Nocturia

Definition

- The International Continence Society (ICS): voiding that occurs during the hours of sleep .

Hashim et al., 2017; van Kerrebroeck et al., 2002

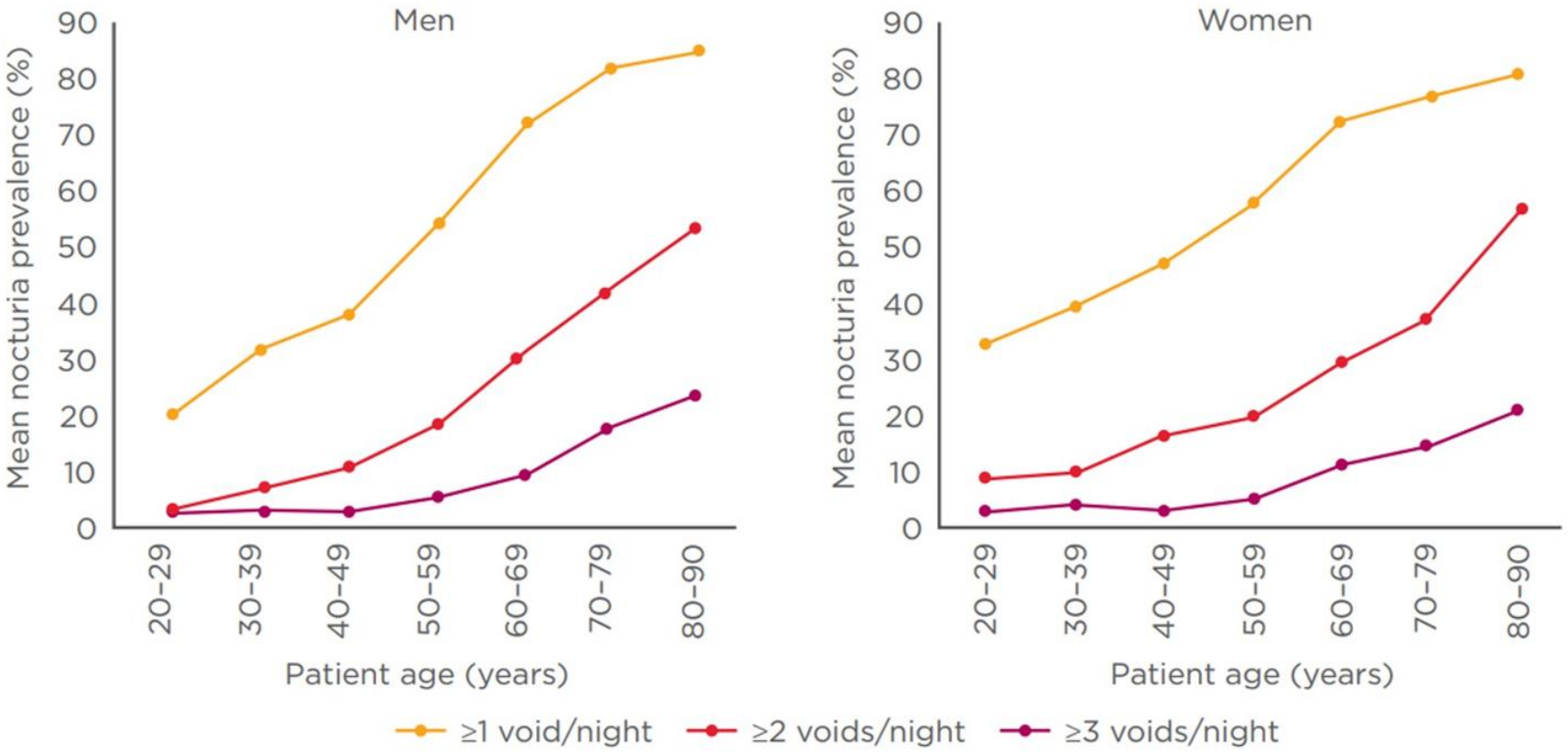
- van Kerrebroeck: waking one or more times to void during the hours of sleep; each void is preceded and followed by sleep

- The definition of nocturia does not take into account the patient's degree of bother.

