

Overactive Bladder: Where We Are and Where We Are Going

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Abstract

Overactive bladder (OAB) is a heterogeneous syndrome estimated to affect approximately 10% to 15% of men and women globally. OAB not only negatively impacts quality of life but also results in a significant financial burden to both patients and health systems. Therefore, it is crucial that OAB is properly addressed. This manuscript provides a general review of the diagnostic algorithm for OAB and treatment per the AUA/SUFU guidelines, and an overview of new developments in OAB therapy. Given the wide array of therapeutic options that currently exist and those that are currently under development, there is tremendous opportunity to treat OAB successfully and positively affect our patients' lives.

Introduction

Impact of Overactive Bladder

Overactive bladder (OAB) affects approximately 10% to 15% of men and women, with some estimates placing prevalence as high as 27% for men and 43% for women[1-3]. Individuals with OAB have been shown to have poorer quality of life, higher rates of depression, and decreased rates of sexual fulfillment when compared with individuals who do not have OAB[4]. In a cohort of several North American and Western European nations, OAB-related expenses amounted to. €1.2 billion per year[5]. With the high prevalence of OAB, the aging population, and the associated cost to the system, proper management of OAB is essential. This manuscript provides an overview of current treatment options and a discussion regarding new developments in advanced therapies.

Defining Overactive Bladder

OAB was first described as a clinical entity in the late 1980s[6]. The American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) OAB guidelines acknowledge the challenges in defining OAB, as reflected by the number of statements that are based upon expert opinion rather than scientific publications. Joint work by the International Urogynecological Association (IUGA) and International Continence Society (ICS) defines OAB as “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection (UTI) or other obvious pathology”[7]. **Figure 1** shows an algorithm proposed by the authors to guide the evaluation of patients with OAB symptoms. While not a guideline, this pathway can offer clinicians, particularly those not familiar with OAB management, a structured approach to managing these patients.

Key Words

Overactive bladder, therapeutics, urgency urinary incontinence

Competing Interests

None declared.

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Abbreviations

AUA	American Urological Association
BPH	benign prostatic hypertrophy
BTX	onabotulinumtoxinA
CNS	central nervous system
DO	detrusor overactivity
GSM	genitourinary syndrome of menopause
MRI	magnetic resonance imaging
OAB	overactive bladder
PRO	patient-reported outcomes
RCT	randomized control trial
SNM	sacral neuromodulation
SUFU	Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction
SUI	stress urinary incontinence
UDS	urodynamics
US	ultrasound
UTI	urinary tract infection
UUI	urge urinary incontinence

Methods

A comprehensive literature search was performed using PubMed regarding (1) the pathophysiology of OAB, (2) treatment options for OAB, and (3) special considerations with respect to OAB management. Approach to treatment is presented per the AUA/SUFU guidelines, summarizing lifestyle modifications (first-line), pharmacotherapy (second-line), and surgical and interventional therapies (third-line), and concluding with a discussion regarding new treatment developments in advanced therapies.

Pathophysiology

Several etiologies for OAB have been defined: (1) myogenic detrusor overactivity (DO), (2) overactive signaling by the central nervous system (CNS) causing micturition (neurogenic), and (3) alterations within the urothelium of the lower urinary tract[8,9]. The myogenic hypothesis attributes DO to changes within the bladder smooth muscle that result in increased excitability and spontaneous contraction[10]. In vivo tissue studies have suggested that structural changes within the detrusor muscle in OAB could allow for increased conduction of electrical impulses with resultant contraction among a large proportion of muscle cells[11].

In the neurogenic hypothesis, bladder overactivity is attributed to increased neuroplasticity within the CNS[12]. Maladaptive sensory signaling from pelvic sensory nerves can instigate DO and precipitate OAB[13]. Two neurotrophins, specifically brain-derived

neurotrophic factor (BDNF) and nerve growth factor (NGF), have been implicated in OAB. These are modulators of neural plasticity, and individuals with OAB symptoms have demonstrated detectable amounts of these molecules in their urine[14–17]. Additionally, individuals with OAB exhibit varying degrees of functional connectivity in the cortex on functional MRI (fMRI) studies[18,19], and interestingly, sacral neuromodulation has been demonstrated to cause cerebral activity on fMRI[20], emphasizing the role of CNS function in OAB.

