

Overactive Bladder Presented by

Moise Mamouzette, MD

**Department of Obstetrics and Gynecology
North Shore-Long Island Jewish Health System
Franklin Hospital Medical Center
Valley Stream, New York**

Definition

INCONTINENCE:

Involuntary loss of urine or stool in sufficient amount or frequency to constitute a social and/or health problem. A heterogeneous condition that ranges in severity from dribbling small amounts of urine to continuous urinary incontinence with concomitant fecal incontinence

How Common is Incontinence?

- **Prevalence increases with age (but it is not a part of normal aging)**
- **25-30% of community dwelling older women**
- **10-15% of community dwelling older men**
- **50% of nursing home residents; often associated with dementia, fecal incontinence, inability to walk and transfer independently**

Urinary Incontinence is Often Under-Diagnoses and Under-Treated

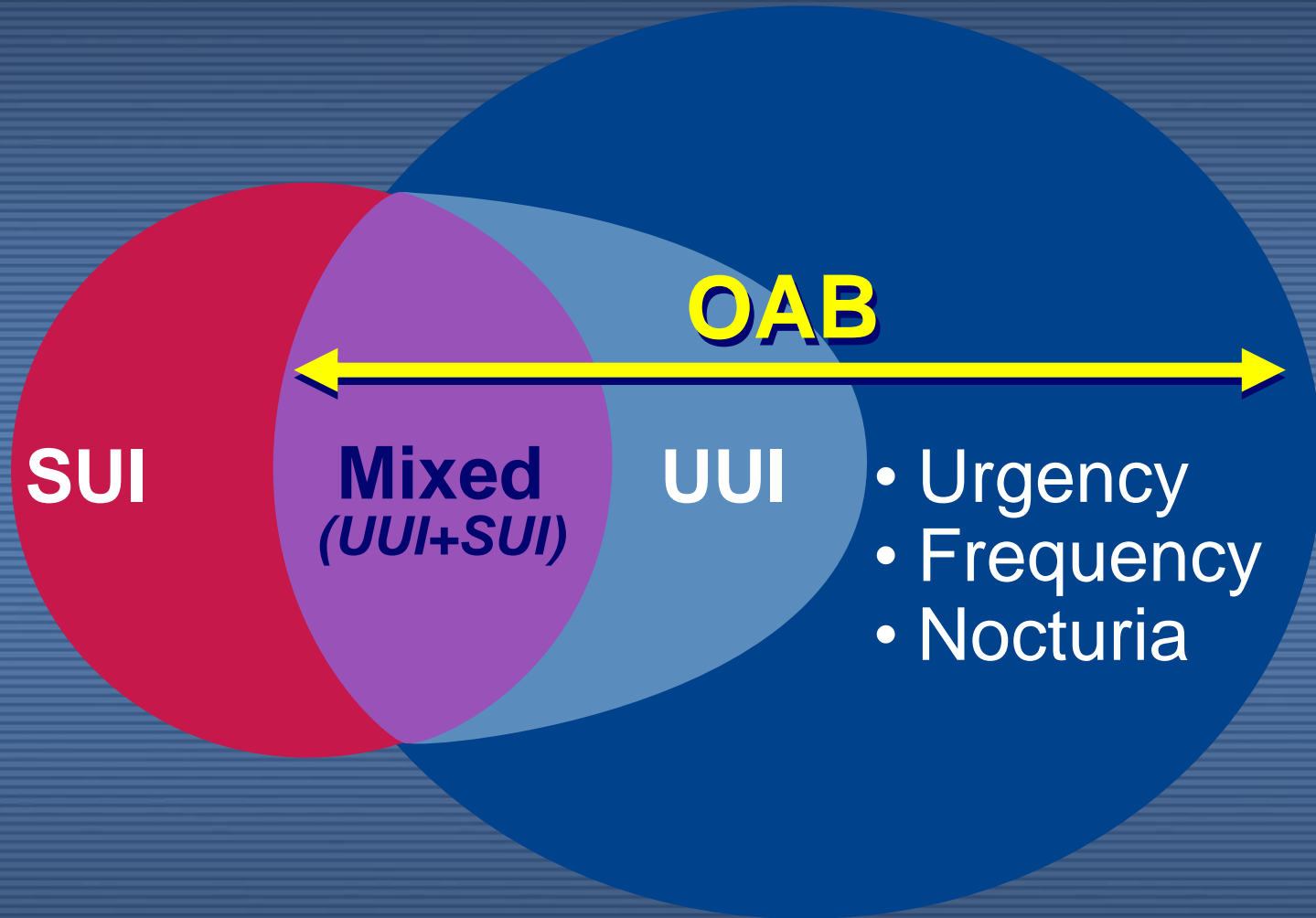
- **Only 32% of primary care physicians routinely ask about incontinence**
- **50-75% of patients never describe symptoms to physicians**
- **80% of urinary incontinence can be cured or improved**

2002 ICS Terminology: Overactive Bladder

OAB defined based on symptoms

- Urgency, with or without urge incontinence, usually with frequency and nocturia
- In the absence of pathologic or metabolic conditions that might explain these symptoms