TERM	DEFINITION
Night	The period between going to bed with the intention of sleeping and waking with the intention of arising
Nocturia	Waking one or more times to void during the hours of sleep; each void is preceded and followed by sleep
Total urine volume (TUV)	Total volume of urine produced during a 24-hour period
First-morning void	The first void after waking with the intention of rising
Nocturnal urine volume (NUV)	Total volume of urine passed during the night, including the first-morning void
Maximum voided volume (MVV)	The largest single voided volume in a 24-hr period
Nighttime frequency or actual number of nightly voids (ANV)	The number of voids recorded from the time the individual goes to bed with the intention of sleeping, to the time the individual wakes with the intention of rising
Nocturia index (Ni)	Ni = NUV/MVV; when Ni > 1 NUV exceeds maximum storage capacity and nocturia or enuresis occurs
Nocturnal polyuria	Nocturnal volume >20%-33% of total 24-hr volume (age dependent), other definitions include: NUV >6.4 mL/kg NUV >0.9 mL/min (54 mL/h) NUV >1.5 mL/min (>90 mL/h)
Nocturnal polyuria index (NPi)	NPi = NUV/TUV; if NPi > 0.20-0.33 (age dependent); patient has nocturnal polyuria
Predicted number of nightly voids (PNV)	PNV = Ni − 1, used for calculation of NBCi
Nocturnal bladder capacity index (NBCi)	NBCi = ANV − PNV; NBCi > 0 indicates that nocturia will occur at voided volumes < MVV. NBCi >2 associated with severe nocturia
Global polyuria	24-hour voided volume of >2.8 L in a 70-kg adult (>40 mL/kg)
Nocturnal enuresis	Voiding occurring during sleep

BJU Int 90(Suppl 3):16–17, 2002.

Prevalence of nocturia



EMJ Urol. 2017;5[1]:32-37.

Association with early mortality

- Nocturia affects both quality and quantity of life.
- Nocturia affects sleep efficiency and sleep latency.
- Nocturia can be a symptom of serious systemic illnesses including hypertension, diabetes, heart disease, and kidney disease.

Association with early mortality

- Nocturia as a risk factor for future development of both metabolic syndrome and early mortality as a result of its proxy effect on sleep impairment.

  Hall et al., 2008; Pesonen et al., 2014

- Nocturia is among the LUTS most strongly associated with falls and is a risk factor for hip fractures (regardless of age).

  Parsons et al., 2009

Evaluation

- The cause of nocturia can be multifactorial and complex
  - The evaluation of nocturia should be focused and systematic, beginning with a complete history and physical examination.

- History of medication use
  - Lithium: the possibility of global polyuria as a result of drug-induced nephrogenic diabetes insipidus.

- A frequency-volume chart or a voiding diary is the single most useful tool in evaluating and classifying the cause of nocturia.

Evaluation

- Physical findings
  - peripheral edema resulting from cardiac disease, nephrotic syndrome, or venous insufficiency
  - obesity and short neck might be suggestive of obstructive sleep apnea

- Risk factors for nocturia
  - Men: snoring, obesity, antidepressant usage, restless legs syndrome, and prostate cancer
  - Women:obesity, urinary urgency, snoring, diabetes, restless legs syndrome, and coronary artery disease

Evaluation

- Nighttime is defined as the period between going to bed with the intention of sleeping and awakening with the intention of arising.

van Kerrebroeck et al., 2002

- **Nocturnal urine volume (NUV)**
  - **T**he sum of all nocturnally voided volumes plus that of the first-morning void, because the urine in the latter void is produced during the hours of sleep.

- **Nocturnal polyuria index (NPi)**
  - The percentage of urine produced during nighttime (calculated as NUV/total 24-hour urine volume).

Evaluation

- In healthy adults 21 to 35 years of age, the mean NPi = 0.14 versus those 65 years of age and older, whose mean NPi = 0.34.

Rembratt et al., 2002

- ICS has defined nocturnal polyuria:
  - NPi greater than 20% (0.20) in young adults and greater than 33% (0.33) in patients older than 65 years of age when 24-hour urine production is within normal limits.

van Kerrebroeck et al., 2002

Evaluation

- Global polyuria also can cause an individual to awaken to void during the hours of sleep.

