AN OVERVIEW OF OAB

Including evaluation of and management approaches for overactive bladder (OAB)
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THE BLADDER: 
Anatomy and Normal Function
**BLADDER ANATOMY: A REFRESHER**

The bladder wall has 3 layers\(^1\)

- Internal layer (*mucosa*)—the epithelium, which appears smooth when the bladder is full, but contracts into folds when the bladder empties
- Middle layer (*detrusor muscle*)—the detrusor muscle, which is responsible for emptying the bladder
- External layer (*fibroelastic connective tissue*)—this layer expands with the distention of the bladder

The detrusor is the muscular layer of the bladder\(^1,2\)

- It also has 3 layers, with intermingled smooth muscle fibers arranged into inner and outer longitudinal layers and a middle circular layer
- The changes in the thickness and organization of the detrusor layer may contribute to the bladder’s ability to accommodate increasing volumes of urine
- Micturition depends on the contraction of the neurally mediated detrusor

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**References:**

The bladder serves 2 main functions

- To store urine
- To void urine

Filling/storage phase

- This phase makes up the majority of the micturition cycle
- The bladder relaxes to store urine
- The urinary sphincter closes with high resistance to stop urinary flow

Emptying/voiding phase

- The bladder contracts to void urine
- The urinary sphincter opens to allow urinary flow

NEUROLOGIC CONTROL OF THE BLADDER: THE AUTONOMIC NERVOUS SYSTEM

- Regulation of bladder storage and voiding involves both sympathetic and parasympathetic control.
- Storage and voiding of the bladder are primarily regulated by 2 neurotransmitters—norepinephrine and acetylcholine—respectively.
- Norepinephrine, released from the sympathetic nerves, activates certain adrenergic receptors—\( \beta_3 \)-ARs and \( \alpha_1 \)-ARs—in the bladder to relax the detrusor muscle and close the internal sphincter.
- Muscarinic receptor function is mediated by acetylcholine which controls the contraction of the detrusor muscle and relaxation of the internal sphincter muscle to facilitate voiding.

AUTONOMIC NERVOUS SYSTEM: 
THE SYMPATHETIC DIVISION

The sympathetic division facilitates storage via activation of β-receptors on the bladder body and via activation of α-receptors in the bladder base and outlet.

- Bladder storage makes up the majority of the micturition cycle.

Norepinephrine, released from the sympathetic nerves, activates β3-ARs and α1-ARs in the bladder to relax the detrusor muscle and close the internal sphincter.

- Three different types of β-ARs are expressed in the human bladder: β1-AR, β2-AR, and β3-AR. In an experiment to determine β-AR subtype expression, β3-AR was found to make up 97% of the total β-AR messenger RNA (mRNA) in bladder tissues. The β1-AR and β2-AR subtypes make up 1.5% and 1.4% of the total β-AR mRNA, respectively.

- Both α1-ARs and α2-ARs are expressed in the lower urinary tract in humans. Activation of noradrenergic pathways contracts the urethra to maintain continence at the onset of the storage phase of micturition. Although expressed in the bladder to a lesser degree than β-receptors, α1 predominates in the bladder neck.

Expression of $\alpha$-ARs in the bladder

- Both $\alpha_1$-ARs and $\alpha_2$-ARs are expressed in the lower urinary tract in humans
  - Activation of noradrenergic pathways contracts the urethra to maintain continence during the storage phase of micturition
  - $\alpha_1$ predominates in the bladder neck

- Norepinephrine binds to $\alpha_1$-ARs, which are expressed in the urethra, resulting in the closing of the internal sphincter and an increase in urine volume
  - Contraction of the internal sphincter is mediated by both the sympathetic and pudendal nerves

Expression of β-ARs in the bladder

- Sympathetic nerves determine the duration of the urine storage phase during the micturition cycle\(^1\)
  - Norepinephrine released from sympathetic nerves activates \(\beta_3\)-AR in the human detrusor muscle to relax the bladder

