desmopressin is a synthetic analog of AVP and a selective  $V_2$  receptor agonist
- It increases water reabsorption in the distal tubule and collecting ducts, concentrates the urine, and decreases urine production



DESMOPRESSIN FORMULATIONS  
REDUCE NOCTURIA BUT ARE ASSOCIATED  
WITH A RISK FOR HYPONATREMIA<sup>1,2</sup>

AVP=arginine vasopressin.

1. Weiss JP, et al. *BJU Int.* 2011;108(1):6-21. 2. Ebell MH, et al. *J Urol.* 2014;192(3):829-835. 3. Amerman E. In. *Human Anatomy and Physiology.* 2nd ed: 2018:941-984.

# Newer Versions of Desmopressin Have to Be Safer

## NOCTIVA™ Is Engineered to Be Different

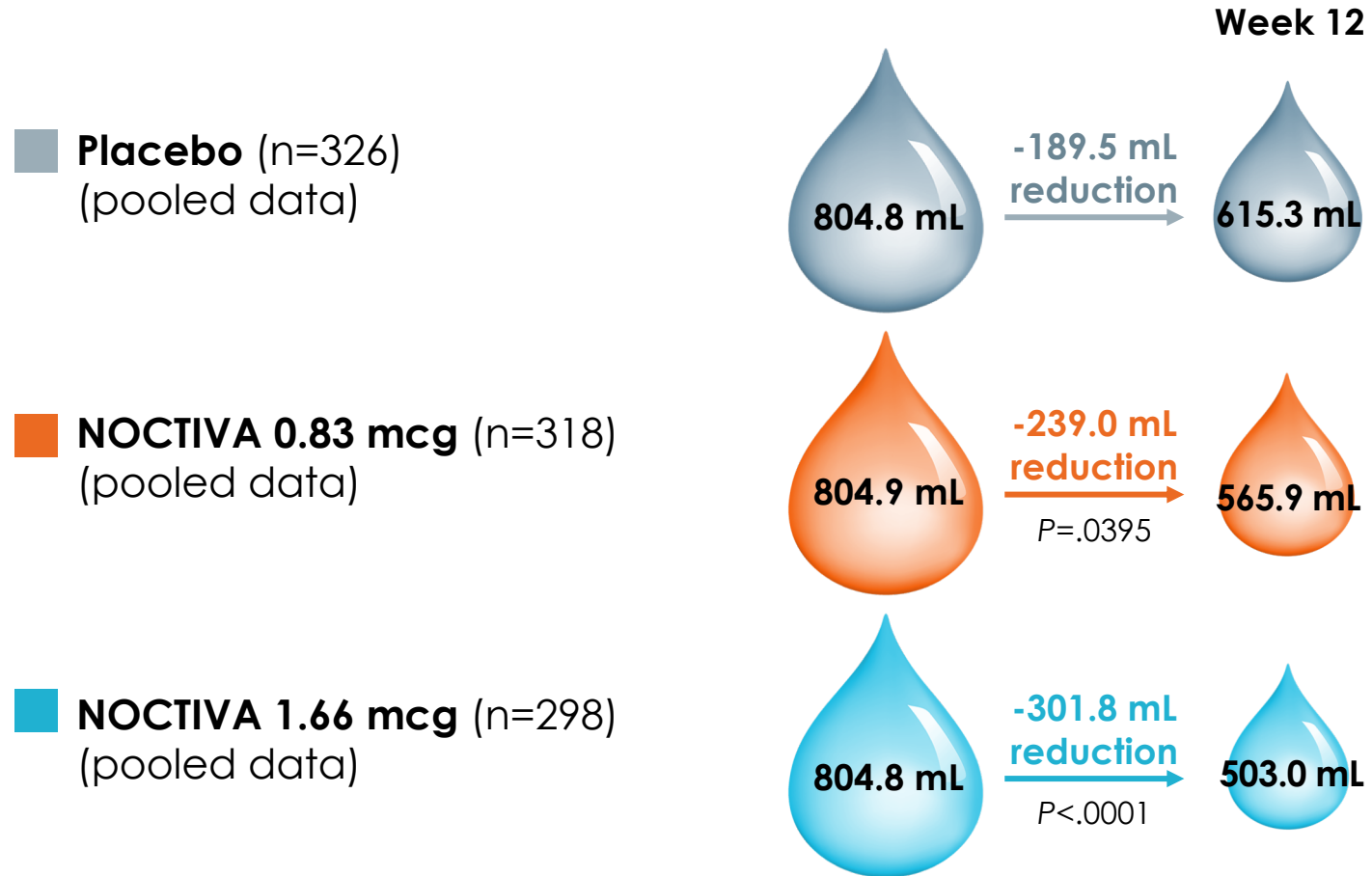
### High Bioavailability (8%)<sup>1</sup>

