



Evaluation and Treatment of Overactive Bladder in Women

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Learning Objectives: On completion of this article, the reader should be able to: 1) describe how to diagnose and evaluate uncomplicated overactive bladder (OAB); 2) summarize the available treatment of options for the management of OAB; and 3) recognize when to refer patients to a specialist with expertise in OAB management.

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Abstract

Overactive bladder (OAB) is a symptom complex that includes urinary urgency, frequency, urgency incontinence, and nocturia. It is highly prevalent, affecting up to 12% of the adult population, and can significantly impact quality of life. The diagnosis of OAB is made by history, physical examination, and a urinalysis to rule out underlying infection or other concerning potential etiologies. The need for additional testing is based on the initial evaluation findings, and is recommended in cases of underlying urinary tract infection, microscopic hematuria, obstructive voiding symptoms, and symptoms refractory to previous treatments. Initial management includes behavioral modification with attention to total daily fluid intake, avoidance of bladder irritants, treatment of constipation, weight loss, timed voiding, urge-suppression techniques, and pelvic floor physical therapy. Options for oral medications include antimuscarinic agents and β adrenergic agents, and can be used following or in conjunction with behavioral treatment. For patients refractory to behavioral therapy and oral medications, consideration should be given to referral to a specialist (eg, a urologist or urogynecologist) for discussion of more advanced therapies such as sacral neuromodulation, percutaneous tibial nerve

stimulation, and intradetrusor injection of onabotulinumtoxinA. These more advanced treatments have favorable efficacy compared with oral agents in randomized trials, although each has a unique risk/benefit profile and shared decision-making with the individual patient is crucial. Here, we review pertinent considerations in the clinical evaluation and management of OAB in women.

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Overactive bladder (OAB) is a symptom complex defined by the International Continence Society and International Urogynecologic Association as “urinary urgency, usually accompanied by frequency and nocturia with or without urinary incontinence in the absence of pathologic or metabolic conditions that might explain these symptoms.”¹ It is highly prevalent, affecting up to 12% of the adult population, and can have a significant negative impact on quality of life.² Urinary urgency, which is “a sudden compelling desire to pass urine which is difficult to defer,” is the most defining feature of OAB.¹ Urinary frequency is constituted by greater than seven voids during the daytime hours, and nocturia is one or more voids that interrupt sleep. Urge urinary incontinence is the involuntary loss of urine associated with urgency to void.^{1,3} Notably, patients with an underlying neurologic diagnosis potentially impacting their bladder function (eg, spinal cord injury, multiple sclerosis, or Parkinson disease) may need additional evaluation beyond routine OAB care and are outside of the scope of this review. For management of voiding symptoms in these patients, consideration should be given to specialty referral.

DIAGNOSIS AND EVALUATION OF OAB

The diagnosis of OAB is made based on history, physical examination, and urinalysis to rule out a urinary tract infection or other conditions that might result in similar symptoms.³

History

A thorough history is the initial step to the evaluation of OAB. Discussion should include a qualitative and quantitative assessment of symptoms and urinary urgency, daytime

voiding frequency, nocturia, and urinary incontinence episodes.⁴ An assessment of the severity of symptoms can be made by the number of pads used, influence on quality of life, and/or the use of validated questionnaires.³ The duration of symptoms, amount of total daily fluid intake, intake of bladder irritants (eg, carbonated drinks, artificial sweeteners, caffeine, and alcohol), and the use of medications such as diuretics should also be documented. Additional pelvic floor symptoms (eg, bowel dysfunction, pelvic organ prolapse, or dyspareunia) may also be present and comanaged. A review of the medical history for neurologic disease (eg, multiple sclerosis, spinal cord injury, Parkinson, or cerebrovascular accident), endocrine conditions (eg, diabetes mellitus, or diabetes insipidus), other genitourinary conditions, prior pelvic surgeries, malignancy, and radiation should be performed. Regarding prior pelvic surgeries, particular attention should be paid to previous anti-incontinence procedures (eg, urethral slings, urethral bulking agent injection, or retropubic suspensions), and the use of transvaginal mesh or other pelvic organ prolapse surgeries. The presence of pelvic pain or dyspareunia usually points away from the diagnosis of OAB, and more towards a diagnosis of pelvic floor tension myalgia, large muscle group dysfunction (hip/paraspinal), interstitial cystitis/painful bladder syndrome, or other causes of pelvic pain, such as endometriosis.³ Many of these women may have concomitant urinary symptoms due to underlying pelvic floor muscle response/spasm.