- All 3 \(\beta\)-ARs are expressed in the human bladder, but \(\beta_3\)-messenger RNA (mRNA) predominates\(^2\)
  - The \(\beta_1\)-AR and \(\beta_2\)-AR subtypes make up 1.5% and 1.4% of the total \(\beta\)-AR mRNA, respectively

- While \(\beta\)-ARs are expressed in the detrusor muscle, they are also found in the urothelium, which contributes to the regulation of bladder function\(^3,4\)
  - During the storage phase, the urothelium stretches in tandem with the bladder wall when the bladder starts filling with urine

Norepinephrine binds to $\beta_3$-ARs on the detrusor muscle, resulting in bladder relaxation.

Norepinephrine binds to $\alpha_1$-ARs, resulting in the closing of the internal sphincter and increased storage of urine.

The parasympathetic division primarily mediates bladder contraction

- Bladder voiding is primarily regulated by this division

Muscarinic receptors, a component of the parasympathetic nervous system, are activated by acetylcholine

- There are 5 subclasses of muscarinic receptors: M₁, M₂, M₃, M₄, and M₅
- The muscarinic receptors can be found in urothelial cells
  - M₂ and M₃ are the predominant muscarinic receptors found in the bladder
  - M₃-receptors are important for normal bladder contraction, while M₂-receptors may play a more prominent role in certain disease states (demonstrated in vitro)
  - Binding of acetylcholine to M₃-receptors on the detrusor muscle activates a signaling pathway that leads to bladder contraction and voiding

Muscarinic receptors play an important role in bladder contraction

- Muscarinic receptors can be found on urothelial cells\textsuperscript{1,2}
- $M_2$- and $M_3$-receptors are the predominant muscarinic receptors found in the bladder\textsuperscript{3-5}
  - Binding of acetylcholine to $M_3$-receptors on the detrusor muscle activates a signaling pathway that leads to bladder contraction and voiding
  - $M_3$-receptors appear to be important for normal bladder contraction, with $M_2$-receptor activation serving a more prominent role in certain disease states (demonstrated \textit{in vitro})

Acetylcholine binds to muscarinic receptors (M3) on the detrusor muscle, resulting in bladder contraction.

AN INTRODUCTION TO OAB:
Definition, Prevalence, and Impact
**OAB DEFINED**

OAB is a clinical diagnosis characterized by a sudden, urgent need to urinate, with or without urine leakage, usually with daytime and nighttime frequency, in the absence of a urinary tract infection (UTI) or other obvious pathology.¹

The 4 key OAB symptoms are¹ ²

- **Urgency**, the hallmark symptom of OAB, which can be described as a sudden, compelling desire to pass urine that is difficult to defer.

- **Frequency**, which is defined as having to void too often during waking hours.

- **Nocturia**, or the experience of waking at least once during the night to void.

- **Urge urinary incontinence**, which is the involuntary leakage or loss of urine accompanied by, or immediately preceded by, urgency.

OAB is a common condition that affects millions of people¹

According to a 2005 Internet-based, cross-sectional, population-representative survey

- An estimated 46 million adults (36%) aged ≥40 years of age in the United States report OAB symptoms at least “sometimes”*
  - In men, prevalence of OAB symptoms at least “sometimes” and at least “often” was 27.2% and 15.8%, respectively
  - In women, prevalence of OAB symptoms at least “sometimes” and at least “often” was 43.1% and 32.6%, respectively

*129.3 million (2005 US Census: adults ≥40 years of age) x 35.6% (in the total sample, prevalence of OAB symptoms at least “sometimes” was 35.6%) = 46.02 million US adults ≥40 years of age reported symptoms of OAB at least “sometimes.”¹

Study Design: An Internet-based, cross-sectional, population-representative survey of 10,584 women and 9416 men ≥40 years.¹

A separate study predicts that, in North America overall, the prevalence of OAB will increase by 18.4% from 2008 to 2018²†

