Management of Overactive Bladder and Urge Incontinence

An expert overview of the step-wise approach to management of this common and costly condition.

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Overactive bladder is a clinical syndrome consisting of four key symptoms: urgency, frequency, nocturia, and urgency incontinence. The International Continence Society (ICS) defines OAB as the presence of “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of UTI or other obvious pathology.”

Management of patients suffering from overactive bladder (OAB) and associated urinary urge incontinence (UUI) continues to challenge physicians worldwide, as they represent a complex spectrum of a highly prevalent condition affecting up to 27 percent of men and 43 percent women of the global population.

In the US alone, 33 million adults have OAB and urge incontinence. This condition is more prevalent than other chronic health disorders, such as diabetes, heart disease, and asthma.

From the individual patient’s perspective, OAB can have a substantial and multidimensional impact on a person’s life, since participation in social and occupational activities can be greatly limited by lack of bladder control and incontinence. Furthermore, OAB is associated with high rates of anxiety and depression and comorbidities, especially among older adults greater than 65 years of age. From a global economic standpoint, the cost burden of OAB diagnosis and treatment is staggering the total cost of urinary incontinence and OAB was estimated to be $19.5 and $12.6 billion in year 2000, and has been expected to rise rapidly due to the aging population. Unfortunately, these figures may be underestimated since only 40–50 percent of patients with OAB sought medical treatment.

Thus, it is paramount to improve understanding of OAB among healthcare providers in order to optimize therapy and minimize morbidity. This article will review the key points in pathophysiology, diagnosis, and treatment of overactive bladder and urge urinary incontinence.

OAB and associated incontinence is a highly prevalent condition with significant psychosocial, medical, and economic burden. It is crucial to accurately distinguish OAB symptoms from other associated disease entities, such as infection, malignancy, neurologic disease, and anatomic defects, which must be addressed as part of a comprehensive treatment algorithm. Optimal management of this complex syndrome is aimed at relieving symptoms to improve quality of life with clinically effective and minimally invasive treatments.
PATHOPHYSIOLOGY OF OAB

The main task of urinary storage and voiding is performed by the bladder, a muscular reservoir that distends to store urine at a low pressure without leakage and pumps to expel urine efficiently and voluntarily. Histologically, it is made up of three layers: the outer adventitial connective tissue layer, a middle smooth muscle layer comprising the functional detrusor, and an innermost urothelial lining that provides an elastic and impervious barrier.

Although the bladder function of urine storage and voiding may be conceptually simple, the process of micturition involves a sophisticated integration of peripheral autonomic, somatic, and central nervous systems on the smooth and striated musculature of the lower urinary tract, which includes the bladder and urethra. Failure to coordinate these neural pathways can manifest in various degrees of voiding dysfunction, including detrusor overactivity and urinary incontinence.

The pontine micturition center in the brainstem coordinates urinary storage function of the bladder via the spinal reflex pathways. As the bladder fills with urine, it leads to increased wall tension that activates bladder afferent nerves, which then reflexively activate sympathetic outflow to the lower urinary tract from the lumbosacral spinal cord. This results in internal sphincter contraction via the hypogastric nerve, as well as external sphincter and pelvic floor striated muscle contraction via the pudendal nerve. At the same time, there is inhibition of sacral parasympathetic outflow to the detrusor muscle, which results in bladder relaxation. These coordinated pathways of detrusor inhibition and bladder outlet excitation maintain continent, low-pressure storage of urine.

Pathologic bladder conditions such as OAB are often associated with detrusor overactivity (DO), characterized by involuntary detrusor contractions observed during urodynamic testing. Multiple factors may influence DO, such as hormonal changes, bladder outlet obstruction (BOO), aging, ischemia, and concomitant neurologic conditions. There are multiple theories on the development of OAB and DO. Traditionally, DO was thought to result from abnormal central processing of bladder afferent signaling, which can be due to decreased capacity to handle increased afferent information or from a decrease in tonic inhibition of afferent impulses. Bladder contractions often seen during normal bladder filling may be suppressed by increase in suprapontine inhibition; however, suprapontine inhibition may be impaired in conditions such as stroke. As a result, this type of neurologic insult can lead to involuntary detrusor contractions and sensory urgency and frequency from low-intensity afferent input and at lower bladder volumes.