High bioavailability allows for **low dosing**.<sup>2,3</sup>

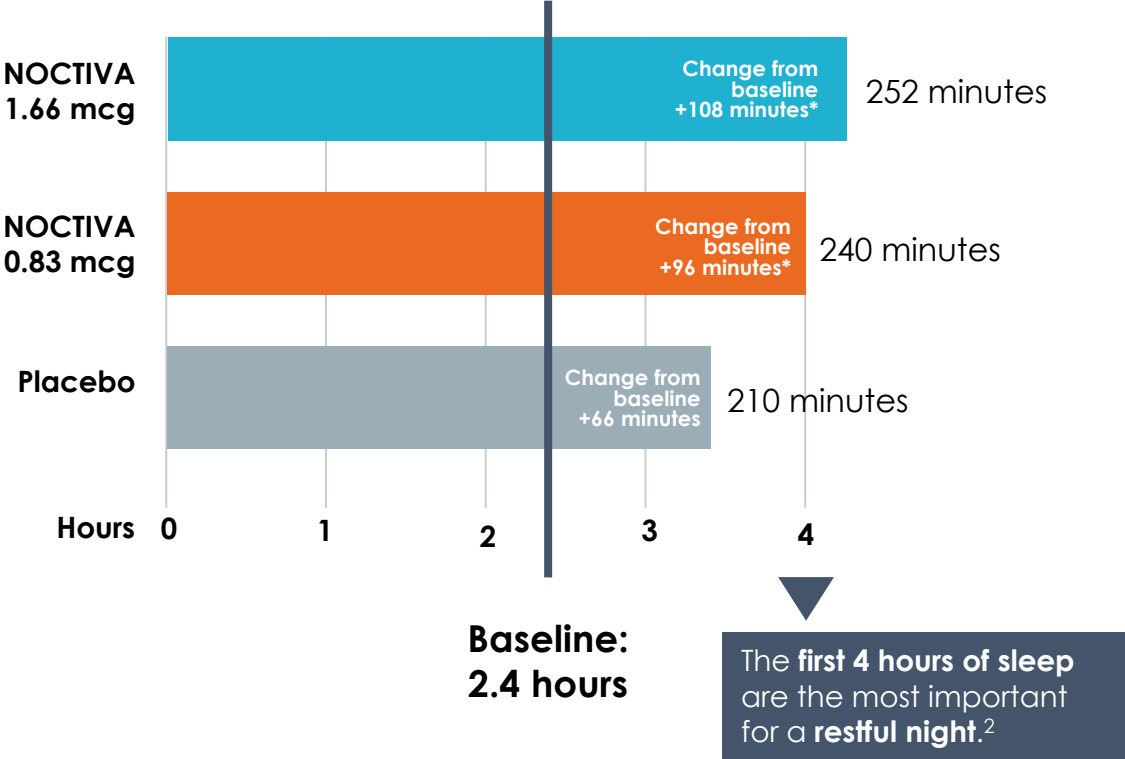
### Short Antidiuretic Effect<sup>5</sup>

The peak plasma concentration results in an **antidiuretic effect that lasts 4-6 hours**.<sup>1</sup>