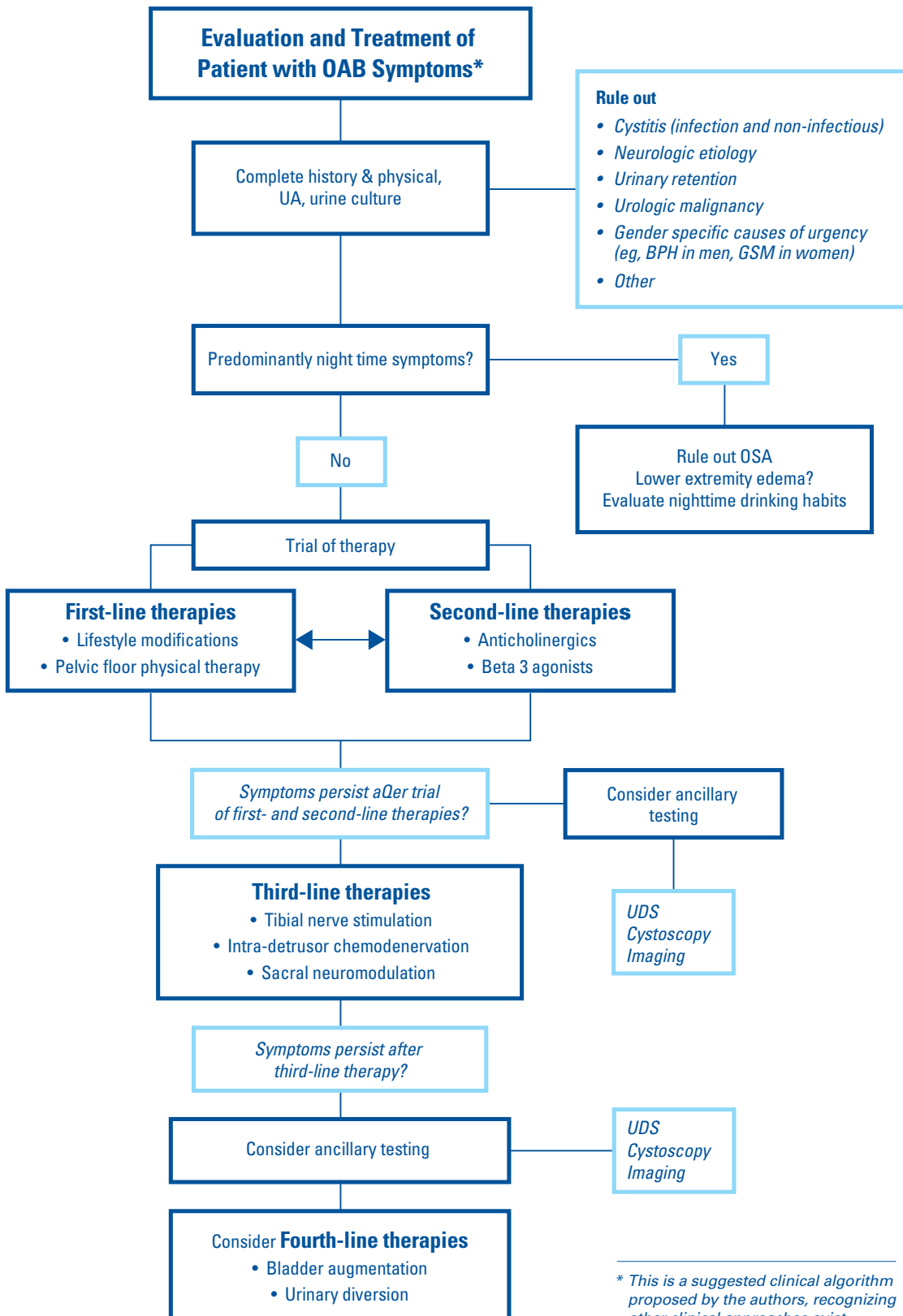
Regarding the urothelial hypothesis, research in rat models indicates that chronic urothelial injury, as modeled by intravesical injection of protamine sulfate into rats, can cause increased urinary frequency and decreased voided volumes[21]. A related hypothesis postulates that OAB symptoms may also be urethrogenic, that is, arising from the urethra[22]. Specifically, low urethral tone and subsequent stress urinary incontinence (SUI) or contact of urine with the proximal urethra can stimulate the proximal urethral afferent nerves that can initiate micturition via the urethrovesical reflex and, in some cases, cause symptoms of OAB. Newer areas of exploration for OAB pathophysiology include the role of sex hormones, mood disorders, and the effect of the urinary microbiome[23].