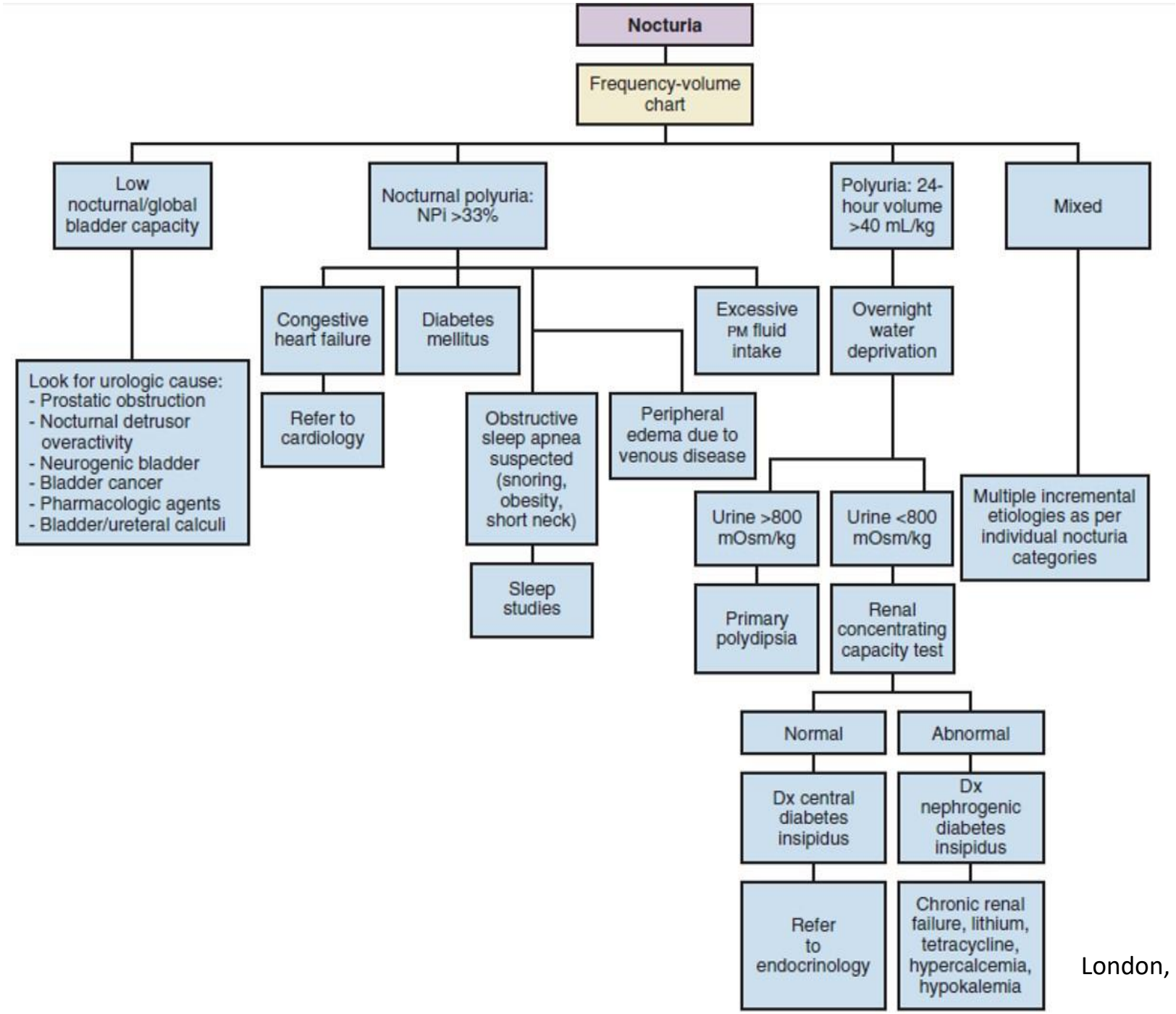
- Global polyuria is defined as 24-hour urine output greater than 40 mL/kg causing both daytime urinary frequency and nocturia .

Oelke and van Kerrebroeck, 2012

Diary-Based Classification of Nocturia

NOCTURIA CATEGORY	UNDERLYING MEDICAL CONDITIONS
Nocturnal polyuria	Excessive nighttime fluid intake Peripheral edema Obstructive sleep apnea Diabetes mellitus Congestive heart failure
Diminished global or low nocturnal bladder capacity	Ureteral calculi Bladder calculi Pharmacologic agents Anxiety disorders Learned voiding dysfunction Cancer of bladder, prostate, or urethra Neurogenic bladder Nocturnal detrusor overactivity Prostatic obstruction
Global (24-hour) polyuria	Primary polydipsia Diabetes insipidus Diabetes mellitus

London, 2012, UNI MED Verlag AG, p 72



London, 2012, UNI MED Verlag AG, p 73

Nocturnal Polyuria

Epidemiology and Causes

- Among patients with nocturia, nocturnal polyuria seems to be quite common.