The myogenic hypothesis is another popular theory on OAB genesis, which purports that uninhibited detrusor contractions results from progressive denervation and bladder wall hypertrophy caused by chronic conditions such as BOO, normal aging, and neurogenic insult. These morphologic changes can lead to upregulated, spontaneous, or involuntary bladder contractions associated with motor urgency symptoms of OAB. More recent findings have focused on urothelial and suburothelial dysfunction as the root pathogenesis of OAB. It has been proposed that there is an increased amount of acetylcholine (Ach) released from the urothelium during bladder filling, above and beyond the typical basal Ach release in OAB patients. The increase in Ach release from neuronal and nonneuronal (urothelial) sources heightens the bladder sensitivity to neurotransmitters, which subsequently leads to increased afferent signaling in the suburothelium and detrusor that is perceived as “sensory urgency.” It is this latter mechanism that is increasingly thought to be the target for the actions of antimuscarinic medications.

DIAGNOSIS

Proper management of patients with OAB begins with comprehensive evaluation, which entails complete history and physical, three day voiding diary, urinalysis, and post-void residual (PVR) check. The main focus during the initial assessment is to accurately depict the symptomatology, determine the severity, and detect any underlying and/or co-existing conditions that may be correctable, since OAB frequently overlaps with other lower urinary tract dysfunction.
Detailed history can uncover crucial information such as neurologic symptoms, radiation exposure, prior urologic surgery, traumatic injury, and use of diuretics, which can affect bladder and sphincteric function. Voiding diary can help distinguish nocturnal polyuria, polydipsia, and diabetes insipidus from OAB. Special consideration must be given to the elderly and debilitated patients who are at high risk for polypharmacy (See Table 1), baseline dementia, and other conditions that may complicate evaluation and management. Thorough physical exam may demonstrate enlarged prostate, high grade pelvic organ prolapse, decreased rectal tone, subtle dimpling in the lower back, anterior vaginal mass, and other positive findings that give valuable insight and can direct the treatment plan.

Adjunctive tests such as cystoscopy and multi-channel videourodynamics would be indicated for those patients who have elevated PVR, mixed urinary incontinence, prior anti-incontinence surgery, or any suspicion for neurogenic etiology in order to further investigate any possible obstruction, degree of sphincteric incompetence, and cystometric parameters which will need to be considered as part of the overall treatment plan. Use of disease specific validated quality of life questionnaires should be utilized to document baseline function and follow therapy outcomes.

**FIRST LINE TREATMENT: BEHAVIORAL MODIFICATION**

Behavioral modification is offered as the first-line treatment because it is effective in reducing OAB symptoms and relatively non-invasive. It can be tailored to address the individual patient’s needs and capacities by utilizing the various components of behavioral treatments, which include voiding diary, timed voiding, pelvic floor muscle training, and urge suppression techniques (distraction, self-assertions), biofeedback, electrical stimulation, fluid management, caffeine reduction, dietary changes (avoiding bladder irritants), weight loss and other life style changes. In addition, behavioral therapies have the advantage that they can be combined with all other therapeutic techniques.

The literature provides clear support for the efficacy of bladder training (incremental voiding schedules done with distraction and self-assertions) and behavioral training (pelvic floor muscle training with urge suppression techniques). Frequency as well as incontinence episodes can be reduced by 50 to 80 percent in both men and women. With strict adherence, behavioral treatment can be generally either equivalent to or superior to medications in terms of reducing incontinence episodes, improving voiding parameters such as frequency and nocturia, and improving quality of life.