OAB Treatment Guidelines

The AUA/SUFU OAB guidelines provide a framework clinicians can use to diagnose and stratify patients with OAB. As acknowledged in the guidelines, there is a lack of evidence-based publications in the current literature regarding the diagnosis of OAB. A clinical principle in the guidelines suggests that the initial evaluation for uncomplicated OAB requires only a thorough history and physical examination and a urinalysis to rule out conditions that may mimic OAB, such as urinary tract infection or malignancy. Use of adjunct tests such as urine cultures or post-void residuals can be incorporated as deemed necessary. The guidelines also clarify that UDS, cystoscopy, and renal imaging are not indicated in the initial workup. Clinicians should also consider how OAB symptoms may manifest in select populations, such as men with benign prostatic hypertrophy (BPH) or women with genitourinary syndrome of menopause (GSM).

The guidelines stratify OAB treatment into several tiers: first-line (behavioral and non-pharmacologic), second-line (pharmacologic therapy), third-line (surgical and interventional therapies) and fourth-line (urinary diversion or bladder augmentation)[1]. This discussion focuses on the first 3 tiers.

FIGURE 1.
Suggested clinical algorithm for management of OAB



First-Line Therapy

First-line therapy for OAB includes low-risk behavioral interventions, although much of the data supporting these therapies is drawn from non-randomized controlled trials (RCT). In a study of pelvic floor biofeedback for OAB symptoms in women, 9 weeks of EMG-based biofeedback for pelvic floor muscle therapy resulted in significant symptom improvement[24]. A review exploring the role of pelvic floor muscle therapy traditionally used for SUI found the use of similar regimens in patients who had urinary urgency and OAB symptoms effectively reduced symptoms[25].

In a comprehensive review regarding urinary symptoms in overweight and obese women, weight loss showed no benefit in the reduction of urinary urgency[26]. However, in a cohort of morbidly obese patients who underwent laparoscopic sleeve gastrectomy, patients experienced a significant improvement in OAB symptoms as measured by a 3-day voiding diary and improvement on the OAB short form questionnaire. The mean reduction in BMI following surgery was 9 kg/m², suggesting that the magnitude of weight loss to reduce symptoms may be unattainable for many patients[27].

Smoking and dietary habits, particularly consumption of carbonated beverages, alcohol, and caffeine, can cause OAB symptoms. Accordingly, lifestyle modifications aimed at reducing smoking and dietary triggers can result in an improvement of OAB[28]. Finally, an association between functional constipation and OAB has been shown[29–31], but these studies do not specifically report on the effect of treating constipation and relief of OAB.

Second-Line Therapy

Anticholinergics

Anticholinergics are a well-established pharmacotherapy for OAB[1]. There are 5 described subtypes of muscarinic receptors, of which M2 and M3 are found in highest concentration within the bladder. While the M2 receptor is predominant in the bladder, the M3 receptors are most strongly associated with micturition control[32]. A review examining the effectiveness of anticholinergics versus behavioral therapy concluded that anticholinergics outperformed non-pharmacologic interventions for improvement in OAB symptoms[33].

While dry mouth and constipation are the most frequent side effects of anticholinergic medications, cognitive side effects can be profound, particularly amongst older individuals. The rates of discontinuation of anticholinergics in trial settings have been shown to be as high 80%[34]. In a case– control study conducted in the United Kingdom, anticholinergic exposure was associated with dose-dependent increased odds of developing dementia[35]. This relationship has been well

documented and demonstrated, particularly in older individuals[36–38]. At a molecular level, trospium's bulky quaternary amine structure limits its penetration across the blood–brain barrier, thereby reducing unwanted cognitive effects[39,40].

Beta-3 agonists

Beta-3 agonists represent a newer class of OAB medication. Studies have demonstrated that mirabegron is equally efficacious as anticholinergics in their reduction of OAB symptoms[41–43]. Potential side effects include hypertension and cardiac arrhythmia[44]. In a study examining the safety profile of mirabegron, there was a slight increase in hypertension with this drug compared with placebo and only among individuals over 75 (7% versus 5%)[45]. The absence of hypertension risk has also been reaffirmed on meta-analysis[46]. In an observational study from the UK, improvements in both quality of life and health status were seen for patients on mirabegron, with over 50% persisting on the drug at 12 months[47].

