Overactive Bladder: A Better Understanding of Pathophysiology, Diagnosis and Management

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Purpose: We reviewed current information regarding the updated definitions, prevalence, etiologies, disease burden, and management of OAB from a number of perspectives, including professional impact and patient quality of life.

Materials and Methods: Published literature and current treatment concepts were reviewed regarding the understanding and management of OAB.

Results: OAB is a symptom syndrome including urinary urgency with or without urinary incontinence, usually with frequency and nocturia. Approximately 17% of the adult population experience OAB. There are evolving theories regarding its pathophysiology and the mechanism of action of the most commonly prescribed pharmacological therapy (antimuscarinic agents). Treatment primarily revolves around improving quality of life.

Conclusions: Behavioral therapy combined with pharmacological therapy often will bring about acceptable outcomes for patients with OAB. Modalities such as botulinum toxin injections, neuromodulation, and various surgical interventions also are showing encouraging results in more refractory patients.

Key Words: bladder, urinary incontinence, muscarinic antagonists, behavioral medicine

The definition of OAB has been evolving over the years as the syndrome has come to be studied more diligently. The ICS now defines OAB as urgency, with or without urge UI, usually associated with frequency and nocturia. The symptoms must be exhibited in the absence of pathological or metabolic disorders (e.g., urinary tract infection, bladder cancer or benign prostatic enlargement) that might otherwise cause such symptoms. Urgency is the primary symptom; OAB would not be diagnosed without the complaint of urgency. It can, however, be diagnosed without the complaint of incontinence. Approximately two-thirds of patients with OAB do not experience involuntary leakage of urine; OAB in the absence of UI is termed “OAB dry.” Note that a component of the previous definition, fear of leakage and/or fear of pain from a full bladder, is no longer included in the definition of OAB.

Since urgency is the key symptom, it becomes important to define it. The ICS defines urgency as a “sudden compelling desire to void that is difficult to defer.” The word desire is used rather than urge, because urge is a normal phenomenon that we all feel when the bladder is full. The desire is termed as “sudden” to avoid confusion with the gradual increase in sensation that is also a normal phenomenon.

Despite the availability of a formidable definition, clinicians often find that patients, especially in clinical practice, do not understand exactly what is meant by “urgency.” Likewise, in many studies purporting to measure or record urgency, an incorrect definition was used, most commonly a strong desire to void. This is something to take into consideration when reading literature regarding studies that evaluate “urgency.”

Urgency is the primary driver of all symptoms of OAB. It leads to frequency and OAB related nocturia, as well as to urge UI in the approximately one-third of patients with OAB who suffer from UI. According to the ICS definition, frequency is defined as urination 8 times or greater per 24 hours. Nocturia, which is simply waking to urinate during sleep hours, generally is only considered a clinical problem if the frequency is greater than 2 times per night. (Nocturia will be discussed in greater detail elsewhere in this supplement.)

Epidemiology of OAB

OAB overlaps with other subtypes of LUT dysfunction (fig. 1). As noted, approximately a third of all patients with OAB experience incontinence and, thus, they are classified as having urge UI, which is synonymous with “OAB wet.” Stress UI, which involves failure of the urethra and pelvic floor to withstand pressure created by such stressors as sneezing or laughing, does not fall within the OAB syndrome; however, many patients suffer from UI and/or urgency with mixed symptoms (urgency and stress). The combination of stress UI with urge UI constitutes “mixed UI,” while stress UI accompanied by urgency but not urge UI constitutes “mixed symptomatology.” As figure 1 illustrates, a large portion of patients suffer from OAB dry. These patients experience urgency and frequency but not UI.
Two major epidemiological studies have been performed regarding the prevalence of OAB, 1 in Europe and 1 in the United States. Both indicate a similar prevalence of approximately 17% of the general adult population. The United States study, which was done by the National Overactive Bladder Evaluation program, found that 16.5% of adults (18 years or older), or approximately 33 million people, met the criteria for OAB. The portion of patients with OAB in the European study was 16.6% in a population of adults 40 years or older in 6 countries. This does not mean that 17% of the population requires treatment for OAB, because not everyone will have severe uncontrollable symptoms. This issue of what level of symptoms warrant treatment is a subject of ongoing discussion.