**SECOND LINE TREATMENT: PHARMACOTHERAPY**

Second-line treatment with oral or transdermal antimuscarinics or β3-adrenoceptor agonists is offered to patients who have not achieved satisfactory improvement on behavioral modification alone. Pharmacotherapy can be effective but commonly associated with non-life-threatening side effects, which can compromise quality of life. Antimuscarinic medications are the foundation of pharmacologic therapy for symptoms associated with OAB. The currently available drugs in this class (oxybutynin, tolterodine, solifenacin, darifenacin, trospium, and fesoterodine) have similar mechanism of action by muscarinic receptor blockade but with few notable differences. Although most of the agents are tertiary amines, trospium is a quaternary amine and does not cross the blood–brain barrier. This drug may be better suited for elderly patients who are at higher risk for CNS side effects. Of these drugs, oxybutynin is the only one with transdermal patch and transdermal gel applications. This application bypasses...
liver metabolism that results in less dry mouth and constipation. All of the medications are available in extended-release (ER), once-daily preparations. Only oxybutynin, tolterodine, and trospium are available in immediate-release (IR) preparations, which allow flexibility in dosing.

The main side effects of antimuscarinics are dry mouth, constipation, dry or itchy eyes, blurred vision, dyspepsia, UTI, urinary retention, and impaired cognitive function. Rarely, life-threatening side effects such as arrhythmias have been reported. An extensive review of the randomized trials that evaluated pharmacologic therapies for OAB (including trials with placebo control groups as well as trials with active treatment comparison groups) revealed no compelling evidence for differential efficacy across medications.

For those patients who do not respond to or cannot tolerate antimuscarinics, beta 3 adrenergic receptor agonists mirabegron may be offered. There is a growing body of evidence suggest that mirabegron has similar efficacy to antimuscarinics, and is relatively safe, albeit limited to 12 weeks.

Behavioral and drug therapies are often used in combination in clinical practice to optimize patient symptom control and QoL. A limited literature indicates that initiating behavioral and drug therapy simultaneously may improve outcomes, including frequency, voided volume, incontinence and symptom distress. In patients who are not adequately improved on behavioral or drug therapy alone, there also is evidence that continuing the initial therapy and adding the alternate therapy using a stepped approach can produce additional benefit.

**THIRD LINE TREATMENT: BOTULINUM TOXIN A, TIBIAL NERVE STIMULATION, AND SACRAL NEUROMODULATION**

The refractory OAB group of patients present with unendurably bothersome urinary urgency with or without incontinence that has failed initial trial of behavioral modification and/or pharmacotherapy due to poor efficacy or intolerable side effects. Current treatment options for refractory OAB patients who fail adequate trial of conservative therapy—usually a combination of behavioral modification, pelvic floor rehabilitation, and pharmacotherapy for at least four to eight weeks—include botulinum toxin A therapy, percutaneous tibial nerve stimulation (PTNS), and neuromodulation.

**Botulinum toxin A**

Clinicians may offer intradetrusor botulinum toxin A (100U) as third-line treatment in the carefully selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. Botulinum toxin A is one of seven serotypes of neurotoxin derived from *Clostridium botulinum* and inhibits acetylcholine and adenosine-5'-triphosphate (ATP) release at the parasympathetic presynaptic nerve terminal, resulting in reversible chemo-denervation and flaccid muscle paralysis. Botulinum toxin A is typically injected into the detrusor in 10–30 sites with a total dose of 100–300U. Optimal dose for botulinum toxin A was defined in a Phase II, multicenter, 12-week, randomized, double blind study where 313 patients with idiopathic, refractory OAB (wet) received 50, 100, 150, 200, or 300U of intradetrusor botulinum toxin A or placebo.

Durable efficacy was observed for all onabotulinumtoxin A dose groups of at least 100U. Furthermore, doses at least 150U contributed minimal additional or clinically relevant improvement in symptoms. This study also noted dose-dependent increases in post void residual and infection.
rates, despite the significant improvement in subjective outcomes. Other disadvantages with this modality are the need for repeat treatment at six to nine months and the added costs of the drug, which is covered by some insurance companies for non-neurogenic group of patients.

Percutaneous tibial nerve stimulation
Percutaneous tibial nerve stimulation (PTNS) was developed in the late 1990s to stimulate sacral nerve roots through less invasive, peripheral pathways. This therapy consists of temporarily implanting a small, disposable needle near the medial malleolus of the ankle and undergoing stimulation of the underlying tibial nerve during 12 weekly 30-min sessions. Several recent studies have focused on the efficacy in treating patients with OAB refractory to medical therapy. In a recent randomized, multicenter, controlled study comparing PTNS to tolterodine extended-release, the authors noted comparable decrease in urgency, frequency, incontinence episodes, nocturia. Voided volume also improved.