Recently approved, vibegron is a novel beta-3 agonist that has also shown efficacy in placebo-controlled studies including reduction of micturition episodes and urge incontinence episodes[48,49]. Furthermore, recent RCT data showed no difference in the rates of hypertension between patients on vibegron versus placebo[50].

Despite a higher per-pill cost of beta-3 agonists, recent studies have demonstrated a similar cost-effectiveness between beta-3 agonists and anticholinergics. This increased cost-effectiveness has been attributed to decreased discontinuation of beta-3 agonists, leading to improved quality of life, decreased need for third-line therapies, and decreased health care use due to adverse events[51–54].

Third-Line Therapy

Third-line therapies represent a rapidly growing category of OAB treatment, although they remain underutilized[55]. Existing third-line therapies include bladder chemodenervation with onabotulinumtoxinA (BTX), percutaneous tibial nerve modulation (PTNM), and sacral neuromodulation (SNM).

Bladder chemodenervation with onabotulinumtoxinA

Chemodenervation involves the prevention of pre-synaptic release of acetylcholine (ACh) thereby averting excitation of ACh-dependent smooth muscle within the detrusor and reducing bladder contractions[56]. Data also suggest that the toxin may decrease sensory input during bladder filling via its effect on ATP-regulated signaling mechanisms[56–58].

BTX is administered cystoscopically with injections distributed throughout the bladder[59,60]. Complete

resolution of urinary incontinence has been shown to be higher amongst those receiving BTX (27%) compared with those on anticholinergics (13%)[\[61\]](#). BTX also outperforms placebo for the reduction of OAB symptoms, with 2.95 fewer daily UUI episodes compared with 1 fewer observed with a placebo after 12 weeks of treatment[\[58\]](#). BTX injection also appears to be of therapeutic value for all patients with idiopathic OAB, regardless of whether DO is present on pretreatment urodynamics[\[62\]](#). One of the potential risks of BTX is urinary retention. However, the definition of retention is not standardized across the BTX reports, and this has contributed to the widely variable (2% to 35%) rates reported in the literature. The risk of retention appears to be dose-dependent[\[63–66\]](#). Studies have demonstrated a median of 7.6 months of symptom relief following BTX injection[\[67\]](#). There are data suggesting that the production of neutralizing antibodies can result in tachyphylaxis with successive treatments with BTX. However, this risk has been drastically lowered with newer formulation of the toxin[\[68\]](#).

Percutaneous tibial nerve modulation

Performed in the clinic setting, PTNM involves 12 weekly in-office sessions during which a 34-gauge needle is placed cephalad to the medial malleolus and posterior to the tibia. The posterior tibial nerve is stimulated at varying frequencies with an external generator. The hypothesized mechanism of action involves modulation of bladder contraction via both afferent and efferent pathways of the tibial nerve[\[69,70\]](#).

PTNM has shown success in patients with refractory OAB. In a study of patients undergoing a 12-week study course, a 25% reduction in mean daytime urinary urgency, a 35% reduction in number UUI episodes, and a 21% reduction in nighttime frequency was reported[\[71\]](#). Adverse effects of PTNM are rare and include bruising, pain, and bleeding at the needle site[\[59\]](#). PTNM therefore remains a well-tolerated and efficacious option for the treatment of OAB. Despite this, there remains a high drop-out rate, with retrospective data indicating an over 40% discontinuation rate[\[72\]](#), similar to the drop-out rates reported with BTX. Only 40% to 60% of patients receive a second injection, with subsequent treatments decreasing even further[\[73–75\]](#).

The updated OAB guidelines include a specific statement that the guidelines do not represent a step-by-step algorithm that must be followed in successive order. Consequently, a study that showed success with PTNM in drug-naïve OAB patients was of interest. In a single-arm study of drug-naïve OAB patients with >3 UUI episodes a day, 78% of patients saw a 50% reduction in their UUI episodes, with 40% achieving complete continence[\[76\]](#).