Data from the National Overactive Bladder Evaluation study indicate that 37% of patients with OAB experience incontinence, while 63% do not. The prevalence of both OAB wet and OAB dry increases with age. OAB dry is more common in men (13.6% vs 7.6% in women overall), and OAB wet is more common in women (9.3% vs 2.4% in men overall). Urge UI in men is often associated with benign prostatic hyperplasia or benign prostate obstruction, which will both be discussed in another section of this supplement.

The impact of OAB on QOL is considerable. The highly validated Short Form with 36 questions, a health related QOL survey, shows OAB to cause QOL limitations and/or impairment in domains including physical activity, psychological well-being, social activity, sexual activity, occupational productivity, and domestic logistics. Psychological well-being is commonly mentioned. Patients often express loss of self-esteem, fear of becoming incontinent in public, and depression. As discussed by Abrams et al, the incidence of depression associated with OAB is on the same scale as that of numerous other chronic conditions, including diabetes, rheumatoid arthritis, and hypertension.

OAB also can be a contributing factor to fall related injuries in the elderly population. In a study by Brown et al, 19% to 42% of community dwelling women 65 years or older experienced falls; 4% to 9% of these falls resulted in fractures. The high incidence of urge UI in this population was determined to be an independent risk factor in women experiencing 1 or greater urge UI episode per week, with the risk of falls and fractures being increased by 26% and 34%, respectively. The authors noted frequency, nocturia, and “rushing to the bathroom” as being likely to increase the risk of falling in elderly women. In consideration of the morbidity and mortality associated with hip fracture in older women, it is important to identify these individuals with OAB and properly treat them.

**PATHOPHYSIOLOGY**

Because the bladder is a smooth muscle organ attached to the CNS, it is logical to assume that the pathophysiology of OAB is neurogenic and/or myogenic in origin. The neurogenic etiology is easier to conceptualize, and within that realm, the simplest to understand is that of decreased suprapontine inhibition of the micturition reflex, such as that following a cerebrovascular accident. Other examples of neurogenic etiology of OAB would be damaged axonal paths in the spinal cord, increased LUT afferent nerve input, loss of peripheral inhibition, and enhancement of excitatory neurotransmission in the micturition reflex pathway. Common causes of these phenomena include stroke, spinal cord injury and multiple sclerosis.

The myogenic theory is applicable mostly to patients with bladder outlet obstruction, owing to an increase in intravesical pressure, which subsequently causes partial neurological denervation of the bladder smooth muscle. Spontaneous action potential generation is generally limited in bladder smooth muscle and is not propagated from cell to cell. However, when the smooth muscle is denervated, there is an increase in the number of spontaneous action potentials and in the ability of the action potentials to propagate from cell to cell. Rather than causing a normal detrusor contraction that would empty the bladder, this denervation results in “micromotions” of the detrusor smooth muscle that give rise to increased intravesical pressure and stimulation of afferent receptors in the detrusor smooth muscle. The receptors provide feedback to the CNS and cause the sensations associated with OAB.

Another of the new ideas being proposed is that ACh is released from the urothelium in an amount greater than normal during bladder distention, or the sensory receptors in the urothelium are more sensitive to the ACh that is released. The subsequent feedback to the CNS creates the sensation of urgency that drives OAB. There is increasing evidence that the urothelium is involved in sensory function, including the release of neurotransmitters in response to stimuli.

Another hypothesis is that, rather than experiencing no activity in the postganglionic efferent nerve during filling/storage (the normal state), patients with OAB experience an abnormal leak of ACh from efferent fibers, causing micromotions in bladder smooth muscle and stimulate the CNS, creating the sense of urgency.

