AN OVERVIEW OF OAB

Including evaluation of and management approaches for overactive bladder
<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Bladder: Anatomy and Normal Function</td>
<td>3-14</td>
</tr>
<tr>
<td>An Introduction to OAB: Definition, Prevalence, and Impact</td>
<td>15-24</td>
</tr>
<tr>
<td>OAB: Evaluation and Diagnosis</td>
<td>25-29</td>
</tr>
<tr>
<td>OAB: Treatment Approaches</td>
<td>30-34</td>
</tr>
<tr>
<td>Summary</td>
<td>35</td>
</tr>
</tbody>
</table>
THE BLADDER: Anatomy and Normal Function
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.

Adequate storage depends on a relaxed bladder and a closed outlet, while efficient voiding depends on an adequate bladder contraction coordinated with relaxation of the bladder outlet\(^3\).

The bladder serves 2 main functions\(^1\):

- To **store** urine
- To **void** urine

**Filling/storage phase\(^1,2\)**

- 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
- A moderately full bladder holds approximately 500 mL (1 pint) of urine, but can hold nearly double that if necessary, with a maximum capacity of 800-1000 mL

**Emptying/voiding phase\(^1\)**

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

Regulation of bladder storage and voiding involves both sympathetic and parasympathetic control. Storage and voiding of the bladder are primarily regulated by two neurotransmitters—norepinephrine and acetylcholine—respectively. Norepinephrine, released from the sympathetic nerves, activates the adrenergic receptors (ARs), \( \alpha \)-ARs and \( \beta \)-ARs, in the bladder to relax the detrusor muscle and close the internal sphincter, respectively. The muscarinic receptors (M1 to M5) are mediated by acetylcholine and control the contraction of the detrusor muscle and relaxation of the internal sphincter muscle to facilitate voiding.

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 the ARs—β-AR and α-AR—in the bladder to, respectively, 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. The β₃-AR made up 97% of the total β-AR messenger RNA (mRNA) in bladder tissue samples in an experiment to determine β-AR subtype expression, making it predominantly responsible for detrusor muscle relaxation. The β₁-AR and β₂-AR subtypes made 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 predominate 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\(^1\)
  - Activation of noradrenergic pathways contracts the urethra to maintain continence during the storage phase of micturition\(^2\)
  - $\alpha_1$ predominates in the bladder neck\(^3\)

- 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\(^4\)
  - 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.
  - Norepinephrine released from sympathetic nerves activates β-ARs in the detrusor muscle to relax the bladder.

- All 3 β-ARs are expressed in the human bladder, but β₃-messenger RNA (mRNA) predominates.
  - The β₁-AR and β₂-AR subtypes make up 1.5% and 1.4% of the total β-AR mRNA, respectively.

- While β-ARs are expressed in the detrusor muscle, they are also found in the urothelium, which contributes to the regulation of bladder function.
  - During the storage phase, the urothelium stretches in tandem with the bladder wall when the bladder starts filling with urine.

AUTONOMIC NERVOUS SYSTEM: THE SYMPATHETIC DIVISION\(^1\) (CONT’D)

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: M\(_1\), M\(_2\), M\(_3\), M\(_4\), and M\(_5\).
- The muscarinic receptors can be found in urothelial cells
  - M\(_2\) and M\(_3\) are the predominant muscarinic receptors found in the bladder
  - M\(_3\) receptors are important for normal bladder contraction, while M\(_2\) receptors may play a more prominent role in certain disease states (demonstrated in vitro)
  - Binding of acetylcholine to M\(_2\) and M\(_3\) receptors on the detrusor muscle signals the bladder to contract so voiding can occur

References:
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 $M_2^-$ and $M_3^-$ receptors on the detrusor muscle signals the bladder to contract so voiding can occur

  - $M_3^-$ receptors appear to be important for normal bladder contraction, with $M_2^-$ receptor activation serving a more prominent role in certain disease states (demonstrated in vitro)

References:
AN INTRODUCTION TO OAB:
Definition, Prevalence, and Impact
Overactive bladder (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 are\(^1,2\):

- **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

**References:**
OAB is a common condition that affects millions of people\textsuperscript{1,2}

According to an Internet-based, cross-sectional, population-representative survey

- An estimated 46 million adults (36%) ≥40 years of age in the US report OAB symptoms at least “sometimes”\textsuperscript{*}
  - 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

\textsuperscript{*}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.”\textsuperscript{1}

Study Design: An Internet-based, cross-sectional, population-representative survey of 10,584 women and 9,416 men ≥40 years of age.\textsuperscript{1}

A separate study predicts that, in North America overall, the prevalence of OAB will increase by 18.4% from 2008 to 2018\textsuperscript{2†}

\textsuperscript{1}Calculated 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 LUTS, OAB, UI, and LUTS/BOO in 19,165 men and women in 5 countries.\textsuperscript{2}

1 in 3 US adults ≥40 years of age reported symptoms of OAB at least “sometimes”

*Adults who had experienced urgency or urge incontinence in the last 4 weeks and defined occurrence as at least “sometimes.”

Data were gathered in the Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS), a population-based, cross-sectional survey conducted in the United States, United Kingdom, and Sweden. In the US, 20,000 men and women aged 40 years or older were recruited from Internet-based panels developed from consumer and voter databases. All respondents were asked to complete a series of questions about their symptoms.¹

• Data from the NOBLE Program show that the prevalence of OAB symptoms without incontinence increases with age in both men and women.

• However, OAB with incontinence is more common in women than in men at all ages, especially in the elderly (see chart).