¹Calculated with an estimation model using gender- and age-stratified prevalence data from the EPIC study along with gender- and age-stratified worldwide and regional population estimates from the US Census Bureau International Data Base. EPIC is a large, population-based, cross-sectional telephone survey that assessed the prevalence of lower urinary tract symptoms (LUTS), OAB, urinary incontinence, and LUTS/bladder outlet obstruction in 19,165 men and women in 5 countries.²

According to EpiLUTS*, a 2005 internet-based, cross-sectional, population-representative survey, the prevalence of OAB symptoms increases with age in both men and women†

Adults reporting urgency or urge urinary incontinence and frequency of OAB symptoms at least “sometimes”

*EpiLUTS is Epidemiology of Lower Urinary Tract Symptoms.
†In this study, prevalence of OAB symptoms at least “sometimes” was 35.6%, which is approximately 1/3 of the total sample. From a 2005 Internet-based, cross-sectional, population-representative survey of 10,584 women and 9416 men ≥40 years of age.

OAB comes with a significant financial cost¹

• Data from epidemiologic studies indicate significant increases in
  — Diagnostic tests
  — Medical and surgical therapy
  — Hospitalizations
  — Skin irritations
  — Infections

Employers experience a cost in the form of employee absenteeism and reduced work productivity²,³

BURDEN OF OAB: ECONOMIC\(^1\) (CONT’D)

Annual total OAB costs in 2007 in the US: $66 billion

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<tr>
<th>Direct nonmedical costs</th>
<th>Direct medical costs</th>
<th>Indirect costs</th>
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<td>$44</td>
<td>$1433</td>
<td>$426</td>
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Average Per Capita Costs, 2007: $1925

Estimated Per Capita Costs vs National Costs,\(^*\) 2007-2020\(^†\)

- **2007**
  - $1925\(^‡\)
  - $65.9 billion\(^*\)

- **2015**
  - $1944\(^‡\)
  - $76.2 billion\(^*\)

- **2020**
  - $1970\(^‡\)
  - $82.6 billion\(^*\)

\(^*\)Total OAB population.

\(^†\)77% of the projected annual total costs of OAB from 2007 to 2020 could be attributed to the direct medical costs incurred by an increasingly elderly population.

\(^‡\)Average per patient.

Findings are based on a review of the medical literature, practice guidelines, and Medicare and managed care fee schedules from 2005 to 2010.

**Direct medical costs** included primary care and specialist physician visits, prescriptions (Rx) and over-the-counter (OTC) medications, physical therapy, surgery, and emergency departments.

**Direct nonmedical costs** included pantiliners, disposable pads, and skin protection.

**Indirect costs** included lost productivity.

OAB can intrude into many aspects of a person’s life

- Patients with OAB typically restrict their activities and may experience¹,²
  - Sleep disruption
  - Depression
  - Work disruption
  - Decreased ability to carry out daily activities
  - Negative impact on intimacy

To cope with symptoms of OAB, many patients employ elaborate behaviors aimed at hiding and managing urine loss. It is important that the healthcare provider (HCP) assesses the presence of OAB symptoms, as most patients are reluctant to discuss their symptoms with HCPs.

OAB: Evaluation and Diagnosis
Which urinary symptoms does the patient have?¹

• Clinician should carefully assess duration of bladder symptoms and baseline symptom levels to ensure that symptoms are not the consequence of some other condition

• Assess bladder storage symptoms associated with OAB (e.g., urgency, urgency incontinence, frequency, and nocturia)

• Assess other bladder storage problems (e.g., stress incontinence episodes)

• Assess bladder emptying (e.g., hesitancy, straining to void, prior history of urinary retention, force of stream, and intermittency of stream)

Diary to determine number of voids, frequency of incontinence episodes, volume of each void, associated urgency, and pad use¹

Quality of life¹

• Is it affecting daily activities (sleep, work)?