**DIAGNOSIS AND TREATMENT**

Understanding that not all patients will require treatment for OAB, it is important to determine the severity and precise symptomatology. The initial evaluation should include a thorough history, physical examination, urinalysis, and bladder diary (fig. 2). Since OAB symptoms can be early signs of underlying and/or remediable conditions, special attention should be focused on detecting them. The most
common diagnosable causes of OAB are neurogenic bladder, prostatic obstruction in men, and urethral obstruction from pelvic organ prolapse and prior surgery in women.\textsuperscript{13–17} The Appendix shows a more complete list.

The history begins with a detailed account of the precise nature of patient symptoms. The patient should be asked how often he or she urinates during the day and night, how long he or she can comfortably go between urinations and how long micturition can be postponed once he or she gets the urge. It should be determined why he or she voids as often as he or she does. Is it because of urgency, or is it merely out of convenience or an attempt to prevent incontinence? If incontinence is present, is it stress (occurs during coughing, sneezing, rising from a sitting to standing position, or exercise), urge, or mixed. Is the patient aware of the incontinence or just finds himself or herself wet? The severity of incontinence should be graded. Are protective pads worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they worn? Do they become saturated? How often are they worn? Do they become satisfied? How often are they wore?
and the CNS. The difficulty with prescribing any type of pharmacological agent for OAB is the lack of uroselectivity. All currently prescribed agents, including α-adrenergic blockers and antimuscarinics, affect more than just the LUT. This creates the unwanted side effects (e.g., dry mouth, constipation, dizziness, and headache) that are commonly experienced with treatment. Nevertheless, pharmacological therapy offers a positive benefit-to-risk ratio in many patients with OAB. The only oral drug class to demonstrate proof of concept (i.e., efficacy in humans) is the antimuscarinics. These are anticholinergic agents that act on motor receptors on peripheral smooth muscle, and perhaps on sensory receptors as well, providing a median 70% to 80% decrease in OAB symptoms.

Of the 5 subtypes of muscarinic receptors, M2 and M3 are located in smooth muscle, indicating them to be potential targets for the treatment of OAB. Human bladder smooth muscle contains primarily M2 receptors (70% to 80%), along with M3 receptors (20% to 30%). M2 receptors have been demonstrated to evoke smooth muscle contraction, which is the primary stimulus for bladder contraction. It has been postulated that M2 and M3 receptors are involved not only in motor (effenter) activation, but also in sensory (afferent) activation as well. The activation of M2 receptors may reverse sympathetically mediated smooth muscle relaxation during the filling/storage phase of micturition; there are additional mechanisms by which M2 receptors may cause smooth muscle contraction. M1 receptors are found in the brain, glands (e.g., salivary), and sympathetic ganglia. To our knowledge, the ideal receptor blockade profile for optimal treatment of OAB has yet to be determined.

Five antimuscarinics are currently approved in the United States for the treatment of OAB: darifenacin, oxybutynin, solifenacin, tolterodine, and trospium. (A sixth, propiverine, is available in Europe.) Studies of these agents have demonstrated similar efficacy (70% to 75%) for decreasing UI episodes. Bear in mind that efficacy outcomes can be determined and defined in many ways; it is important to try to compare identical outcomes in identical populations when reviewing the literature.

Theoretical edges across this drug class may ultimately be shown to be real edges. They include issues related to drug-drug interactions, ability to cross the blood-brain barrier (thereby, affecting the M1 receptors in the brain), cardiac effects, concentration/clearance in urine, and receptor profiles. All of the antimuscarinics indicated for OAB have received excellent ratings (level 1, grade A) from the pharmacology committee of the ICI. The rating means that well performed, randomized, controlled studies have demonstrated efficacy and acceptable side effect profiles. The table lists the agents that have been used for the management of OAB, along with their ICI ratings.