Spectrum of Urinary Incontinence and OAB

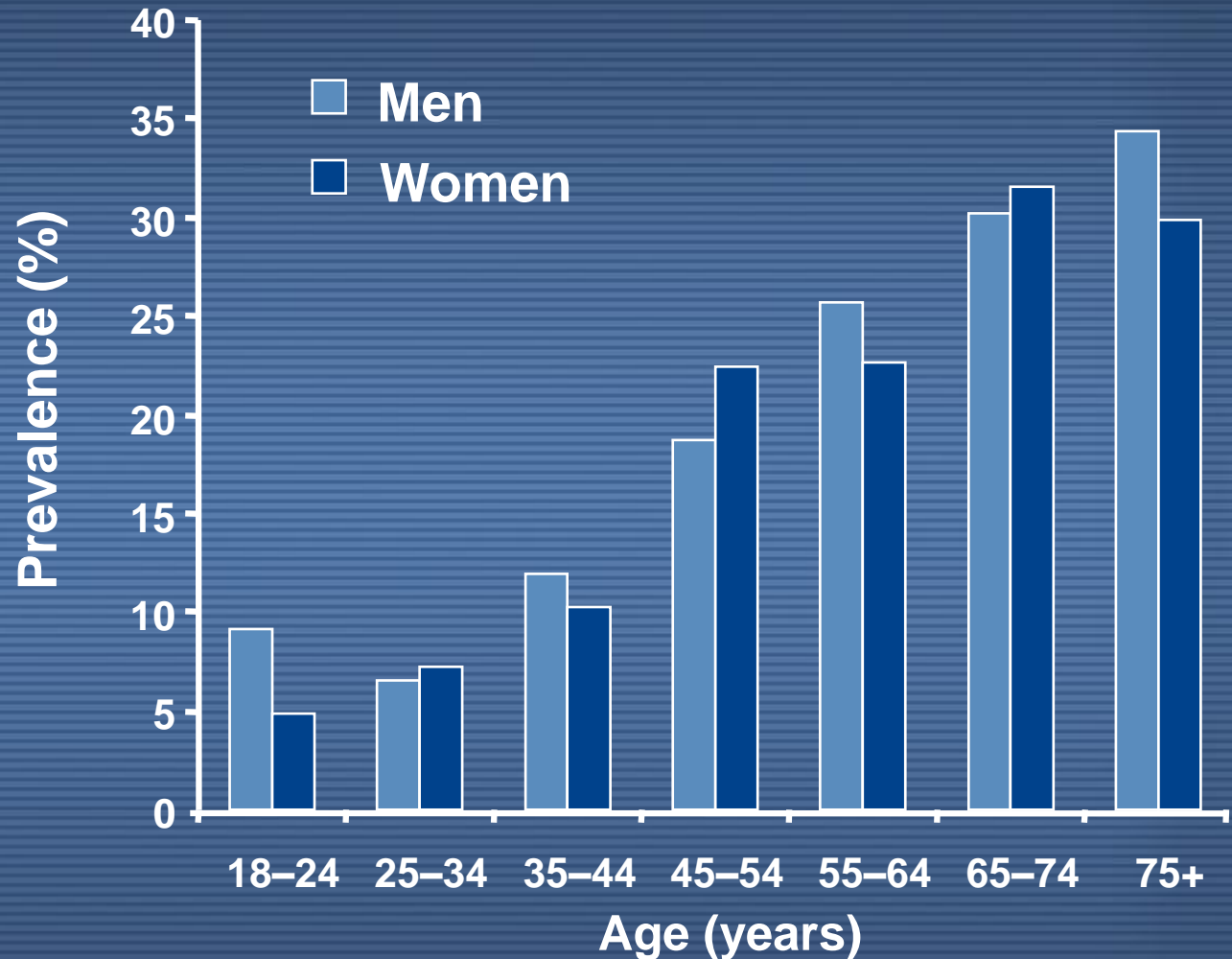


National Overactive Bladder Evaluation (NOBLE) Program

- **Large US prevalence study for OAB**
 - **November 2000–January 2001**
 - **17,231 households contacted**
 - **5,204 completed interviews**
 - **4,160 controls, 1,044 cases**
- **Conclusions**
 - **Over 33 million OAB sufferers (16.6% of population)**
 - **63% OAB dry; 37% OAB wet**
 - **OAB significantly impairs health related quality of life, even in those without urge incontinence**

Prevalence of OAB in the US

- Overall, 16.6% had symptoms of OAB
- Prevalence of OAB increased with age



Potential Impact of OAB on Quality of Life

Physical

- Limitations or cessation of physical activities

Psychological

- Guilt/depression
- Loss of self-esteem
- Fear of:
 - being a burden
 - lack of bladder control
 - urine odor

Sexual

- Avoidance of sexual contact and intimacy

Quality of Life

Occupational

- Absence from work
- Decreased productivity

Social

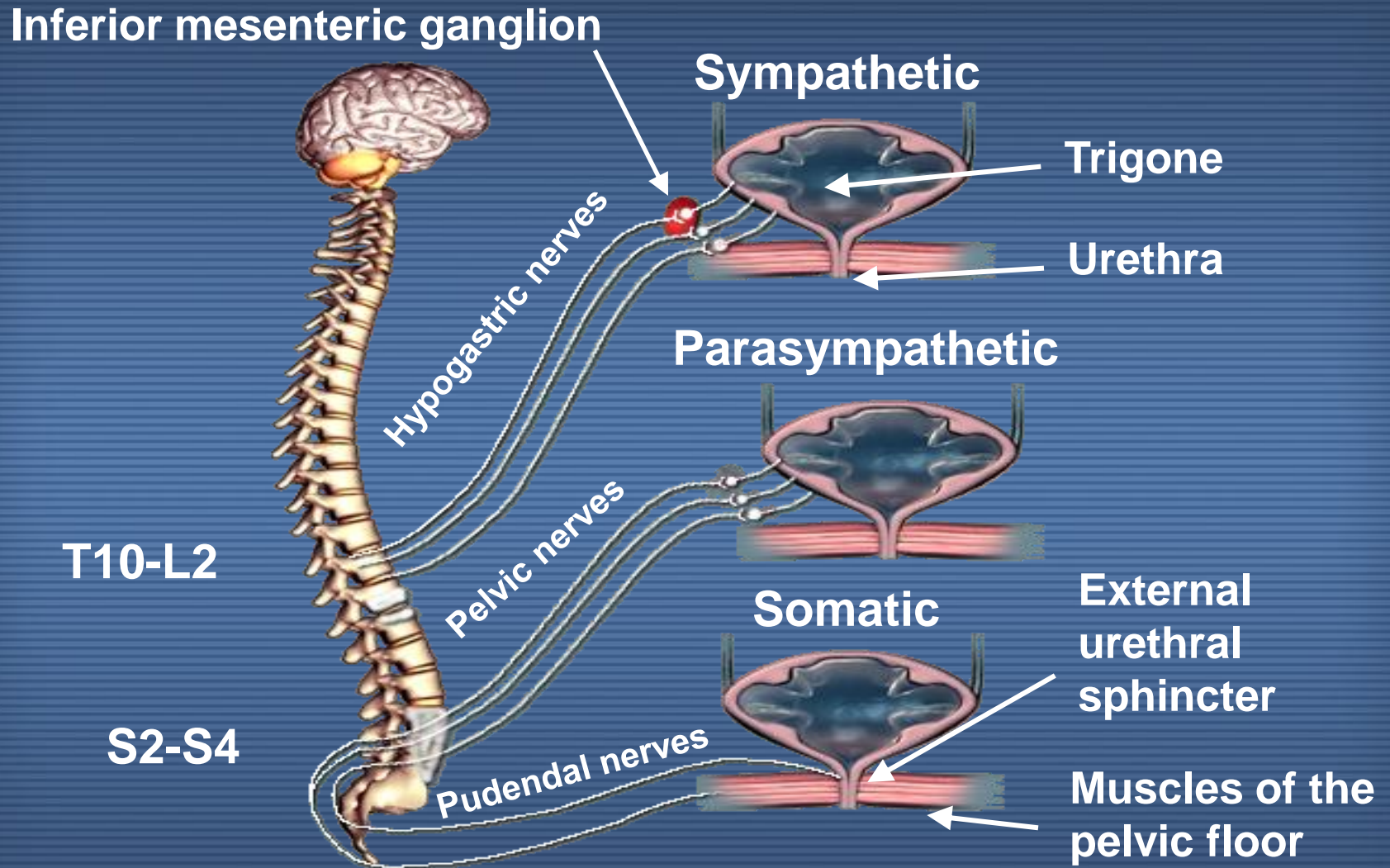
- Reduction in social interaction
- Limiting and planning travel around toilet accessibility

Domestic

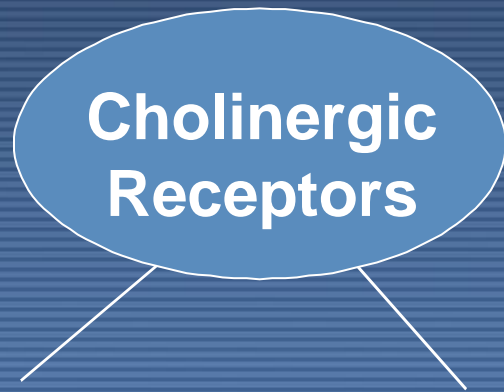
- Requirements for specialized underwear, bedding
- Special precautions with clothing