• Is it interfering with sexual and social activities?

Factors that may lead to a complicated OAB condition

- Neurologic diseases (i.e., stroke, multiple sclerosis, and spinal cord injury)
- Mobility deficits
- Medically complicated/uncontrolled diabetes
- Chronic pelvic pain
- History of recurrent urinary tract infections (UTIs)
- Pelvic prolapse or pelvic surgery
- Pelvic cancer (bladder, colon, cervix, uterus, prostate) and pelvic radiation
- Patients with urgency incontinence, particularly younger patients or patients with extremely severe symptoms, could represent an occult neurologic condition
- Patients who have failed multiple antimuscarinics to control OAB symptoms

Diagnosing OAB can be complicated by hurdles within the HCP/patient dialogue

- Patients may be experiencing OAB symptoms, but do not initiate the conversation with their HCP
- Miscommunications may occur due to lack of a clear, in-depth discussion of OAB symptoms, comorbidities, and medical history

Most cases of OAB can be diagnosed based on a patient history and symptom assessment (including degree of bother and effect on daily activities), a physical examination, and a urinalysis.\textsuperscript{1}

Initial workup of uncomplicated OAB is symptom-based and does not require invasive testing\textsuperscript{1}

As per AUA guidelines, the following assessments may be performed:

**Physical Examination\textsuperscript{1,2}**
- Neurologic
- Mental status
- Weight/Body mass index (BMI)
- Abdomen
- Genitalia

**Urinalysis\textsuperscript{1,2}**
- Rule out urinary tract infections (UTIs), glucosuria, hematuria, proteinuria, etc.

**Post-void residual (PVR) measurement**\textsuperscript{*}
- PVR should be measured with an ultrasound bladder scanner or a catheter immediately after the patient voids
- PVR is not necessary for patients who are receiving first-line behavioral interventions or for uncomplicated patients (i.e., patients without a history of or risk factors for urinary retention) receiving antimuscarinic medications

*Not recommended for uncomplicated OAB.

CONSIDERATIONS FOR DIAGNOSING COMPLICATED OAB

- Urodynamic testing
- Cystoscopy
- Diagnostic renal ultrasound
- Diagnostic bladder ultrasound

DIAGNOSING OAB: RULE OUT OTHER CAUSES OF SYMPTOMS

Local pathology\(^1,2\)
- Infection
- Bladder stones
- Bladder tumors
- Interstitial cystitis
- Outlet obstruction

Medications\(^2\)
- Diuretics
- Antidepressants
- Antihypertensives

Metabolic factors\(^1\)
- Diabetes
  - Polydipsia
  - Polyuria

Review of Systems\(^2\)
- Sexual and bowel function
- Recent weight gain or loss
- Lower extremity edema
- Depression and anxiety

OAB: Treatment Approaches
AUA/SUFU: OAB TREATMENT GUIDELINES

FIRST LINE
- Behavioral therapies for all patients
- May be combined with oral agents

SECOND LINE
- Oral agents and transdermal preparations
- Dose modification or switch to a different oral agent if inadequate efficacy or poor tolerability

THIRD LINE
- Intradetrusor onabotulinumtoxinA
- Peripheral tibial nerve stimulation (PTNS)
- Sacral neuromodulation (SNS)
- Other surgical options

AUA/SUFU, American Urological Association/Society of Urodynamics Female Pelvic Medicine and Urogenital Reconstruction. Adapted from the AUA/SUFU treatment guidelines.