# Decreases Nocturnal Urine Production



# Decreased Urine Production Equals Decreased Bladder Filling



# HISTORICAL FEARS ABOUT DESMOPRESSIN

- DECREASING SODIUM
- DECREASING SODIUM
- DECREASING SODIUM
- DECREASING SODIUM
- DECREASING SODIUM
- DECREASING SODIUM





# HYPONATREMIA\* INCIDENCE: 12-WEEK CLINICAL TRIALS<sup>1</sup>

## Overall Hyponatremia

Serum Sodium Concentration (mmol/L)	Placebo N=349	Noctiva™ 0.83 mcg N=354	Noctiva™ 1.66 mcg N=341
130-134, n (%)	18 (5.2)	33 (9.3)	42 (12.3)
126-129, n (%)	0	8 (2.3)	7 (2.1)
≤125, n (%) <sup>†</sup>	1 (0.3)	0	5 (1.5)

## Hyponatremia by Age

Serum Sodium Concentration (mmol/L)	<65 years			≥65 years		
	Placebo N=144	Noctiva 0.83 mcg N=148	Noctiva 1.66 mcg N=146	Placebo N=205	Noctiva 0.83 mcg N=206	Noctiva 1.66 mcg N=195
130-134, n (%)	7 (4.9)	8 (5.4)	14 (9.6)	11 (5.4)	25 (12.1)	28 (14.4)
126-129, n (%)	0	2 (1.4)	0	0	6 (2.9)	7 (3.6)
≤125, n (%)	0	0	0	1 (0.5)	0	5 (2.6) <sup>†</sup>

\*Hyponatremia was defined as serum sodium level ≤125 mmol/L with or without symptoms or serum sodium level between 126 and 129 mmol/L with clinical symptoms associated with hyponatremia.<sup>2</sup>

<sup>†</sup>Of the 5 patients with serum sodium ≤125 mmol/L, all were ≥65 years old, 4 were men, and onset ranged from 6 days to 12 weeks after start of dosing; 4 patients were taking concomitant systemic or inhaled glucocorticoid, and 3 patients were taking a nonsteroidal anti-inflammatory drug (NSAID).<sup>1</sup>

1. Noctiva [prescribing information]. Chesterfield, MO. Avadel Specialty Pharmaceuticals, LLC. 2. Data on file, NOC-007.





# NOCTIVA™ IMPORTANT SAFETY INFORMATION



## CONTRAINDICATIONS

- Hyponatremia or a history of hyponatremia
- Polydipsia
- Primary nocturnal enuresis
- Concomitant use with loop diuretics or systemic or inhaled glucocorticoids
- Estimated glomerular filtration rate below 50 mL/min/1.73 m<sup>2</sup>
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- During illnesses that can cause fluid or electrolyte imbalance
- New York Heart Association (NYHA) Class II-IV congestive heart failure
- Uncontrolled hypertension

## WARNINGS AND PRECAUTIONS

- Fluid retention: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention. Monitor volume status in patients with NYHA Class I congestive heart failure.
- Nasal conditions: Discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved.

## Monitor Serum Sodium Concentration<sup>1</sup>

Prior to initiating

Within 7 days of starting treatment

Approximately 1 month after initiating treatment or increasing the dose

Periodically after treatment as clinically appropriate

More frequent serum sodium monitoring is recommended for patients  $\geq 65$  years of age and for those at increased risk of hyponatremia.

### If the patient develops hyponatremia

- NOCTIVA™ may need to be **temporarily or permanently discontinued**, and treatment for the hyponatremia instituted, depending on the clinical circumstances, including the duration and severity of the hyponatremia

Please see Important Safety Information for NOCTIVA on slides 29-31.

# DOES ANY SPECIALTY OWN URINE?



DOES ANY SPECIALTY OWN URINE? **NO**

**A PERFECT  
OPPORTUNITY FOR  
SHARED CARE**



# Urologists and Primary Care Must Work Together on This

- Must be able to effectively evaluate and differentiate other diseases
- Must be able to safely treat and monitor

# What This Family Doctor Believes

- Adequate treatment of nocturia requires shared care
- Regardless of the frequency or cause, nocturia results from a production of nocturnal urine that exceeds the capacity of the urinary bladder to comfortably store it
- Therefore, whether nocturia is a symptom or disease is of little relevance in choosing to treat



**What do  
you believe is  
the future  
direction for  
the treatment  
of  
NOCTURIA?**