OAB comes with a significant financial cost¹⁻³

- 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 productivity⁴⁻⁵

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

| Direct medical costs | $1433 |
| Direct nonmedical costs | $66 |
| Indirect costs | $426 |

**Average Per Capita Costs, 2007:** $1925

**Estimated Per Capita Costs vs National Costs,* 2007-2020†**

<table>
<thead>
<tr>
<th>Year</th>
<th>Per Capita Costs</th>
<th>National Costs*</th>
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<tbody>
<tr>
<td>2007</td>
<td>$1925†</td>
<td>$65.9 billion*</td>
</tr>
<tr>
<td>2015</td>
<td>$1944‡</td>
<td>$76.2 billion*</td>
</tr>
<tr>
<td>2020</td>
<td>$1970‡</td>
<td>$82.6 billion*</td>
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*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 5 most recent years of the medical literature, practice guidelines, and Medicare and managed care fee schedules.

**Direct medical costs** included primary care and specialist physician visits, Rx and OTC medications, physical therapy, surgery, 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 incontinence typically restrict their activities and may experience\(^1,2\):
  - 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.\(^1,2\)

- It is important that the HCP assess the presence of OAB symptoms, as, according to one study, ~55% of patients did not mention their OAB symptoms to their HCP.\(^2\) In another study conducted in Europe, 40% of patients did not discuss their symptoms with their HCP\(^2\).
  - This was due either to embarrassment or the misperception that such urologic symptoms are a normal aspect of aging.

Patients with OAB were significantly more likely to suffer from\(^1,^2\)*

- Urinary tract infections (UTIs)
- Falls and fractures
- Depression
- Vulvovaginitis
- Skin infections

* Findings are based on a retrospective cohort study using electronic pharmacy and medical claims data from a regional pharmacy benefits and medical management organization.

• More than half of the patients with OAB had at least 1 of these comorbidities\(^1\)
• In a survey with 919 respondents, patients with OAB incurred 20% more physician visits than people without OAB\(^2\)

OAB: Evaluation and Diagnosis
DIAGNOSING OAB: PATIENT HISTORY

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 (eg, urgency, urgency incontinence, frequency, nocturia)
- Assess other bladder storage problems (eg, stress incontinence episodes)
- Assess bladder emptying (eg, 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 aggravate OAB symptoms include¹

- Neurologic diseases (ie, stroke, multiple sclerosis, 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 dialogue²

- Patients may be suffering with 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

References:
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}

**Physical Examination**\textsuperscript{1}
- Neurologic
- Mental status
- Weight/BMI
- Abdomen
- Genitalia

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

**Post-void residual measurement**\textsuperscript{1*}
- 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 (ie, patients without a history of or risk factors for urinary retention) receiving antimuscarinic medications

\textsuperscript{*Not recommended for uncomplicated OAB}

DIAGNOSING COMPLICATED OAB:
URODYNAMIC TESTING CONSIDERATIONS

- Uroflowmetry\(^1\)
- Cystometry\(^{1,2}\)
- Leak Point Pressure Measurement\(^1\)
- Pressure Flow Study\(^1\)
- Electromyography\(^1\)
- Video Urodynamic Tests\(^1\)
- Post-Void Residual Measurement\(^1\)

DIAGNOSING OAB: RULE OUT OTHER CAUSES OF SYMPTOMS

Local pathology¹-³
- Infection
- Bladder stones
- Bladder tumors
- Interstitial cystitis
- Outlet obstruction

Medications³,⁴
- Diuretics
- Antidepressants
- Antihypertensives
- Sedatives
- Opioids

Metabolic factors¹,²
- Diabetes
  - Polydipsia
  - Polyuria

Review of Systems³
- Sexual and bowel function
- Recent weight gain or loss
- Lower extremity oedema
- Depression and anxiety

OAB: Treatment Approaches
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

- SNS
- PTNS
- Intradetrusor onabotulinumtoxinA
- Other surgical options

SNS=sacral neuromodulation; PTNS=peripheral tibial nerve stimulation.
Adapted from the AUA OAB treatment guidelines.

**BEHAVIORAL THERAPY OPTIONS**

**Bladder Training**
- 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 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 Exercises**
- Focuses on the bladder outlet and the pelvic floor muscle to increase strength and 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

**Biofeedback**
- 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 Management**
- Fluid management can reduce frequency and urgency
- Caffeine reduction, dietary adjustments (avoiding bladder irritants), weight loss, and other lifestyle changes are also recommended

PHARMACOLOGIC THERAPY

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

INVASIVE PROCEDURES

Neuromodulation involves 2 different procedures

- Sacral nerve stimulation (SNS)
- Peripheral tibial nerve stimulation (PTNS)

BotulinumtoxinA (BTX-A)

- Is known to block the release of acetylcholine and paralyzes any muscle into which it is injected
- Precise mechanism of action when injected into the detrusor muscle is unknown

Bladder Augmentation/Augmentation Cystoplasty

- A major operation that increases bladder capacity

Bladder Diversion/Urinary Diversion

- A surgical procedure that creates an opening in the skin of the lower abdomen to access an artificial urine reservoir created from the bowel
  - This reservoir is connected to the bladder and holds the diverted urine until it can be drained into a urostomy bag

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

SUMMARY

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

**OAB involves the following key symptoms:**
- Urgency, with or without incontinence, often with frequency and nocturia

**OAB is a common condition that affects millions of people and comes with economic, health, and quality-of-life burdens**

**OAB can be diagnosed, in most cases, based on:**
- Patient history and symptom assessment
- Physical examination
- Urinalysis

**OAB can be treated in a variety of ways, including:**
- Behavioral therapy
- Pharmacologic therapy
- Invasive procedures