Physiology and Pathophysiology

Innervation of the LUT



Neurotransmitter Receptors



Nicotinic

Muscarinic

α-Adrenergic

β-Adrenergic

M₁ M₂ M₃ M₄ M₅

α₁ α_{2...} α_n

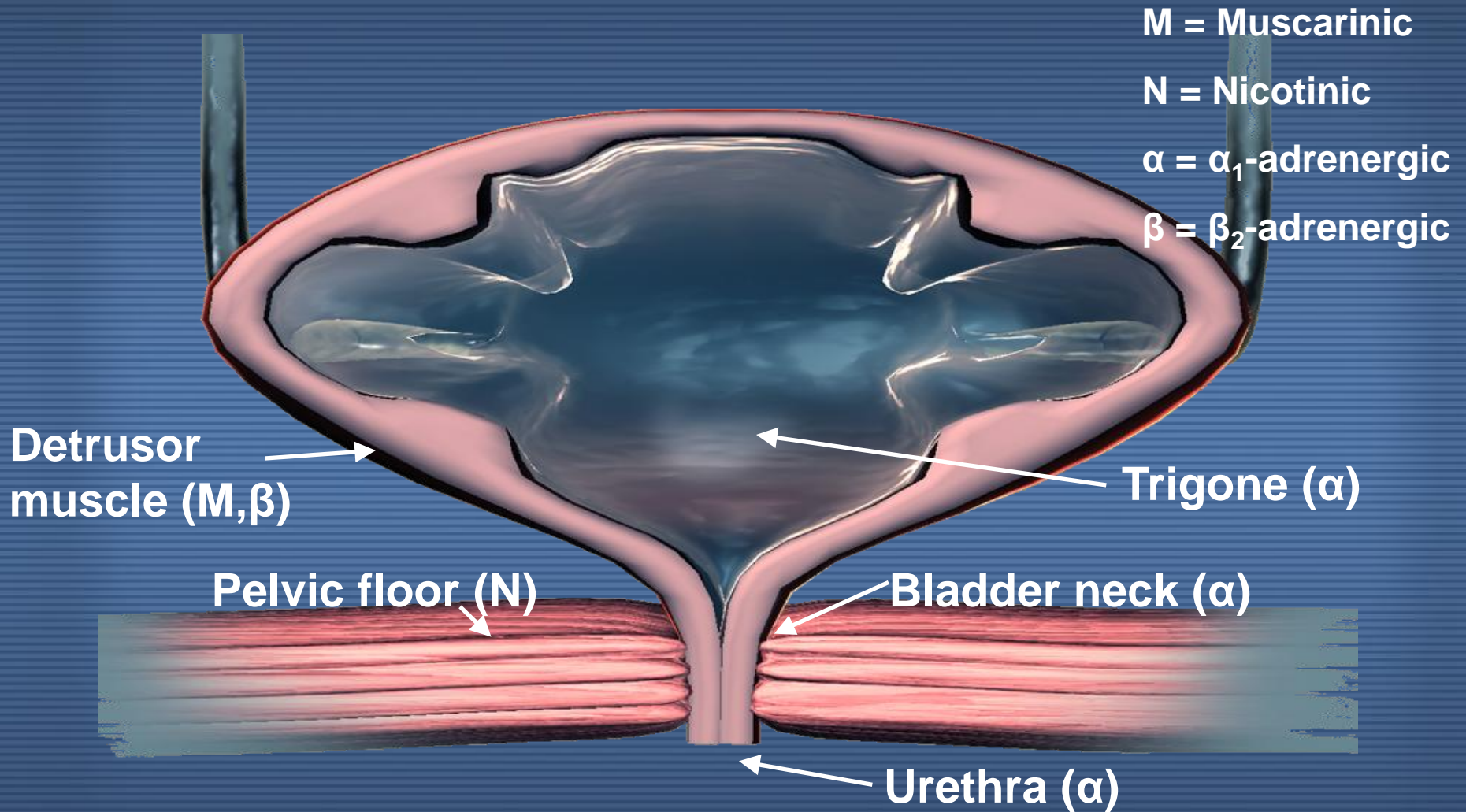
β₁ β_{2...} β_n

Subtypes

Subtypes

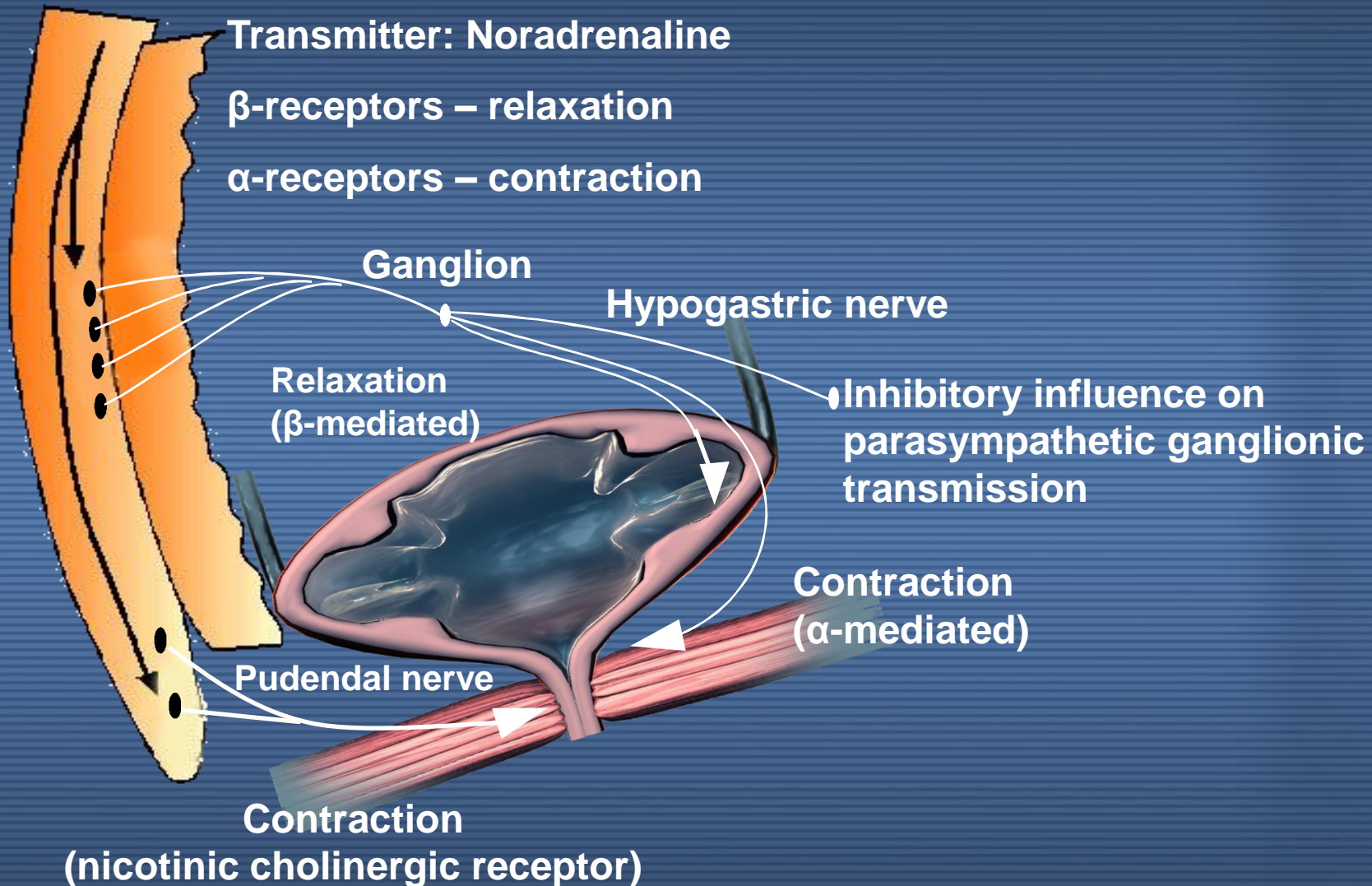
Subtypes

Distribution of Cholinergic and Adrenergic Receptors in the LUT



Adapted from Abrams P, Wein AJ. *The Overactive Bladder: A Widespread and Treatable Condition*. Erik Sparre Medical AB; 1998.