Physical Examination

An abdominal and genitourinary examination should be performed. Pertinent findings on genitourinary exam include an assessment

of pelvic floor muscle strength or tenderness, degree of vaginal mucosal estrogenization, assessment for periurethral masses, pelvic organ prolapse, and concomitant stress urinary incontinence. A general evaluation of cognitive function, the neurologic system including sacral neural pathways (perineal sensation, bulbocavernosus reflex, anal sphincter tone), and lower extremity edema should also be performed.³

Laboratory Tests and Additional Testing

The initial laboratory evaluation of uncomplicated OAB is a urinalysis.³ In the presence of nitrites or leukocyte esterase in the urinalysis or a clinical suspicion of a urinary tract infection, a urine culture should be performed. The presence of hematuria on urinalysis with microscopy (not urine dipstick) in the absence of a benign underlying etiology should prompt additional testing including cystoscopy and upper urinary tract imaging.⁵ A post-void residual (PVR) should be obtained in patients with obstructive symptoms (eg, weak stream, urinary hesitancy, or intermittency), a history of anti-incontinence surgery, suspicion for undiagnosed neurologic disease, and at the provider's discretion. A PVR should also be assessed before starting antimuscarinic drugs in patients at high risk for urinary retention (eg, those with a prior anti-incontinence surgery, subjective weak or slow urinary stream or other obstructive symptoms, sensation of incomplete bladder emptying, or neurologic diagnosis).⁶ Bladder diaries may be used to evaluate the volume and timing of fluid intake and voids (including the volume and circumstance of incontinence episodes) to document baseline symptoms and assess treatment response. A voiding diary can be of particular use in evaluating nocturia, as nocturia may be due to factors other than bladder function, such as excessive nighttime urine production (nocturnal polyuria), cardiovascular disease, sleep apnea, or other parasomnias.⁶ The volume voided is normal or large in nocturnal polyuria, in contrast to the low voiding volumes in OAB.^{6,7} Symptom severity and response can also be evaluated using validated symptom

questionnaires for OAB, such as the Overactive Bladder Symptom Score.⁸ Urodynamics, although not performed for initial evaluation of uncomplicated OAB, may be performed in complicated cases (eg, those with a prior anti-incontinence surgery), when there are refractory OAB symptoms despite previous therapies, and before more advanced OAB treatment options.³ Likewise, in uncomplicated cases, routine cystoscopy or urine cytology are not recommended.³

TREATMENT OF OAB

OAB is a quality-of-life issue and the risk versus benefits of any treatment should be weighed carefully in shared decision-making with the individual patient. Patients and their health care providers should discuss normal urinary function, the current knowledge with regard to OAB, and the advantages and drawbacks of each treatment option. Expectant management in patients not bothered by symptoms represents an acceptable option.

Setting Goals

It is important to determine reasonable therapeutic goals for symptom control before starting therapy. Patients should realize that acceptable symptom control may involve trial and error of the various lines of therapy, and is usually a long-term process requiring adjustments to treatment plans and ongoing re-evaluation of treatments. Patients should also be informed that treatments may improve symptoms, but not necessarily eliminate them.

Behavioral Therapy

Behavioral therapy is considered first-line therapy due to its effectiveness, minimal risk, and robust literature supporting its use.^{3,9,10} In addition to education about normal bladder function, behavioral modification involves gradual total daily fluid intake reduction if polydipsia is present (goal: 1.5-2 L, pending other medical conditions such as urolithiasis), avoidance of bladder irritants, constipation management, weight loss, bladder training with timed voiding, and referral to a pelvic floor muscle

physical therapist with specialization in female pelvic health. Although complete symptom control is less common with these interventions, significant improvements in quality of life have been reported.^{3,11} For example, in a randomized study evaluating weight loss, in the intervention group, a mean weight loss of 8% (7.8 kg) resulted in a 47% decrease in the number of weekly leakage episodes, and 42% reduction in urgency incontinence episodes (controls 28% and 26%).¹⁰ Although considered second-line therapy, simultaneous initiation of medical management along with behavioral therapy is supported by literature.³

