



Grand Rounds
in **UROLOGY**

FDUS 2018

Nocturia: Symptom or Disease?



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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

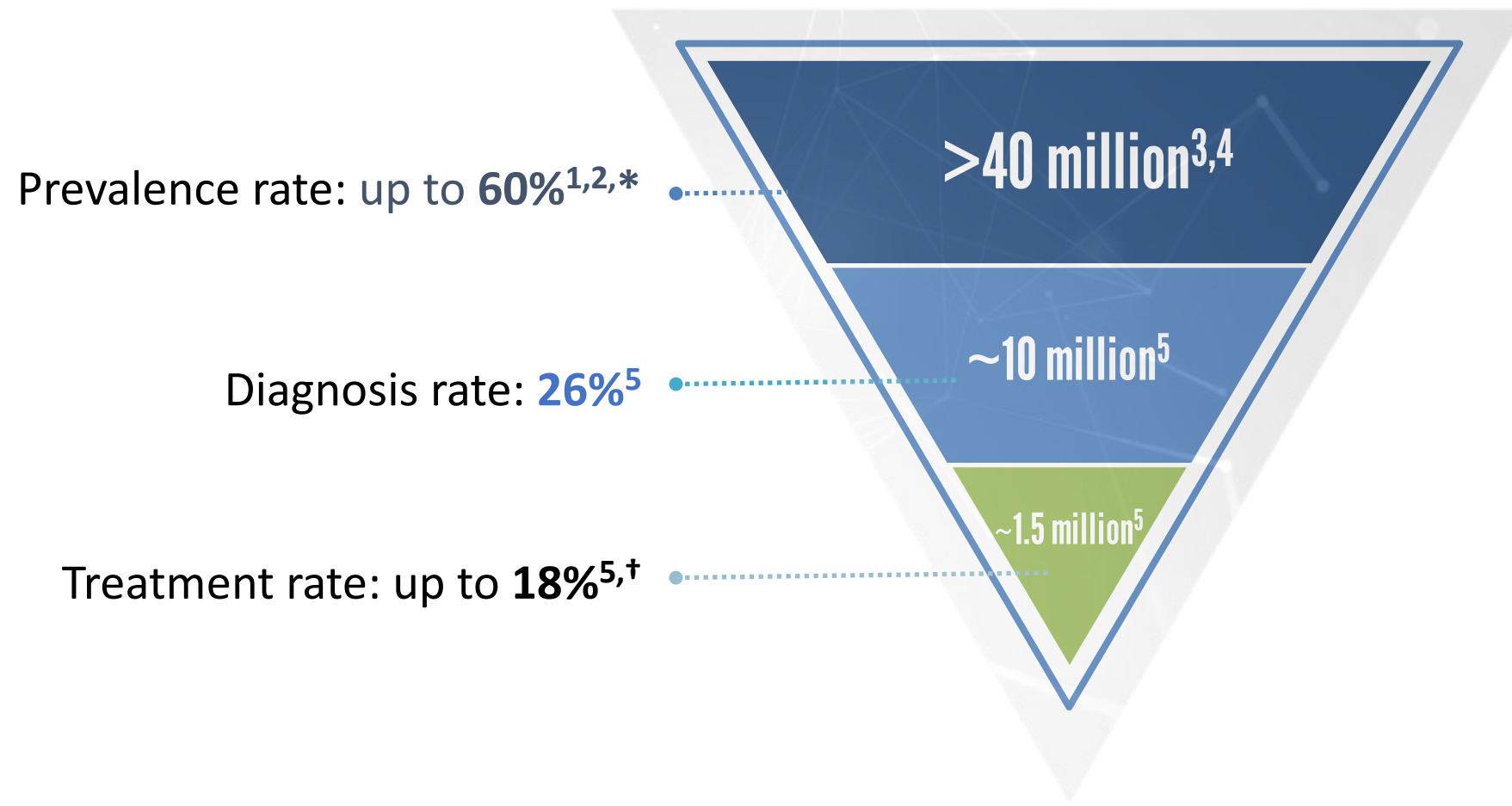
Clinically Meaningful



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 ≥ 2 nightly voids (range in men, 29-59%; range in women, 28-62%).^{1,2}