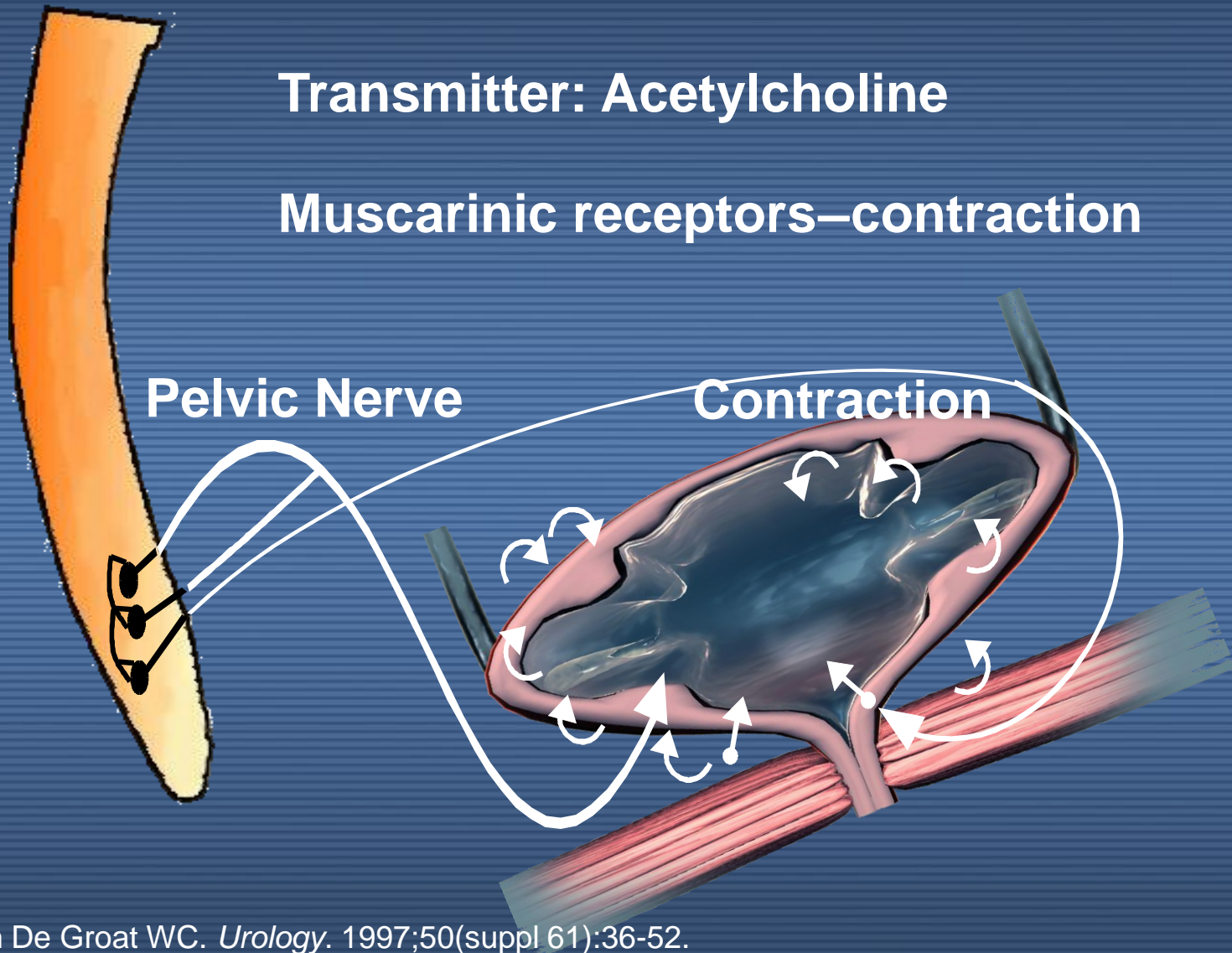
Sympathetic and Somatic Innervation and Receptors



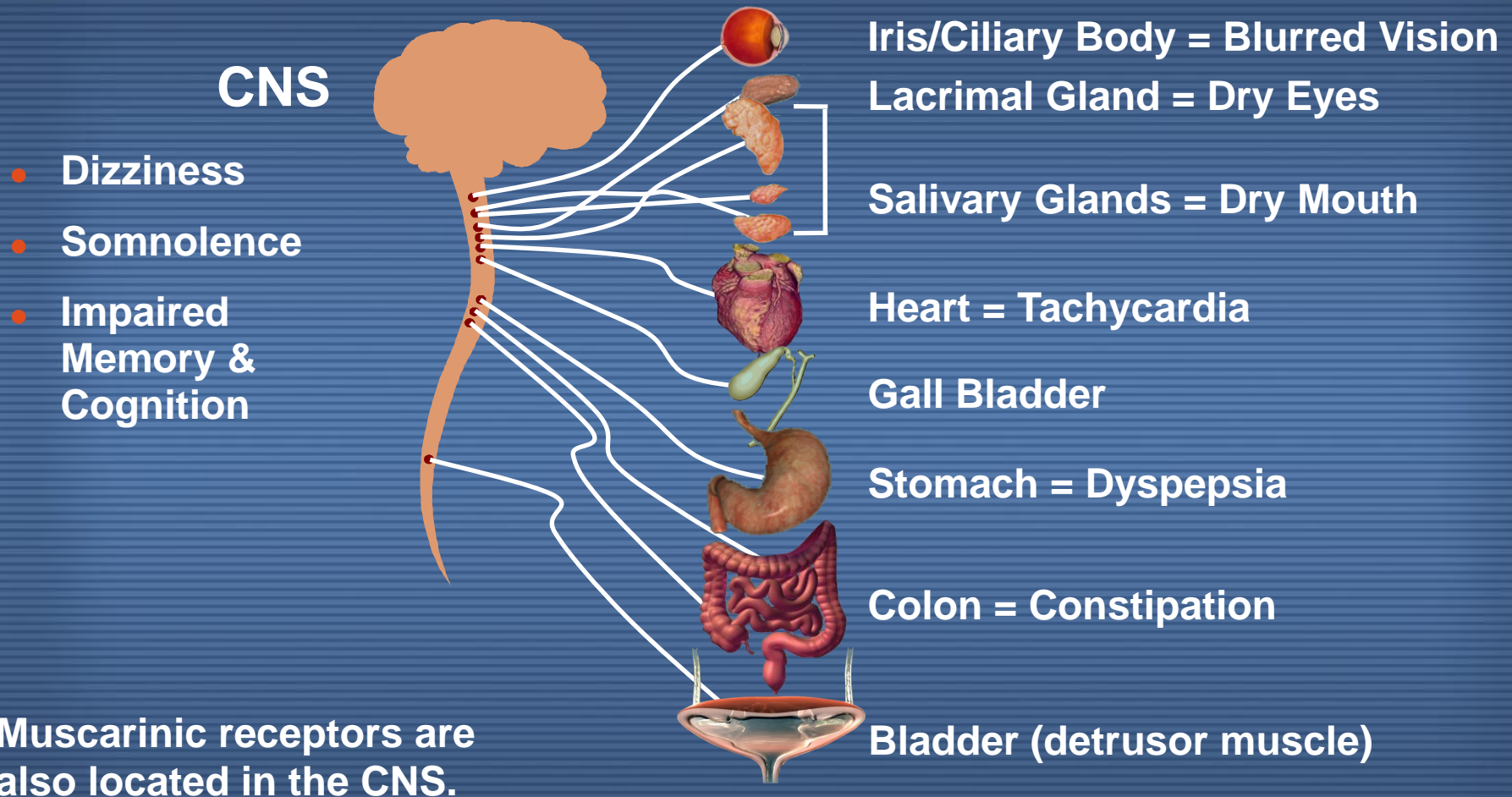
Parasympathetic Innervation and Receptors