- In a population recruited for a pharmacologic study of nocturia, 819 (88%) of 934 subjects with nocturia (more than two voids per night) who completed a voiding diary had nocturnal polyuria (NUV >33% of 24-hour volume).

- The physiology of renal water handling is relevant to an understanding of the pathophysiology of nocturnal polyuria and its treatment.

Nocturnal Polyuria

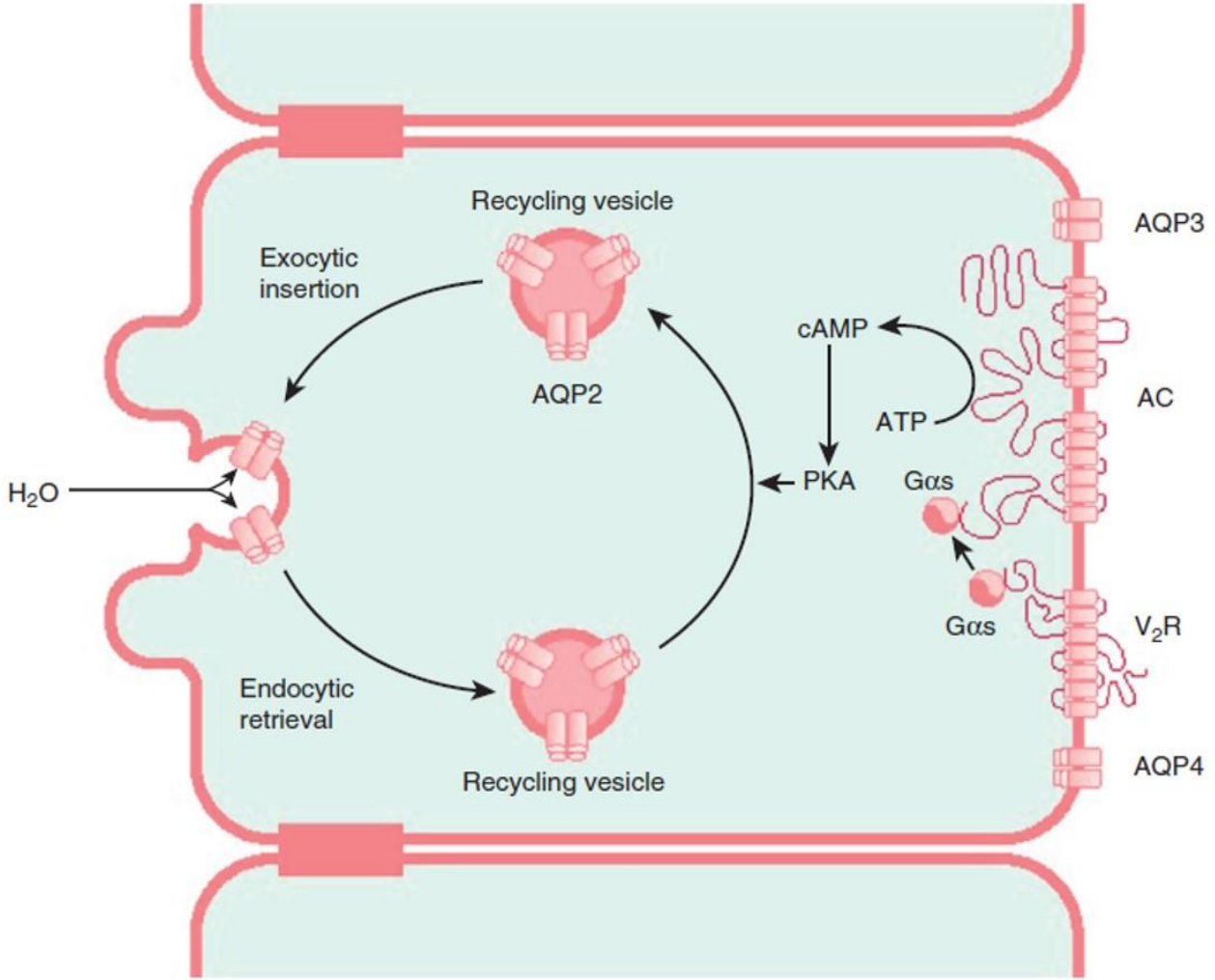
Epidemiology and Causes

- The major determinant of body water is arginine vasopressin (AVP)-regulated water excretion by the kidneys.

- AVP is stimulated by high serum osmolality, hypovolemia, and angiotensin II, and is inhibited by natriuretic peptides and negative feedback via baroreceptors.