†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^{1,2}



Poorer overall and mental health¹



Reduced work productivity¹



Increased falls and fractures³⁻⁶



Increased mortality⁵

Short-Term Consequences⁸

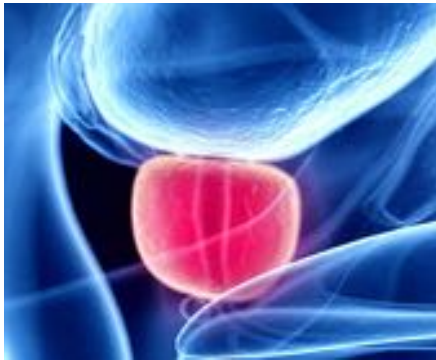
- Increased daytime sleepiness
- Reduced daytime energy
- Longer reaction time
- Reduced psychomotor performance
- Decreased concentration/memory/cognitive function
- Poor mood

Long-Term Consequences⁸

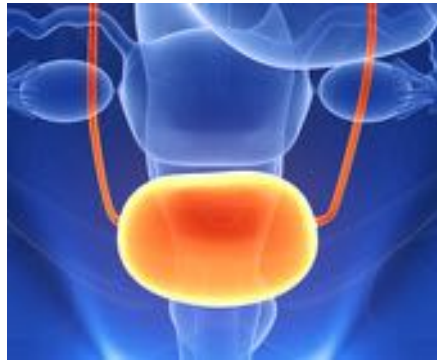
- Depression
- Susceptibility to somatic disease
- Risk of cardiovascular disease
- Risk of car accidents

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 insipidous

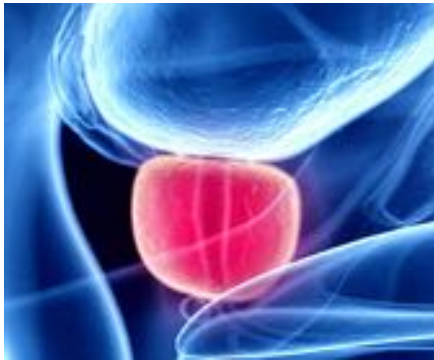
Nephrogenic diabetes insipidous

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)

Sleep disorders or apnea

Congestive heart failure

Renal conditions

Diabetes mellitus

TOO LITTLE ANTIDIURESIS

Circadian defect in secretion

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Nephrogenic diabetes insipidous