Transmitter: Acetylcholine

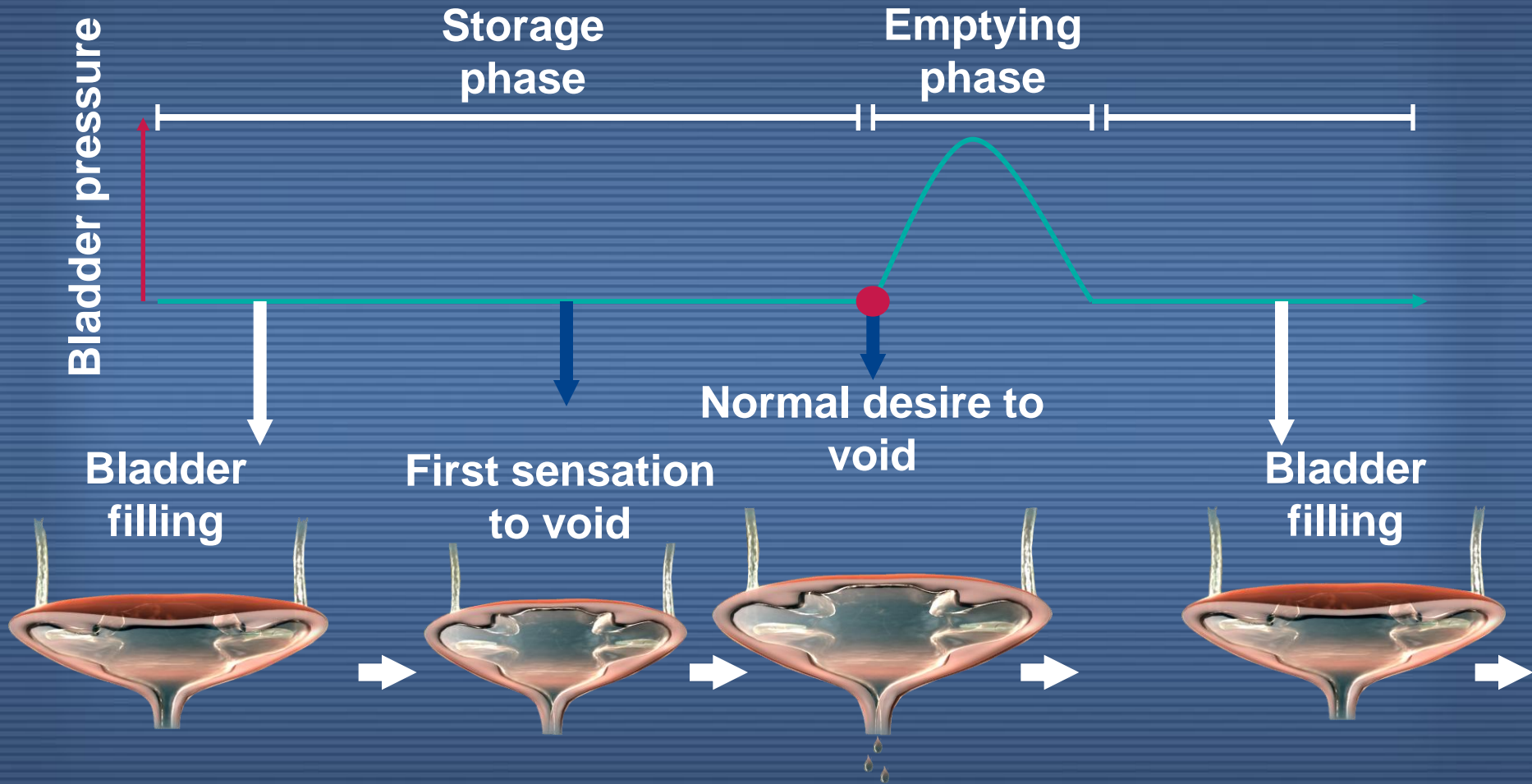
Muscarinic receptors—contraction



Distribution of Muscarinic Receptors in Target Organs of the Parasympathetic Nervous System

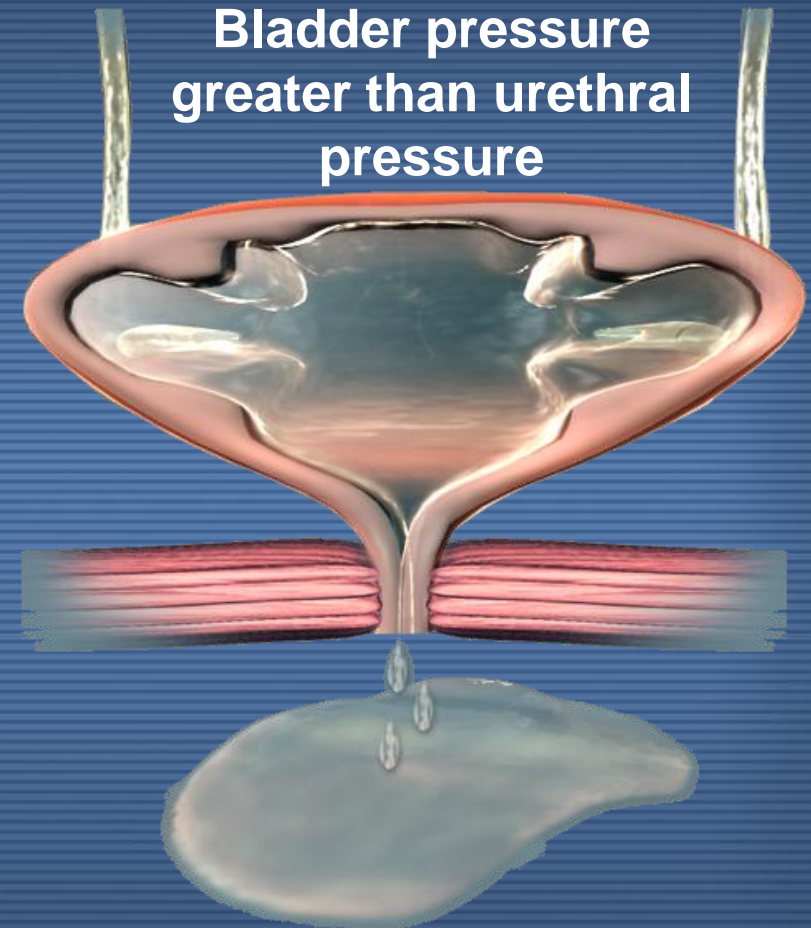


The Micturition Cycle



Characteristic Symptoms of OAB

- Frequency and Urgency
- Urge incontinence



Overactivity: Neurogenic or Myogenic?

- Spinal, supraspinal disease (neurogenic)
- Bladder outlet obstruction (myogenic or neurogenic?)
- Other (myogenic or neurogenic?)
- Aging

Neurogenic Etiology of OAB

- **Loss of central inhibition**
- **Increased LUT afferent input**
- **Enhancement of excitatory neurotransmission in the micturition reflex pathway**
- **Reduced suprapontine inhibition**
- **Damaged axonal paths in spinal cord**

Etiology of OAB: Myogenic Theory

- **Local stretching activates certain neurons mediating “urgency”**
- **Normally this does not spread (no detrusor instability)**
- **If increased electrical coupling occurs, a contraction could spread, resulting in unstable contractions and increased pressure**