Medical Management

Oral medications are considered second-line therapy, and two classes of medications are available: antimuscarinic agents and β adrenergic agents.³ The choice of oral agent is driven by the side effect profile, patient tolerance, and contraindications to use. Complete relief from urgency and urinary urgency incontinence is uncommon with oral medications, although many patients may have significant benefit.^{3,12}

Antimuscarinic Agents. Numerous antimuscarinic medications are available including oxybutynin, darifenacin, solifenacin, tolterodine, fesoterodine, and trospium. In systematic reviews, no single agent has been found to be superior to the others.^{3,13} The side effect profile commonly limits ongoing use and includes dry mouth, dry eyes, constipation, blurred vision, dyspepsia, urinary retention, and impaired cognitive function.^{3,14} Recent data have highlighted the association of antimuscarinic medication use and the risk of cognitive decline, dementia, and Alzheimer's disease, particularly with continued use (>3 years).¹⁴ Additionally, anticholinergic medication use for OAB has been associated with an increased risk of falls or fractures in older patients.¹⁵ When an anticholinergic medication is going to be used, extended-release formulations are preferred as they have significantly less dry mouth than their immediate-release counterparts.³ When cognitive side effects are of specific concern,

consideration should be given to use of the lowest effective dosing, and agents with lower central nervous system penetration (active transport out of central nervous system and quaternary amine structure), such as trospium.^{16,17} Absolute contraindications to antimuscarinic medication use include narrow-angle glaucoma, impaired gastric emptying, and in those patients on solid oral forms of potassium chloride. Relative contraindications include elevated PVR, and impaired or declining cognitive function.³

The response and adverse effect profile among drugs is variable, so if a patient experiences inadequate symptom control (after 4- to 8-week trial) or adverse effects with one drug, then dose escalation (as side effects allow) or a trial of a different therapy is acceptable.³ The general principle for use of antimuscarinic medication is to start at a low dose and slowly increase the dose to achieve acceptable symptom control while balancing the side effect profile. When adequate symptom control is achieved in the setting of bothersome side effects, an attempt to manage side effects should be made. Dry mouth can be mitigated with oral lubricants or mouth washes (avoid alcohol based mouthwash), sips of water, sugar-free candy, or chewing gum.³ Similarly, constipation can be managed with dietary changes, fiber supplementation, stool softeners, laxatives, and regular exercise.³

β Adrenergic Agents. β_3 adrenergic agonists, such as mirabegron, are another class of oral medication available for the management of OAB.⁶ The benefit of this class is avoidance of the anticholinergic side effects, such as dry mouth and constipation. As such, they can be used in patients who are not able to tolerate antimuscarinic medications, or in whom the use of antimuscarinics are to be avoided. Although no randomized comparative data are available, systematic reviews note relatively similar efficacy between these two classes of medications.¹⁸ Mirabegron has higher patient adherence to treatment at 12 months, in comparison with oral antimuscarinic agents, although more than 50% of patients will stop either

medication by 6 months.¹⁹ Side effects of β_3 adrenergic agonists include increased blood pressure, nasopharyngitis, urinary tract infections, and urinary retention. In pooled analysis, the rate of cardiac adverse events (hypertension or arrhythmia) were minor and comparable between the 25-mg and 50-mg doses of mirabegron, and in comparison to an anticholinergic medication (tolteridine).⁶ Severe uncontrolled hypertension is a contraindication to β adrenergic agonist use. Combination of a β_3 agonist with an anticholinergic medication may be beneficial in patients refractory to monotherapy.^{3,20}

Follow-Up. Follow-up after initiation of a line of OAB therapy is important to assess symptom control, compliance, side effects, attainment of treatment goals, and for discussion of alternative management options or specialist referral. Allow for 4 to 8 weeks of behavioral modification or oral medical treatment to establish response, pending side effects limiting the duration of medication use. Patients do not need to undergo every type of treatment to progress to others, including more advanced treatments.⁶