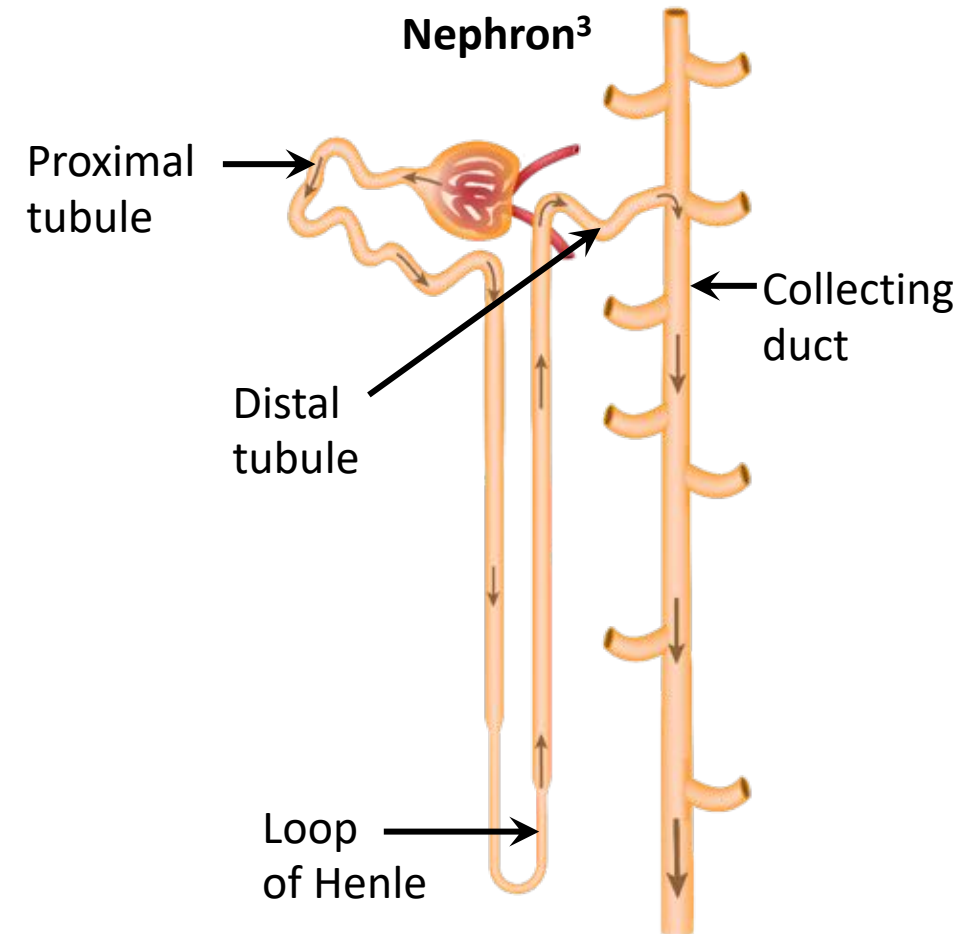


WHEN TREATMENT CALLS FOR PAUSING URINE PRODUCTION

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^{1,2}



Newer Versions of Desmopressin Have to Be Safer

NOCTIVA™ Is Engineered to Be Different

High Bioavailability (8%)¹

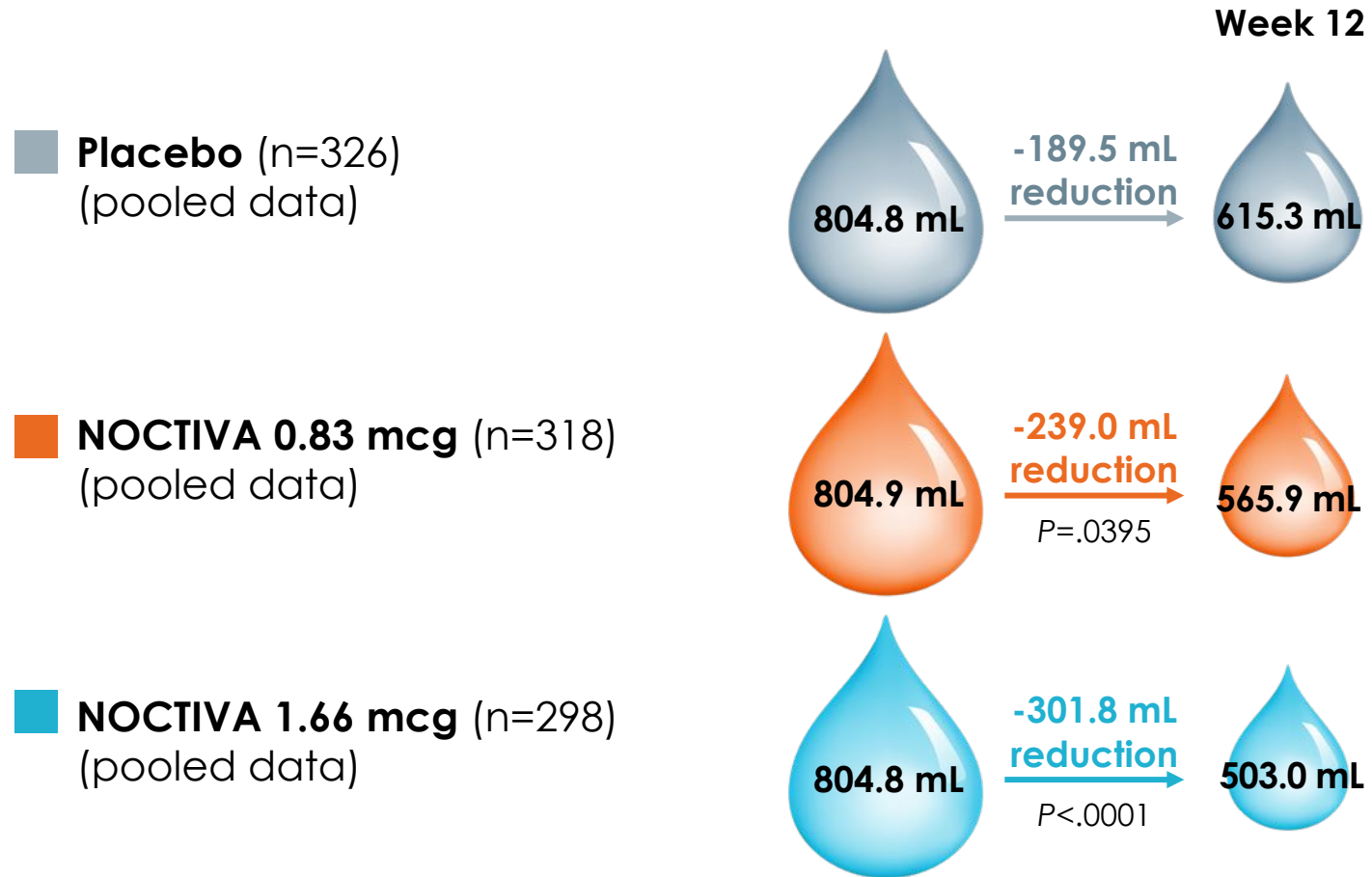
High bioavailability allows for **low dosing**.^{2,3}