Types of Urinary Incontinence

Urge

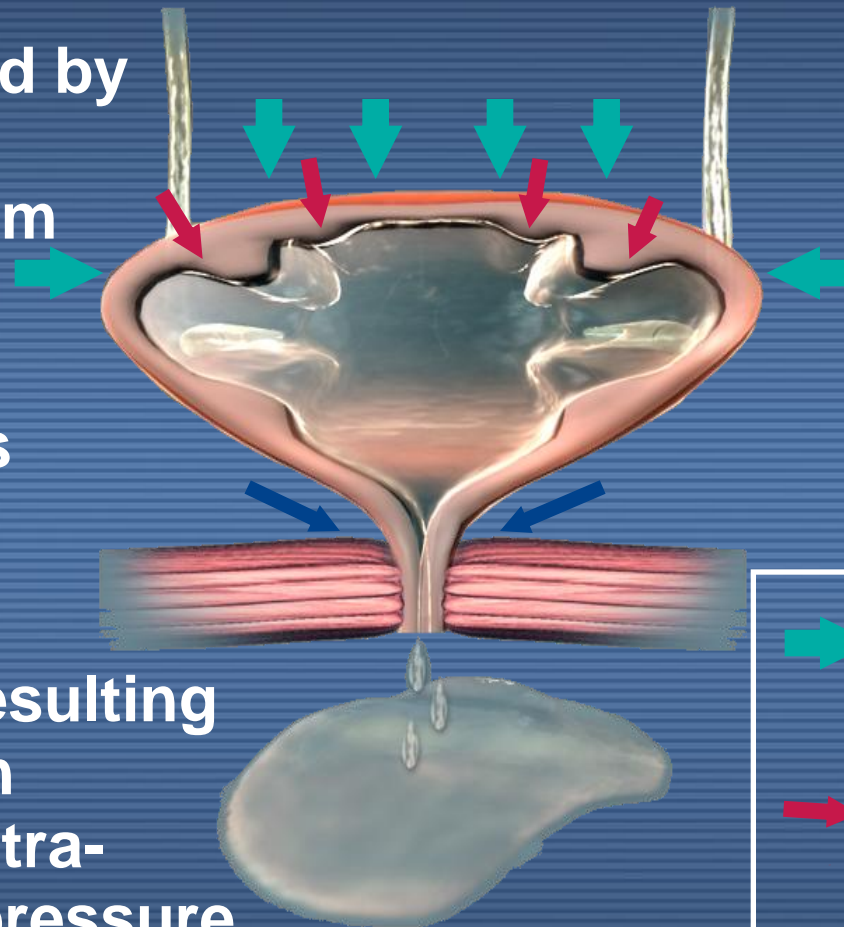
- urine loss accompanied by urgency resulting from abnormal bladder contractions

Stress

- urine loss resulting from sudden increased intra-abdominal pressure (eg, laugh, cough, sneeze)

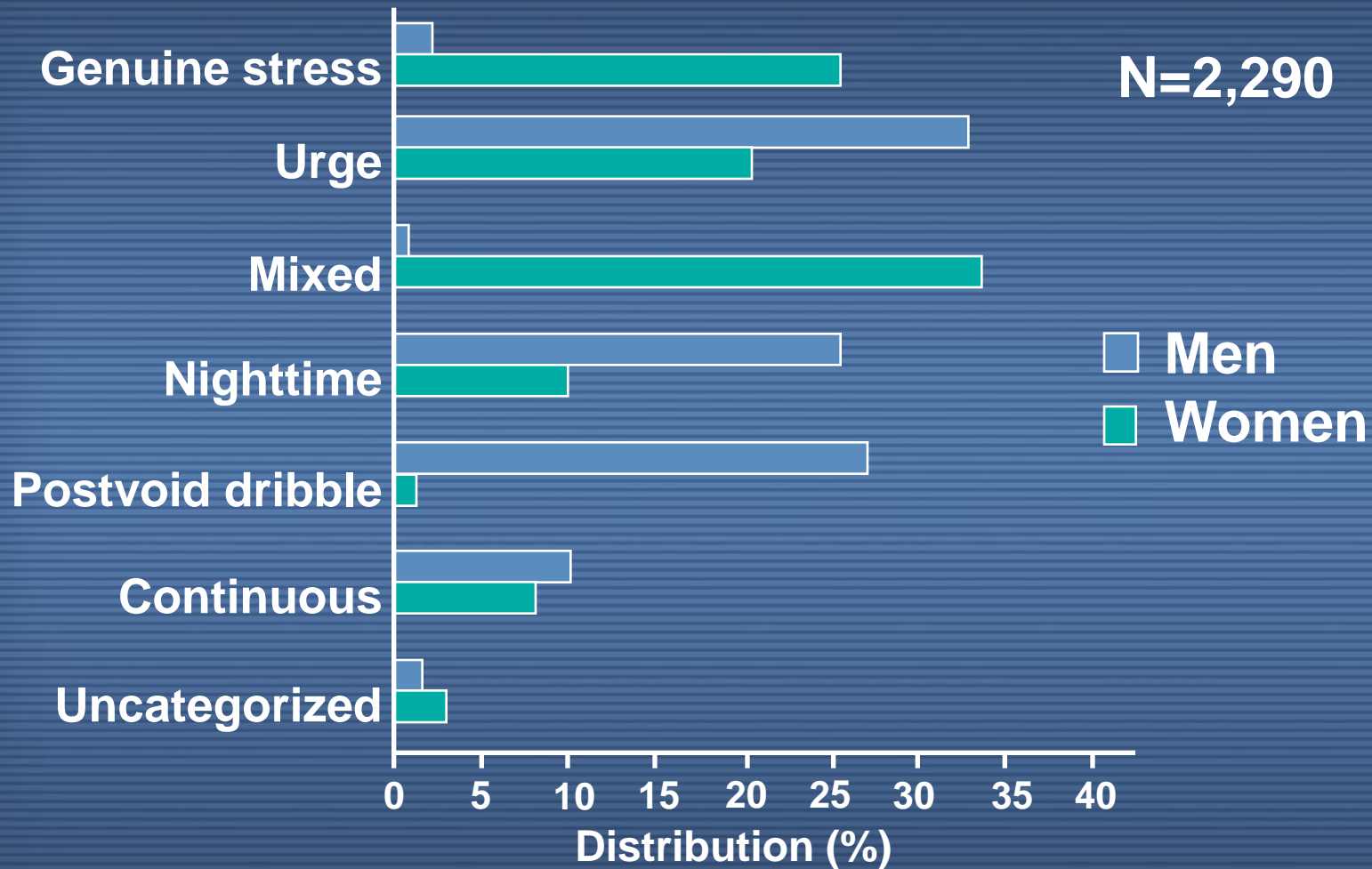
Mixed symptoms

- combination of stress and urge incontinence



- ➡ Sudden increase in intra-abdominal pressure
- ➡ Uninhibited detrusor contractions
- ➡ Urethral pressure

Distribution of Incontinence by Type



Diagnosis of OAB

Diagnosis of OAB

- **A presumptive diagnosis of OAB can be based on**
 - **patient history, symptom assessment**
 - **physical examination**
 - **urinalysis**
- **Initiation of noninvasive treatment may not require an extensive further workup**

A Hidden Condition*

- Many patients self-manage by voiding frequently, reducing fluid intake, and wearing pads
- Nearly two-thirds of patients are symptomatic for 2 years before seeking treatment
- 30% of patients who seek treatment receive no assessment
- Nearly 80% are not examined

* Survey conducted by Gallup Group (European Study).

Barriers to Treatment

- **Patient misconceptions and fears:**

“Part of normal aging or everyday life”

“Not severe or frequent enough to treat”

“Too embarrassing to discuss”

“Treatment won't help”