Advanced Therapies

Beyond the above-mentioned treatments, more advanced therapies exist for managing refractory OAB, including intradetrusor injection of onabotulinumtoxinA, sacral neuromodulation, and percutaneous tibial nerve stimulation.⁶ Each treatment has its own unique risk/benefit profile and proper patient selection and counseling is essential before proceeding with these therapies. In a contemporary sample of national claims data, only 2% of women progressed to these treatments, although referral to a specialist (eg, urology or urogynecology) facilitated counseling and further treatment.¹⁹

Intradetrusor OnabotulinumtoxinA Injection. In 2013, intradetrusor onabotulinumtoxinA was approved by the United States Food and Drug Administration (FDA) for the treatment of OAB symptoms in adults who do not tolerate or adequately respond



FIGURE 1. Cystoscopic intradetrusor injection of onabotulinumtoxinA.

to anticholinergic medications.²¹ The therapy is performed by a cystoscopic injection that can be performed in an office setting with local anesthesia or under sedation in the operating room (Figure 1). The medication (typically 100 units) is injected in roughly 20 aliquots throughout the bladder. The effect of the medication is thought to be secondary to inhibition of presynaptic release of acetylcholine, and as such the muscarinic receptors in the bladder cannot be activated (as is present in OAB).²¹

In several multicenter randomized trials, onabotulinumtoxinA injection had greater efficacy than placebo in improving OAB symptoms.²² More recently, a randomized trial comparing onabotulinumtoxinA injection (200 units) and SNM found a similar degree of symptom improvement between the treatments at 2-year follow-up.²³ In this study, 200 U of onabotulinumtoxinA were used, whereas the initial dose typically used is 100 U, which may impact some of the study findings. Response to the onabotulinumtoxinA injection is transient, with an average time to reinjection of roughly 6 to 7 months.^{24,25} That being said, durable responses with repeat injection have been reported up to 3.5 years in prospective studies.²⁵

Risks of the procedure include hematuria, urinary tract infection, and urinary retention. Given the risk of urinary retention, patients must be willing and able to perform self-catheterization if needed. The rate of urinary retention is variable between studies, but most report a rate between 4% and 10%.^{23,25} If urinary retention is encountered, it lasts on average 8 weeks.²⁵

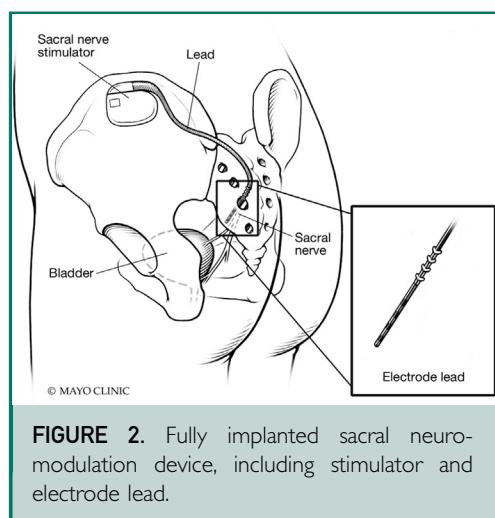


FIGURE 2. Fully implanted sacral neuromodulation device, including stimulator and electrode lead.

Sacral Neuromodulation. Sacral neuromodulation (SNM) is performed via a minimally invasive procedure that uses percutaneous placement of a lead with electrodes through the S3 foramen to stimulate the S3 nerve roots. The lead itself is stimulated by a pulse generator (Figure 2). The leads are thought to modulate the sacral afferent nerves and in turn help balance the neural reflexes among the bladder, sphincter, and pelvic floor muscles. At the time of this review, the Interstim device (Medtronic, Minneapolis, MN) is the only commercially available sacral neuromodulation device FDA-approved for OAB, although other products, such as the Axonics SNM System (Axonics Modulation Technologies, Irvine, CA) are undergoing evaluation.

The SNM procedure is performed in two stages. The first, which can be performed in the office or the operating room (depending on specific clinical details), typically uses fluoroscopic imaging to guide lead placement through the S3 foramen. During the procedure, the lead is tested to evaluate for appropriate motor and sensory responses. The patient then has a trial period, using an external generator, to assess the impact that the therapy has on their symptoms. If they have 50% or better improvement, they can proceed to the operating room for placement of the more permanent lead and/or pulse generator. If there is not a significant improvement in symptoms, the lead is

removed (either in the office or operating room, depending on how it was placed) and the patient can pursue other treatments.