Sacral neuromodulation

Sacral neuromodulation is an operative procedure, performed in 2 stages. During the first stage, a tined lead connected to an external generator is inserted into the S3 foramina. If the patient experiences a $\geq 50\%$ improvement in their symptoms during the 1 to 2 week trial period, a permanent impulse generator (IPG) is inserted into a subcutaneous pocket low back/upper buttock[\[77\]](#). Alternatively, the first stage can be done in the office setting as a peripheral nerve evaluation with temporary bilateral leads, with or without fluoroscopic guidance. If successful, the lead and IPG can subsequently be placed in a single procedure.

SNM has been shown to be well tolerated and more efficacious than standard medical therapy. In a study comparing SNM with anticholinergic medical therapy, 76% of the SNM arm experienced therapeutic success ($\geq 50\%$ improvement) compared with 49% of the medical arm[\[78\]](#). While the ROSETTA trial suggested a slight advantage of BTX over SNM in reducing OAB symptoms, this trial used an unconventional 200-unit dose of BTX, as opposed to the accepted 100 units for idiopathic OAB[\[79\]](#). This initial advantage of BTX was not noted at 2 years. In the 2-year follow-up, 72% of patients randomized to BTX had required a second injection, with half of these individuals requiring a third[\[80\]](#).

In a retrospective analysis of state claims data, 38% of all patients who undergo SNM implantation undergo a lead revision within 5 years of their initial lead implantation, approximately two-thirds for device malfunction and the remaining third for treatment failure[\[81\]](#). Another consideration with SNM is magnetic resonance imaging (MRI) compatibility. In mid-2020, a full-body MRI-compatible lead became FDA-approved and available for implantation; patients can safely undergo a full-body MRI with a 1.5 or 3 Tesla magnet for up to 30 minutes without a rest period. However, it is important to consider the implications of the leads placed before the availability of the new leads, with which patients should not undergo MRI below the neck. A review examining neuromodulation, both PTNS and SNM, for OAB found that overall SNM was both well tolerated and effective in improving OAB symptoms. There are no long-term data describing PTNS success against SNM[\[82\]](#).

New technologies in third-line therapy

New chemodenervation options are being studied. Data suggest that chimeric alternatives to the BTX toxin, such as the BoNT/BMY-WW toxin have stronger affinity for nerve terminal binding, which modulates bladder effects[\[83\]](#). Intravesical instillation of BTX mixed with hydrogel to promote a slower release of drug without

the need for injection has been demonstrated to be well tolerated in interstitial cystitis patients[84]. While BTX hydrogel is still in the trial phase as part of the APOLLO study, the potential to deliver BTX “topically” via urinary catheter as opposed to via cystoscopic injections could significantly enhance the ease of delivery[85].

New technologies for PTNM are also in development. The eCoin is an implantable device, approximately the size of a nickel, that is placed along the course of the patient’s posterior tibial nerve. It can be placed in the office setting and implantation minimizes the need for weekly visits. During clinical trials, 68% of subjects demonstrated at least 50% reduction in UII episodes at 48 weeks[86]. Another investigational technology is the StimGuard device. An internal lead is placed near the posterior tibial nerve, which can be stimulated with an external device that remains with the patient. The ongoing PROTECT trial is a multicenter RCT designed to evaluate StimGuard for non-inferiority of versus traditional SNM for OAB[87].

While traditional SNM devices require a stepwise procedure to insert the leads and subsequently a permanent IPG, the AHLeveeS System from Neuspera Medical Inc. provides an alternative approach. This new device is a miniature implantable stimulator that can be placed into the S3 foramen and differs from the existing SNM technology in that in lieu of an internal IPG, the AHLeveeS System uses an external wireless generator. The use of this device in a small pilot study was seen to produce physiologic responses consistent with adequate stimulation of the S3 nerve root foramina, including bellows and great toe plantarflexion[88]. **Table 1** shows the major third-line therapies and the corresponding emerging technologies for OAB.