Short Antidiuretic Effect⁵

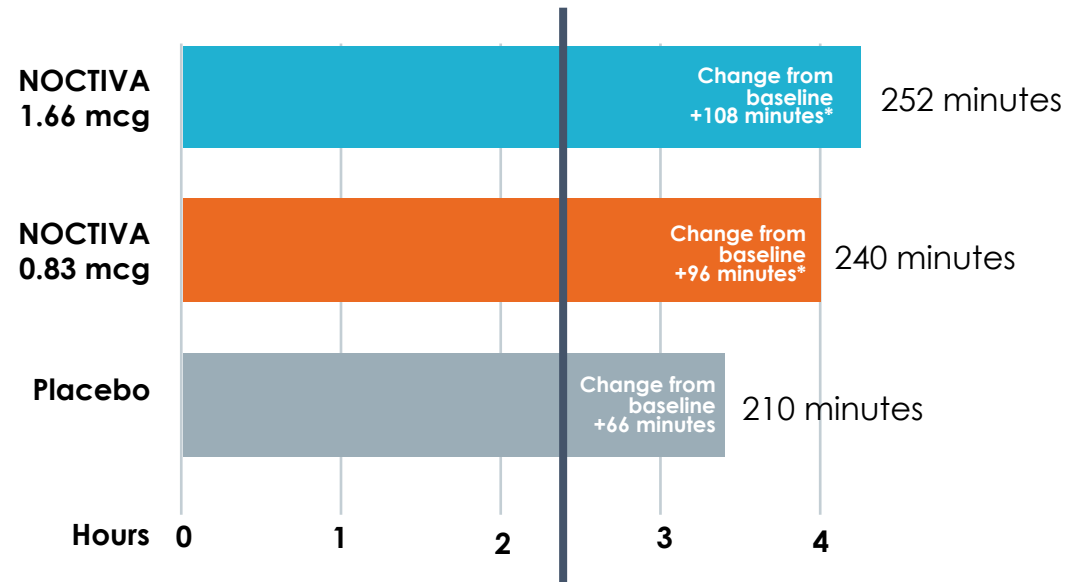
The peak plasma concentration results in an **antidiuretic effect that lasts 4-6 hours**.¹

1. Data on file, NOC-007. 2. Cohn JA, et al. *Expert Rev Clin Pharmacol*. 2017;10(12):1281-1293. 3. Weiss JP, et al. *Neurol Neurobiol*. 2012;31(4):441-447. 4. NOCTIVA [prescribing information]. Chesterfield, MO: Avadel Specialty Pharmaceuticals, LLC. 5. Data on file, NOC-008.

Decreases Nocturnal Urine Production



Decreased Urine Production Equals Decreased Bladder Filling



Baseline:
2.4 hours

The **first 4 hours of sleep** are the most important for a **restful night**.²

HISTORICAL FEARS ABOUT DESMOPRESSIN

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





HYPONATREMIA* INCIDENCE: 12-WEEK CLINICAL TRIALS¹

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 (%) [†]	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) [†]

*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.²

[†]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).¹

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



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 m²
- 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

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
≥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

DOES ANY SPECIALTY OWN URINE?



DOES ANY SPECIALTY OWN
URINE? **NO**
**A PERFECT
OPPORTUNITY
FOR SHARED**



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?**