| International Consultation on Incontinence ratings of OAB pharmacological agents |
|-----------------------------------------------|-----|-------|
| Agent                          | Class          | Level | Grade |
| Darifenacin                        | Antimuscarinic (OAB) | 1    | A     |
| Solifenacin                        | Antimuscarinic (OAB) | 1    | A     |
| Tolerodine                         | Antimuscarinic (OAB) | 1    | A     |
| Trospium                          | Antimuscarinic (OAB) | 1    | A     |
| Atropine                          | Antimuscarinic | 3    | C     |
| Hyoscyamine                       | Antimuscarinic | 3    | C     |
| Propantheline                     | Antimuscarinic | 2    | B     |
| Dicyclomine                       | Mixed action drug | 3    | C     |
| Flavoxate                         | Mixed action drug | 2    | D     |
| Oxybutynin                        | Mixed action drug | 1    | A     |
| Propiverine                       | Mixed action drug | 1    | A     |
| Imipramine                        | Antidepressant  | 3    | C*    |
| Desmopressin                      | Vasopressin analogue | 1 | A†    |
| Alfuzosin                         | α-Adrenergic antagonist | 3    | C     |
| Doxazosin                         | α-Adrenergic antagonist | 3    | C     |
| Tamsulosin                        | α-Adrenergic antagonist | 3    | C     |
| Terazosin                         | α-Adrenergic antagonist | 3    | C     |
| Clenbuterol                       | β-Adrenergic agonist | 3    | C     |
| Salbutamol                        | β-Adrenergic agonist | 3    | C     |
| Terbutaline                       | β-Adrenergic agonist | 3    | C     |
| Flurbiprofen                      | Nonspecific cyclooxygenase inhibitor | 2    | C     |
| Indomethacin                      | Nonspecific cyclooxygenase inhibitor | 2    | C     |

Level 1—randomized controlled clinical trials, 2—good quality prospective studies, 3—retrospective case-control studies, 4—case series and 5—expert opinion, and Grade A—based on level 1 evidence (highly recommended), B—consistent level 2 or 3 evidence (recommended), C—level 4 studies or majority evidence (recommended with reservation) and D—evidence inconsistent/inconclusive (not recommended).
* Should be used with caution.
† Side effects include hyponatremia and water retention.

Note that oxybutynin, which generally is included in the antimuscarinic class, is listed in the table as being a “mixed action drug.” This is due to its additional action of relaxing the detrusor muscle. Imipramine, an antidepressant that some clinicians have used to treat OAB, received a poor rating because of its cardiac effect and the lack of efficacy studies related to OAB. Desmopressin, which often is prescribed for OAB-related nocturia, was rated 1A with a cautionary statement regarding possible side effects of hyponatremia and water retention. The ICI committee assigned unfavorable ratings to the α-adrenergic antagonists and β-adrenergic agonists listed, stating that there was insufficient data to support their routine use for the management of OAB.

As noted, the antimuscarinics indicated for OAB have demonstrated proof of concept; however, their mechanism of action has not been definitely determined. The traditional view is that they interfere with the contractions caused by ACh in bladder smooth muscle. The problem with this view is that it places the timing of the antimuscarinic action within the emptying phase of micturition, a long-held belief in the field of urology. It is now known that antimuscarinics generally do not affect bladder emptying, flow rate, detrusor pressure, or post-void residual urine volume at therapeutic doses. Our new understanding is that antimuscarinics are active during the filling/storage phase of micturition when there is no activity in the cholinergic nerves. ACh can be generated and released from the urothelium and also may “leak” from the cholinergic nerves during bladder filling. While antimuscarinics work to inhibit the attachment of ACh to the contractile receptors in the smooth muscle, they also may inhibit sensory receptors in the smooth muscle and urothelium. It also has been proposed that there are also sensory receptors on these interstitial cells that serve as messengers between the urothelium and the afferent nerves and the urothelium and the smooth muscle; antimuscarinics act to inhibit those as well. In determining which antimuscarinic to prescribe for an individual, it is important to consider the efficacy data specific to the symptoms that the patient is experiencing. While a 70% to 75% decrease in UI episodes is the norm with the OAB specific antimuscarinics, micturition frequency may be decreased only by 20% to 30%, and volume voided may only be increased by 10% to 20%. Well performed studies are those that compare the agent with placebo; they also may
compare 2 or more agents. Comparison studies have not been done with all agents; therefore, different studies should not be compared unless it can be determined that study parameters, populations, and evaluated outcomes (and their definitions) were sufficiently similar.