- AVP causes vasoconstriction via V1a receptors and causes renal reabsorption of water through its action on V2 receptors.

AVP regulation of water reabsorption from renal tubular cells



BJU Int 90[Suppl 3]:1–6, 2002

Nocturnal Polyuria

Epidemiology and Causes

- Other factors that inhibit antidiuretic hormone (ADH) and cause diuresis (inhibit water reabsorption)
  - Prostaglandin E2 (PGE2), atrial natriuretic peptide (ANP), hypercalcemia, hypokalemia, lithium, and tetracyclines

- Obstructive sleep apnea (OSA) is a common cause of nocturnal polyuria.
  - Increased airway pressure leads to hypoxia -> pulmonary vasoconstriction-> increased right atrial transmural pressure -> increase in ANP production -> increased renal sodium and water excretion.

Nocturnal Polyuria

Management

- Treating nocturnal polyuria should begin with a conservative approach.
  - Cessation of fluid intake 4 hours before bedtime
  - The use of compressive lower extremity stockings
  - Administration of diuretics in the mid-afternoon for edema states

- Individuals who have insomnia and nocturia may benefit from behavioral therapy directed at improving the insomnia.

Drug Effects Causing Nocturia

INCREASED URINE OUTPUT
Diuretics
SSRIs (block ADH secretion)[a,b]
Calcium channel blockers (increase ANP, block sodium reabsorption in PCT)[c]
Tetracycline (attenuates ADH via decreases in cAMP accumulation and action)[d]
Lithium (decreases AQP2)[e]

INSOMNIA AND CNS EFFECTS
CNS stimulants
- Dextroamphetamine
- Methylphenidate

Antihypertensives
- α-Blockers
- β-Blockers
- Methyldopa

Respiratory
- Albuterol
- Theophylline

Decongestants
- Phenylephrine
- Pseudoephedrine

Hormones (corticosteroids, thyroid)
Psychotropics
- MAOIs
- SSRIs
- Atypical antidepressants

Dopaminergic agonists (carbidopa)
Antiepileptics (phenytoin)

DIRECT LOWER URINARY TRACT EFFECTS
Ketamine
- Direct bladder toxin

Tiaprofenic acid (Surgam)
- Toxic cystitis

Cyclophosphamide

Campbell Walsh Wein Urology, 12th Edition

- Imipramine (tricyclic antidepressant)
  - Nonsubtype-selective antimuscarinic effects, also shown to have varied effects in modulating AVP release
  - Potentiating renal proximal tubular sodium and water reabsorption in children.

- Nocturia episode reduction in patients with nocturnal polyuria was not significant in antimascarinics use.

Brubaker and Fitzgerald, 2007)

Nocturnal Polyuria

Management

- Treatment of OSA with continuous positive airway pressure (CPAP) can improve nocturia.

- Desmopressin (DDAVP) is a selective V2-receptor agonist that retains the antidiuretic properties of vasopressin but lacks its unwanted pressor activity.

  Vilhardt, 1990

- Desmopressin currently has the following recommendations for the treatment of nocturia:
  - **International Consultation on Incontinence(ICI)**: Grade A (level 1 evidence) (Andersson et al., 2013)
  - **European Association of Urology (EAU)**: Grade A (level 1b evidence) (Gravas et al., 2016)

Nocturnal Polyuria

Management

- Hyponatremia is a well-known undesired effect of desmopressin.

- Women appear to be more sensitive to desmopressin than men in terms of effects on nocturnal urine production and duration of action.

Juul et al., 2011
Yamaguchi et al, 2013

- Current thinking is that desmopressin would be the most appropriate therapy for patients with nocturia related to nocturnal polyuria.

Nocturnal Polyuria

Management

- Patients with nocturnal polyuria unrelated to specific causes such as peripheral edema, cardiopulmonary disease, or sleep apnea may benefit from empiric treatment with desmopressin.

- Desmopressin is associated with increased risk
  - Clinically significant hyponatremia in elderly patients (>65 years)
  - Borderline pretreatment hyponatremia
  - Impaired renal function
  - Small body habitus.