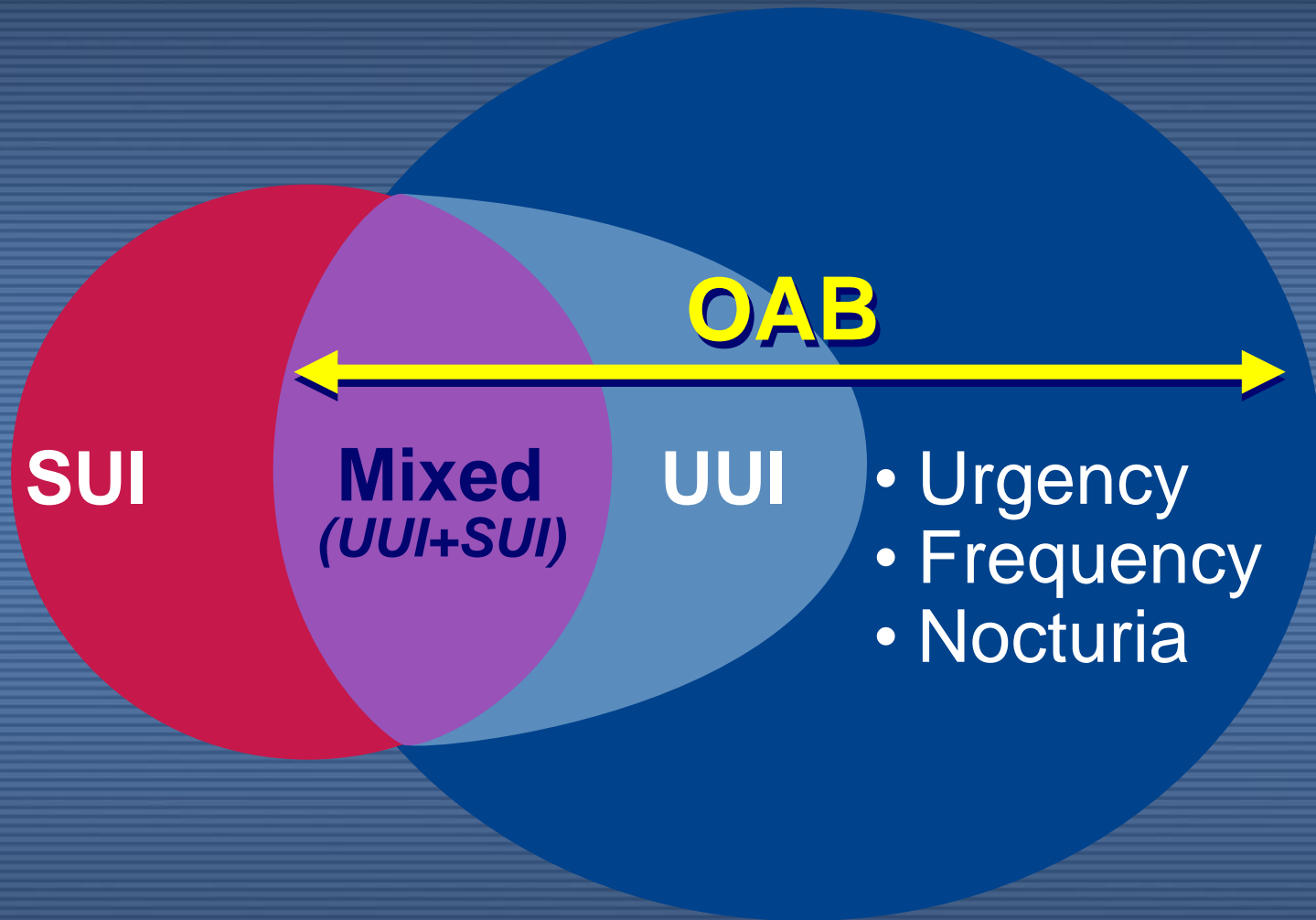
Screening and Diagnosing OAB

“Do you have bladder problems that are troublesome, or do you ever leak urine?”



- **Assess history, symptoms, and test results**
- **Establish a diagnosis**

Spectrum of Urinary Incontinence and OAB



Detrol® LA (tolterodine tartrate extended release capsules) is not indicated for stress incontinence or for the stress component of mixed incontinence.

Questions That May Help Identify Patients Impacted by OAB

- Do you frequently limit your fluid intake or map out restrooms when you are away from home?
- Do you often urinate more than 8 times in a 24-hour period?
- Do you frequently get up 2 or more times during the night to go to the bathroom?
- Do you have uncontrollable urges to urinate that sometimes result in wetting accidents?
- Do you use pads to protect your clothes from wetting?
- Are you bothered or concerned about bladder control?

OAB Screening Can Help Diagnose Other Causes of Bladder Symptoms

- **Local pathology**
 - infection
 - bladder stones
 - bladder tumors
 - interstitial cystitis
 - outlet obstruction
- **Medications**
 - diuretics
 - antidepressants
 - antihypertensives
 - hypnotics & sedatives
 - narcotics & analgesics
- **Metabolic factors**
 - diabetes
 - polydipsia
- **Other factors**
 - pregnancy
 - psychological issues

Differential Diagnosis: Patient History

- Focus on medical, neurologic, and genitourinary symptoms
- Review voiding patterns and symptoms
 - bladder diary
- Review medications
- Evaluate functional and mental status

Differential Diagnosis: Physical Examination

- Perform general, abdominal (including bladder palpation), and neurologic exams
- Perform pelvic and/or rectal exam in females and rectal exam in males
- Observe for urine loss with vigorous cough

Differential Diagnosis: Laboratory Tests

- **Urinalysis**
 - to rule out hematuria, pyuria, bacteriuria, glucosuria, proteinuria
- **Blood work if compromised renal function is suspected or if polyuria (in the absence of diuretics) is present**

Rule Out With Further Inquiry and Examination

- Urinary tract infection
- Overflow from outlet obstruction
- Overflow from underactive detrusor
- Pelvic prolapse
- Atrophic vaginitis
- Pelvic floor dysfunction
- Interstitial cystitis
- Maladaptive behavior
- Diabetes
- Hypoestrogenism
- Bladder disease of unexplained neurogenic origin

Addressing Transient Conditions That Mimic OAB

- **Easily reversible conditions**
 - **urinary tract infection**
- **Associated conditions**
 - **urogenital aging**
 - **bladder outlet obstruction**
 - **prolapse**
 - **stress incontinence**
 - **voiding difficulties**

Medications That May Cause Incontinence

- **Diuretics**
- **Antidepressants**
- **Antihypertensives**
- **Hypnotics**
- **Analgesics**
- **Narcotics**
- **Sedatives**
- **OTC sleep aids and cold remedies**

Differential Diagnosis: OAB and Stress Incontinence

Medical History and Physical Examination


Symptom Assessment

Symptoms	Overactive bladder	Stress incontinence
Urgency (strong, sudden desire to void)	Yes	No
Frequency with urgency (>8 times/24 h)	Yes	No
Leaking during physical activity; eg, coughing, sneezing, lifting	No	Yes
Amount of urinary leakage with each episode of incontinence	Large (if present)	Small
Ability to reach the toilet in time following an urge to void	Often no	Yes
Waking to pass urine at night	Usually	Seldom

When to Consider Further Evaluation

- Symptoms do not respond to initial treatment within 2–3 months
- Hematuria without infection on urinalysis
- Symptoms suggestive of poor bladder emptying (hesitancy, poor stream, terminal dribbling)
- Evidence of unexplained neurologic or metabolic disease

Pharmacotherapy and Invasive Techniques

Management of OAB

- **Pharmacologic**
- **Surgery and other invasive procedures**

Pharmacologic Therapy for the Treatment of OAB

- **Antimuscarinic agents are the mainstay for treating OAB**
- **OAB symptoms reduced by**
 - **inhibition of involuntary bladder contractions**
 - **increased bladder capacity**
- **Treatment can be limited by side effects such as dry mouth, GI effects (eg, constipation), and CNS effects**

Why Treat OAB With Antimuscarinics?