A follow-up study looked at durability of PTNS and concluded that patients completing 12 weekly treatments maintained benefits at 12 months of follow-up. Recent study assessed PTNS with sham treatment and found significant difference between the groups: 54.5 percent of patients reported moderate or marked improvement in their symptoms after PTNS, compared with 20.9 percent after sham therapy. Another group also observed a 71 percent responder rate in patients completing 12 weekly PTNS sessions, with at least 50 percent reduction in urgency incontinence episodes, compared to 0 percent of patients in the sham group.

Sacral neuromodulation
Sacral neuromodulation (SNS) has become the leading treatment option for patients with refractory OAB since the Food and Drug Administration (FDA) approved it in 1997. There is growing body of evidence reporting on the safety and efficacy of this procedure which involves staged placement of an electrode into the third sacral nerve foramen during the test phase of one to two weeks followed by implantation of the pulse generator (Figures). The electrical stimulation delivered to the root of third sacral nerve is thought to modulate reflex pathways of the micturition cycle thus reducing urgency, frequency, and incontinence episodes. Recently, long-term durability of SNS has been reported with 64 percent of patients having at least 50 percent improvement in daily incontinence episodes, daily pad use, number of daily voids, or an increase in voided volume at mean follow-up of 53 months. Another study found overall satisfaction with SNS was high at 90 percent and no correlations were found between the satisfaction rate and pretreatment age, sex, complaint type, sexual dysfunction, or therapy duration. Several studies have reported on high durable success rate from SNS. Most common adverse events of SNS include pain at the stimulator site (3.3 to 19.8 percent of patients), pain at the lead site (4.5 to 19.1 percent of patients), lead migration (1.1 to 8.6 percent of patients), infection/irritation (2.2 to 14.30 percent of patients), electric shock (5.5 to 10.2 percent of patients) and need for surgical revision (6.25 to 39.5 percent of patients). In most studies, the need for surgical revision occurred in greater than 30 percent of patients. There is some evidence that newer, less invasive surgical procedures and tined devices may be associated with fewer adverse events.

Patients undergoing SNS should be carefully counseled on inability to undergo magnetic resonance testing with this device. There is also potential for periodic clinic visits for adjustment and replacement of the pulse generator.

ADDITIONAL TREATMENTS
Surgical intervention remains as the last resort for refractory OAB patients who have exhausted all other options. Augmenting a small functional bladder with a patch of intestine has shown to increase bladder volumes at low filling pressures with high satisfaction rate but may affect emptying ability, since the bladder may become defunctionalized. A less invasive extraperitoneal approach to augmentation cystoplasty by making only a small incision in the peritoneum to harvest a small bowel segment via a Pfannanstiel incision minimizes bowel manipulation, hastens return of bowel function, and shortens hospital stay. For patients who have concomitant urinary incontinence, sling or bladder neck closure with catheterizable stoma can be performed to provide continent mechanisms.

If all else fails, indwelling catheters (including transurethral and suprapubic types) may be an option for those patients who are severely debilitated with limited cognitive function whose quality of life is deeply affected by OAB and associated incontinence. Indwelling catheters are associated with complex UTIs, skin infection, urethral erosion, gross hematuria, and other morbid conditions, which must be carefully managed.

CONCLUSION
OAB and associated incontinence is a highly prevalent condition with significant psychosocial, medical, and economic burden. It is crucial to accurately distinguish OAB symptoms from other associated disease entities, such as infection, malignancy, neurologic disease, and anatomic defects, which must be addressed as part of a comprehensive treatment algorithm. Optimal management of
this complex syndrome is aimed as relieving symptoms to improve quality of life with clinically effective and minimally invasive treatments.

In the past two decades, we have achieved better pharmacologic understanding and technologic innovations to improve management of refractory OAB. Increased awareness of OAB among clinicians can lead to earlier detection and therapy to improve overall quality of life.

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