Pharmacotherapeutic Agents Used to Treat Nocturnal Polyuria

DRUG NAME	DOSE	SIDE EFFECT(S)	CONTRAINDICATION(S)
Furosemide[a]	40 mg PO 6 h before sleep (Dose range 20–80 mg PO in adults. The study mentioned in this text used only 40 mg in the context of nocturia.)	Anorexia Nausea/vomiting Constipation Cramping Diarrhea Blurred vision Hearing loss Tinnitus Headache Orthostatic hypotension Hypokalemia Dehydration Metabolic alkalosis Muscle cramps SLE exacerbation	Hypersensitivity Anuria Hepatic coma Hypovolemia Severe hypokalemia
Imipramine[a]	10 mg, 25 mg, 50 mg (Dose range: 10–75 mg PO qhs)	Prolongs PR interval Prolongs QRS interval Prolongs QTc interval Increases heart rate Lowers T-wave amplitude Torsades de pointes Sudden death	Hypersensitivity Usage of MAOI within 14 days Acute recovery period after MI
Desmopressin[a]	Intranasal: 10 μg/spray; max 40 μg/day (central DI indication only) Noctiva[b] Starting dose: 1.5 μg for patients <65 years. For patients ≥65 or <65 years at increased risk for hyponatremia, starting dose: 0.75 μg Oral: 0.1-mg tablets; max 0.6 mg/day for PNE Melt: 60-, 120-, 240-μg melt tabs Melt "low dose": 25 μg (women) and 50–100 μg (men)	Water intoxication Hyponatremia Flushing Diarrhea Mild abdominal cramps Nausea Increased SGOT Thrombosis Cough Dyspnea Drowsiness Dizziness Headache Abnormal thinking Seizures	Hypersensitivity CrCl <50 mL/min Hyponatremia History of hyponatremia Von Willebrand disease, type IIB Polydipsia Uncontrolled HTN Concomitant use of loop diuretics Concomitant use of systemic or inhaled glucocorticoids Known or suspected SIADH secretion

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Diminished Global and Nocturnal Bladder Capacity

Causes

- Intravesical obstruction
- Idiopathic nocturnal detrusor overactivity (NDO)
- Neurogenic bladder, cystitis (bacterial, interstitial, tuberculous, radiation)
- Cancer of the bladder, prostate, or urethra.

Diminished Global and Nocturnal Bladder Capacity

Management

- Treating bladder outlet obstruction (BOO)
  - Lowering postvoid residual (PVR) volume
  - Increasing functional bladder capacity
  - Reducing global urinary frequency

- α-Blockers, 5-ARIs, antimuscarinics, and antimuscarinics plus α-blockers have been found to result in statistically but questionably clinically significant reductions in nocturia episodes.

Diminished Global and Nocturnal Bladder Capacity

Management

- When 5-ARIs and α-blockers are used in combination, they have the same degree of success as α-blockers alone.

- The optimal group to treat with medications that target the bladder and the prostate appear to be those who have a large number of nocturia episodes (mostly as a response to severe urgency) unrelated to nocturnal polyuria.

Polyuria

Etiology

- Polyuria is defined as 24-hour urine output greater than 40 mL/kg and thus must be diagnosed through use of frequency-volume charts.

- Polyuria is associated with excessive oral intake of fluids (polydipsia).
  - Urinary frequency both day and night because of the global overproduction of urine in excess of bladder capacity.

- Common underpinnings of polyuria
  - Uncontrolled diabetes mellitus
  - Diabetes insipidus
  - Primary polydipsia (dipsogenic, caused by an abnormality of the thirst mechanism, and psychogenic).

Polyuria

Etiology

- Diabetes insipidus is a disorder of water balance in which inappropriate excretion of water leads to polydipsia in an effort to prevent circulatory collapse.

- Diabetes insipidus can be central or nephrogenic.

- Central diabetes insipidus occurs when there is a deficiency in the synthesis or secretion of endogenous ADH.

- Nephrogenic diabetes insipidus is diuresis in the setting of normal ADH secretion, but the kidneys do not respond appropriately to the hormone, as in some patients with chronic kidney disease.

Polyuria

Management

- Patients may benefit from water restriction during the day and night.
- A patient with primary (dipsogenic or psychogenic) polydipsia will have normal urine osmolality on water deprivation tests.
- Dipsogenic polydipsia is associated with a history of a central neurologic abnormality such as a history of brain trauma or radiation.
- Psychogenic polydipsia is a long-term behavioral or psychiatric disorder.

Polyuria

Management

- Diabetes mellitus: controlling glycosuria may improve the polyuria.
- Central diabetes insipidus: may be treated with synthetic vasopressin analogues.
- Patients without diabetes insipidus who are found to have polydipsia: compulsive water drinkers may benefit from psychotherapy.

Weiss, 2012