BEHAVIORAL THERAPY OPTIONS

Bladder Training¹
• Self-monitoring with a bladder diary for 3-7 days is a helpful first step in behavioral therapy
• Helps the patient document the time of each void and incontinence episode to help pinpoint the circumstances at the time of incontinence
• Symptom questionnaires are also useful to quantitate and follow patients’ responses to bladder symptom and bother changes with OAB therapies, as well as document baseline and post-treatment results

Pelvic Muscle Exercises¹,²
• Focuses on the bladder outlet and the pelvic floor muscle to increase strength, control, and urge suppression
• Pelvic floor muscle training and exercise includes pelvic floor relaxation, active use of pelvic floor muscles for urethral occlusion and urge suppression (urge strategies), urge control techniques (distraction, self-assertions), and normal voiding techniques

Biofeedback¹-³
• Patients learn how to properly perform pelvic floor muscle contraction and how to strengthen the urinary sphincter
• A vaginal or perineal pressure sensor worn by the patient relays information about when a muscular contraction has occurred and the strength of the contraction

Fluid/Dietary Management¹
• Fluid management (i.e., reduction in fluid intake) can reduce frequency and urgency
• Caffeine reduction, dietary adjustments (avoiding bladder irritants), weight loss, and other lifestyle changes are also recommended

PHARMACOLOGIC THERAPY FOR OAB

• Oral agents and transdermal preparations
• Dose modification or change to a different oral agent, if inadequate efficacy or poor tolerability

INVASIVE PROCEDURES

Neuromodulation involves 2 different procedures\(^1,2\)
- Sacral nerve stimulation (SNS)
- Peripheral tibial nerve stimulation (PTNS)

BotulinumtoxinA (BTX-A)
- May require frequent post-void residual evaluation and patient may have to self-catheterize\(^1\)

Bladder Augmentation/Augmentation Cystoplasty
- A surgical procedure to increase bladder capacity\(^3\)

Bladder Diversion/Urinary Diversion
- A surgical procedure that may be used in rare cases for severe, refractory, or complicated OAB patients\(^1\)
- Substantial risks are involved, including malignancy, and patients may need long-term intermittent self-catheterization\(^1\)

Invasive procedures should only be considered for carefully selected and thoroughly counseled patients who have been refractory to first- and second-line OAB treatments and are willing to undergo a surgical procedure\(^1\)

• The Medicare HOS is the first patient-reported outcomes measure used in Medicare managed care (Part C)¹
  —HOS is used by the Centers for Medicare & Medicaid Services (CMS) to develop its 5-Star Quality Rating System, which evaluates quality and performance in Medicare Advantage (Part C) Health Plans

• The HOS assessment occurs over a 2-year period of time¹
  —As of 2014, 17 rounds of data have been collected

• Improving bladder control is part of the Medicare HOS
  —HOS contains 4 questions for patients relating to bladder control²
  —These questions are currently under revision and were tested in 2015 to assess quality of care and impact on quality of life³

Questions regarding urinary incontinence, some of which may be relevant for patients with overactive bladder, in the HOS

Many people experience leakage of urine, also called urinary incontinence. In the past six months, have you experienced leaking of urine?

During the past six months, how much did leaking of urine make you change your daily activities or interfere with your sleep?

Have you ever talked with a doctor, nurse, or other health care provider about leaking of urine?

There are many ways to control or manage the leaking of urine, including bladder training exercises, medication and surgery. Have you ever talked with a doctor, nurse, or other health care provider about any of these approaches?

### SUMMARY

The bladder serves 2 main functions—the **storage** and the **voiding** of urine—and is controlled by the **autonomic nervous system (ANS)**

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<thead>
<tr>
<th>OAB involves the following key symptoms</th>
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<tr>
<td>• Urgency, with or without incontinence, often involving frequency and nocturia</td>
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<tr>
<th>OAB is a condition that affects millions of people and comes with economic, health, and quality-of-life burdens</th>
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<tr>
<th>OAB can be diagnosed, in most cases, based on</th>
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<tr>
<td>• Patient history and symptom assessment</td>
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<td>• Physical examination</td>
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<td>• Urinalysis</td>
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<th>OAB can be treated in a variety of ways, including</th>
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<td>• Behavioral therapy</td>
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<td>• Pharmacologic therapy</td>
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<td>• Surgical procedures</td>
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