Definition of Success for Interventions

As the presentation of OAB is heterogenous, defining success in the management of OAB can be challenging. A systematic review published in 2014 sought to assess what current research uses to define success in OAB trials. In this review, number of UII episodes was the most common metric used to assess treatment efficacy, with treatment response defined as a reduction in UII episodes of between 50% and 100% from baseline. Other symptom-based markers of treatment response were number of urgency episodes per day, voids per day, and changes in urodynamic parameters[89]. The adoption of patient-reported outcomes (PROs) has increased in biomedical and clinical research, and PRO tools are now more commonly used in OAB research[90,91]. The use of PROs as opposed to disease-oriented or symptom-based endpoints can provide a standardized means of communicating symptoms between patients and their physicians in the preoperative setting, thereby facilitating improved expectation and goal-setting before medical or surgical intervention for OAB[92].

Special Clinical Considerations

Nocturia

Nocturia, defined as needing to awaken at least one or more times per night to void, is one of the most common lower urinary tract symptoms (LUTS)[93]. While nocturia can be related to urologic disorders such as OAB or BPH, a variety of non-urologic conditions can also cause nocturia. Among these are diabetes, heart failure, and sleep apnea[60,93,94]. In patients with nocturia-predominant OAB symptoms, urologists should investigate possible alternative diagnoses that may explain a patient’s symptoms. In patients with

TABLE 1.

Third-line therapies for OAB and future directions

Therapy	Possible Expansion
Bladder chemodeneration with onabotulinumtoxinA	Chimeric alternate molecules for BpNT/A BTX mixed with hydrogel
Sacral neuromodulation	AHLeveeS implantable generator system
Percutaneous tibial nerve modulation	eCoin implantable device StimGuard implantable device

bothersome nocturia, 24-hour urine testing to evaluate for nocturnal polyuria should be considered, as should referral for sleep studies in patients who have a history of snoring or obstructive sleep apnea.

Considerations for Neurogenic Bladder

LUTS and OAB-like symptoms are highly prevalent in individuals with neurologic conditions, such as stroke or multiple sclerosis[95]. Up to 80% of MS patients will have bladder dysfunction in their lifetime, with 10% of all MS patients demonstrating urinary symptoms as the initial manifestation[96]. The approach to patients with neurogenic bladder can mirror the approach to those without neurologic disease, starting with first- and second-line therapies and escalating to advanced therapies[97]. Pharmacotherapy, particularly anticholinergics, have been shown efficacious in managing OAB amongst those with neurogenic bladder, although higher doses are often required[98]. While BTX is the only FDA-approved therapy for neurogenic bladder, it should be noted that some studies have demonstrated that neuromodulation provides benefit to neurogenic patients with refractory OAB[99].

Sex Differences in Overactive Bladder Management

The genitourinary syndrome of menopause (GSM), previously referred to as vulvovaginal atrophy, refers to all collective genitourinary symptoms associated with a decreasing level of estrogen in perimenopausal women[100]. Twenty percent of postmenopausal women report severe urinary urgency, and nearly 50% of these women have some form of urinary incontinence[101]. Both topical therapies, such as vaginal estrogen, and non-topical options, such as selective estrogen receptor modulators (ospemifene and lasofoxifene in particular), have been shown to improve urinary symptoms among women with GSM[99,100,102]. At the authors'

institutions, women with GSM and a history of breast or gynecological malignancy are frequently treated with local estrogen following consultation with their oncologist and shared-decision making with the patient.

While OAB prevalence is approximately equal between men and women, women are more likely to present with UUI[103]. As alluded to in the AUA/SUFU guidelines, men presenting with OAB-like symptoms should be screened for BPH[1]. However, OAB is still common among men with BPH, with up to 75% of men with BPH having clinical symptoms of OAB or DO on UDS[104]. Therefore, clinicians should consider a concomitant diagnosis of OAB in men with persistent LUTS despite treatment for BPH. In general, although sex-specific factors should be considered in any approach to OAB evaluation, treatment should be patient-specific based on both the presenting symptoms and patient goals of care.

Conclusion

OAB is a complex clinical syndrome that can have a serious impact on patient quality of life. From lifestyle modifications to implantable devices, the wide spectrum of available OAB therapies provides clinicians a large armamentarium to help alleviate OAB symptoms for their patients. This review explores various treatment modalities for OAB along with recent developments, with a particular emphasis on third-line therapies. Despite their high-efficacy rates compared to first- and second-line therapies, third-line treatments for OAB continue to be underutilized. In recent years, however, there has been a rapid growth and development of novel therapies. These new technologies allow for more patient-centered and tailored approaches to managing OAB symptoms, making it an exciting time to be a clinician treating OAB.

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