In terms of symptom control, at the 6-month timepoint in a randomized multi-center trial, SNM had a significantly greater proportion of therapeutic success ($\geq 50\%$ improvement in average leaks/d or void/d) compared with anticholinergic medical therapy (76% vs 49%; $P=.002$).²⁶ The symptom improvement with SNM was then prospectively followed, and the results found to be durable to the 5-year timepoint.²⁷ At baseline, patients with urgency incontinence reported a mean \pm SD of 3.1 ± 2.7 leaks/d and those with urgency-frequency had 12.6 ± 4.5 voids/d, which improved by 2 ± 2.2 leaks/d and 5.4 ± 4.3 voids/d with 5-year longitudinal follow-up of responders.²⁷

Limitations of this treatment modality include the risk of device infection, need for battery replacement over time (average ~ 3 -5 years), potential need for device revision for discomfort at the battery site, lead damage, uncomfortable sensation from the stimulation, or need for device reprogramming.^{23,26,27} Additionally, while the Interstim device has conditional approval for head magnetic resonance images with specific imaging parameters, other forms of magnetic resonance imaging are contraindicated with the device in place.²⁶

In addition to use for medically refractory urinary urgency incontinence (FDA approved 1997) and urinary urgency-frequency symptoms (FDA approved 1999), SNM via Interstim placement is also FDA approved for the management of fecal incontinence (FDA approved 2010) and non-obstructive urinary retention (FDA approved 1999). As such, one unique aspect of the therapy is the ability to treat dual incontinence (bladder and bowel) simultaneously.

Percutaneous Tibial Nerve Stimulation. Percutaneous tibial nerve stimulation (PTNS) is performed via placement of a peripheral needle that stimulates the posterior tibial nerve and was FDA approved for refractory OAB in 2010. The treatment is

performed in an office setting, and involves using a small percutaneous needle electrode (34 Gauge) being inserted near the posterior tibial nerve at the level of the medial malleolus. The needle is then stimulated via an external pulse generator. The electrical impulses are delivered along the tibial nerve to the S3 segment of the pelvic sacral plexus, which allows it to impact voiding reflexes. At the end of the 30-minute treatment session the needle is removed. The treatments are then performed weekly for 12 weeks, with those achieving adequate improvement proceeding to maintenance therapy (roughly every 3 weeks). PTNS has been shown in randomized trials to have significantly better efficacy than anticholinergic medications and sham treatment.^{28,29} In a systematic review of the available studies, PTNS showed a therapeutic success rate ranging from 54% to 59%.³⁰ Compared to SNM, PTNS is less invasive and lower risk, but has lower success rates and is more time intensive.³⁰ Contraindications to this therapy include patients with a bleeding tendency, peripheral neuropathy, cardiac pacemaker, and patients who are pregnant or considering becoming pregnant during treatment.

Other Treatments. The use of an indwelling catheter is not recommended and should be considered as the last resort in select patients due to the risks of urinary tract infection, urethral erosion of the Foley catheter, damage to the bladder neck, and urolithiasis. Management with absorbent pads/garments is preferable to indwelling Foley catheter placement.³ One exception to this may be when urinary incontinence has resulted in progressive decubiti.³ In such an instance, use of a suprapubic catheter would be preferable to a transurethral catheter due to the risk of urethral erosion. In contemporary practice, augmentation cystoplasty and urinary diversion are rarely considered for severe refractory OAB.³

CONCLUSION

OAB is a highly prevalent condition in women. Following a complete history and physical examination, in the setting of a normal urinalysis, clinicians should feel

comfortable with the initial management. Depending on the clinical scenario and patient preference, this may include behavioral modifications, pelvic floor physical therapy, and/or oral medications. In patients with refractory symptoms despite these interventions, consideration should be given to specialty referral for discussion of more advanced therapies such as PTNS, SNM, or intradetrusor injection of onabotulinumtoxinA.

Abbreviations and Acronyms: FDA = United States Food and Drug Administration; OAB = overactive bladder; PVR = post-void residual

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