The appropriate agent for a given individual will have an acceptable balance between efficacy and adverse events. Response to antimuscarinic agents will differ across patients, and it may be necessary to try more than 1 agent and/or titrate dose to strike the optimal balance.

**Novel trends in treatment of OAB.** Management of OAB continues to evolve with the development of a number of new concepts and treatments. Injection of BTX into the bladder or urethra is being investigated in patients with OAB who are refractory to antimuscarinic therapy. It is believed that BTX inhibits the exocytosis of synaptic vesicles, thereby, inhibiting the release of ACh.23 BTX injections are performed as an outpatient procedure; the treatment appears to address not only the hyperactive detrusor muscle related to efferent innervation, but also the hypersensitive bladder afferent nerves that contribute to refractory OAB. BTX has been shown to decrease or eliminate UI for 6 to 9 months in 67% to 73% of patients experiencing neurogenic or idiopathic detrusor overactivity.24–26 Optimal dosing and duration have yet to be determined, but it has been suggested that BTX will become an accepted therapeutic option in patients with OAB refractory to antimuscarinic therapy.27 The treatment is contraindicated in patients with an infection at the injection site or hypersensitivity to BTX.

Neuromodulation is gaining support as a treatment for patients with refractory urge UI. This involves surgical implantation of an electronic device that stimulates the sacral nerves that modulate the bladder, sphincter, and pelvic floor muscles, of which all contribute to urge UI. Abrams et al reviewed pivotal data from a multicenter trial involving patients with urge UI, urinary retention, and/or refractory urgency and frequency.28 Sacral nerve stimulation was effective for a decrease of 50% or greater, or elimination of UI episodes in 76% of patients. No patients in the control group experienced elimination of UI; 7% experienced a decrease of 50% or greater. Neuromodulation is considered a viable strategic option to address either refractory OAB or idiopathic urinary retention after initial conservative therapy has failed.

One of the earlier surgical interventions was augmentation cystoplasty; it can now be performed laparoscopically and still is considered a viable option for severe, refractory urge UI, particularly in neurogenic cases.29 This increases reservoir volume and, by interrupting the surface of the bladder smooth muscle, the detrusor contractions are also interrupted. While shown to result in urinary continence in 67% of patients studied,30 it should be considered only in the most severe cases and likely requires clean intermittent catheterization.

**CONCLUSIONS**

While OAB is a constellation of symptoms, the primary driver of the syndrome is urinary urgency. Only about a third of patients with OAB experience UI. New theories to explain the pathophysiology of OAB are being investigated. Maintenance of a bladder diary will assist in a differential diagnosis of the specific type of OAB, which will help determine the treatment. Currently, the most effective regimen includes behavioral therapy combined with antimuscarinic therapy. Newer, more invasive treatments are showing promise in treating refractory patients, particularly those in whom incontinence is of neurogenic origin.

**APPENDIX**

### Etiology of OAB Symptoms

<table>
<thead>
<tr>
<th>Neurogenic</th>
<th>Nonneurogenic</th>
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<tbody>
<tr>
<td>Stroke</td>
<td>Bladder infection</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Bladder outlet obstruction (eg benign prostatic hyperplasia in men; pelvic organ prolapse, urethral diverticula in women)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Post-surgical (eg anti-incontinence surgery)</td>
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<tr>
<td>Spinal cord injury</td>
<td>Bladder tumor</td>
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<tr>
<td>Myelodysplasia</td>
<td>Bladder stones and foreign body</td>
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<tr>
<td>Transverse myelitis</td>
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</tbody>
</table>

### Abbreviations and Acronyms

- ACh = acetylcholine
- BTX = botulinum toxin A
- CNS = central nervous system
- ICI = International Consultation on Incontinence
- ICS = International Continence Society
- LUT = lower urinary tract
- OAB = overactive bladder
- QOL = quality of life
- UI = urge incontinence

### REFERENCES