- Detrusor contraction in the normal bladder is primarily mediated via muscarinic receptors
 - release acetylcholine from cholinergic nerves
 - stimulation of muscarinic receptors on the detrusor smooth muscle

Clinical Effects of Antimuscarinic Therapy

- **Stabilizing effect on bladder (detrusor) muscle**
- **Diminishes frequency of involuntary bladder contractions**
- **Increases functional bladder capacity**
- **Delays initial urge to void**

Role of M₂ and M₃ Receptors in Mediating Detrusor Muscle Contraction

- M₂ and M₃ receptors cause contraction in vitro and in vivo
 - M₃ activation stimulates phospholipase C and generates inositol triphosphate (IP₃)
 - M₂ receptors inhibit sympathetically mediated relaxation which promotes more efficient bladder emptying

Efficacy of Anticholinergic Therapy: Uroselectivity

- **Clinical utility of antimuscarinic agents can be limited by their lack of receptor selectivity, which is responsible for classical peripheral anticholinergic side effects:**
 - **dry mouth**
 - **constipation**
 - **blurred vision**
 - **tachycardia**
 - **effects on cognitive function**
 - **somnolence**

Muscarinic Receptors in the Bladder

M₂ receptors may have a more important functional role in certain disease states:

- Aging
- Neuropathic bladders
- Outflow obstruction

Considerations for Choosing a Muscarinic Receptor Antagonist

- Provides efficacy by inhibiting involuntary bladder contractions
- Does not prevent normal micturitions
- Is selective for the bladder over other organs, resulting in reduced side effects and improved tolerability
- Provides clinical effectiveness—the optimal balance of efficacy, tolerability, and compliance/persistency

Anticholinergic Agents

- Atropine (hyoscyamine sulfate)
- Propantheline bromide
- Oxybutynin
- Tolterodine

Atropine (hyoscyamine sulfate)

- Belladonna alkaloid
- Racemic mixture:
 - D-hyoscyamine
 - L-hyoscyamine: responsible for anticholinergic actions
- Controlled studies of effects on bladder hyperactivity are lacking
- International Consultation on Incontinence (ICI):
Not recommended for clinical use based on lack of evidence from controlled, randomized clinical trials

Propantheline Bromide

- **Quaternary ammonium compound with poor absorption**
- **Nonselective muscarinic receptor antagonist**
- **Usual adult dosage is 15 to 30 mg every 4 to 6 hours**
- **Surprising lack of evaluable data for effective treatment of bladder hyperactivity**
- **ICI: Physiologically/pharmacologically effective and recommended based on good-quality randomized controlled trials**

Oxybutynin

- Potent muscarinic receptor antagonist with some degree of selectivity for M₃ and M₁ receptors
- ICI: Physiologically/pharmacologically effective and recommended based on good-quality randomized controlled trials

Oxybutynin Extended-Release

- Achieves steady-state concentration of R- and S-isomers of oxybutynin for 24 hours with a single dose
- Active ingredient identical to that of immediate-release oxybutynin
- Uses osmotic pressure for drug delivery
- FDA approval based on studies that showed equivalent efficacy to immediate-release oxybutynin

Tolterodine

- **Nonselective muscarinic receptor antagonist**
- **Animal studies have shown that tolterodine has demonstrated selectivity for bladder smooth muscle over salivary glands; however, no substantial evidence has supported the clinical relevance of this finding**
- **Approved for the treatment of OAB or unstable bladder in 47 countries, with more than 2 million people treated worldwide**
- **ICI: Physiologically/pharmacologically effective and recommended based on evidence from good-quality randomized trials**

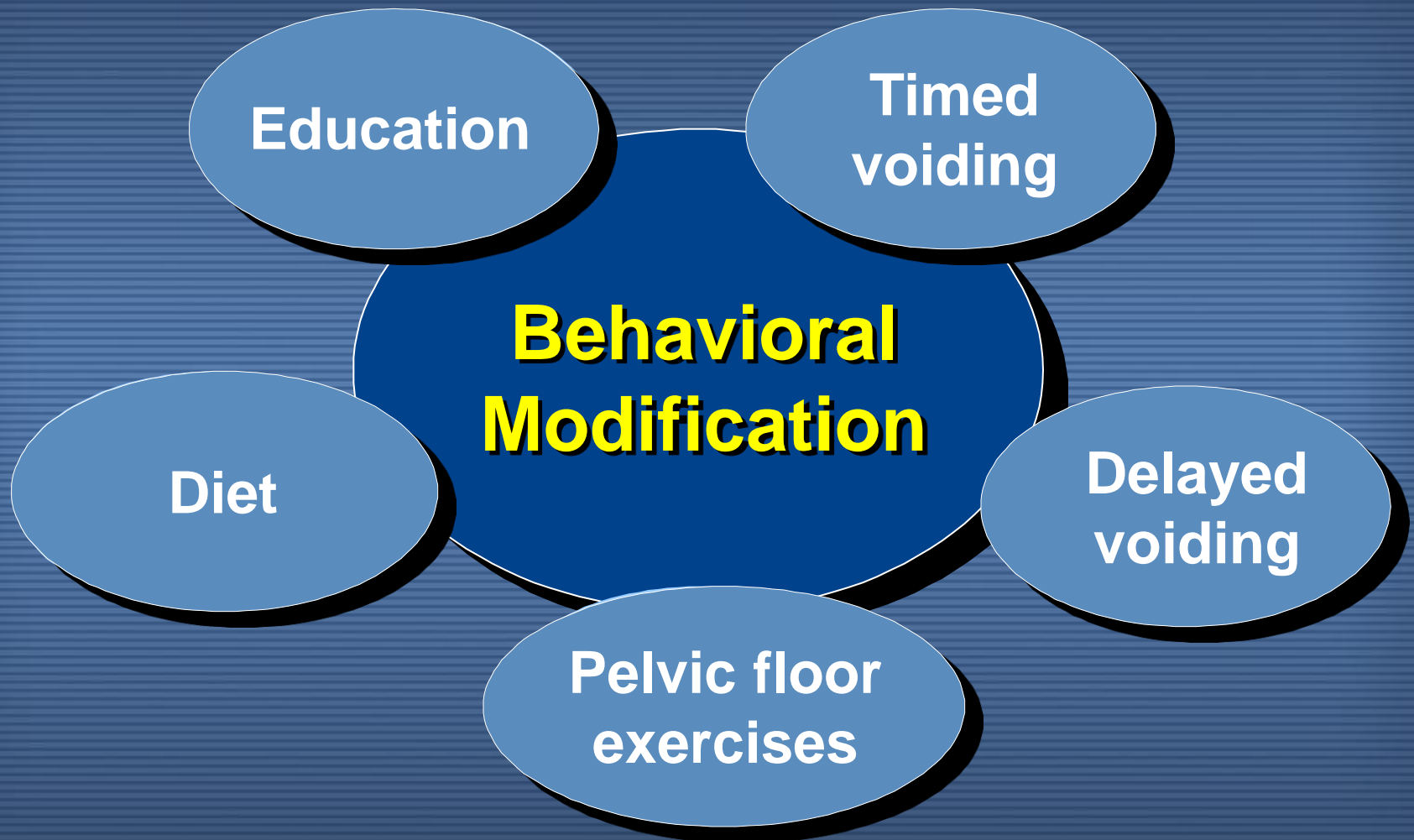
Tolterodine Extended-Release (LA)

- **Once-daily formulation of tolterodine approved for the treatment of OAB**
- **Lower incidence of dry mouth than tolterodine reported in one clinical study**
- **Drop-outs due to adverse events comparable to placebo**
- **Convenience of once-daily dosing**

Surgery and Other Procedures for OAB Management

- **Electrical stimulation to counter detrusor overactivity**
- **Bladder denervation**
- **Transvaginal decentralization (Ingelman-Sundberg)**
- **Enterocystoplasty**
- **Neuromodulation of pudendal nerve via implantable stimulator**

Nonpharmacologic Treatments



Combined Behavioral and Drug Therapy for Urge Incontinence

“Whether drug and behavioral therapy are combined from the onset or used sequentially in a stepped program, the evidence from the present study is that **two interventions combined have a greater potential to enhance outcome than could be achieved by either intervention alone.**”

Antimuscarinic Agents

- Tolterodine (Detrol[®] LA)
- Oxybutynin (Ditropan XL[®], Oxytrol[™] patch)
- Investigational compounds:
 - Solifenacin
 - Darifenacin
 - Trospium