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American Urological Association (AUA)/
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The AUA/SUFU Guideline on the Diagnosis and Treatment of Idiopathic Overactive Bladder (2024)

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SUMMARY

Purpose

The purpose of this guideline is to provide a clinical framework for the diagnosis and treatment of idiopathic non-neurogenic overactive bladder.

Methodology

An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases, as well as the Cochrane Library, for systematic reviews and primary studies evaluating diagnosis and treatment of overactive bladder from January 2013 -November 2023. Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. Following the study selection process, 159 studies were included and were used to inform evidence-based recommendation statements.

GUIDELINE STATEMENTS

EVALUATION/DIAGNOSIS

1. In the initial office evaluation of patients presenting with symptoms suggestive of OAB, clinicians should:
    a. obtain a medical history with comprehensive assessment of bladder symptoms,
    b. conduct a physical examination, and
    c. perform a urinalysis to exclude microhematuria and infection.

    (Clinical Principle)

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2. Clinicians may offer telemedicine to initially evaluate patients with symptoms suggestive of OAB, with the understanding that a physical exam will not be performed and urinalysis should be obtained at a local laboratory (or recent lab results reviewed, if available). *(Expert Opinion)*

3. Clinicians may obtain a post-void residual in patients with symptoms suggestive of OAB to exclude incomplete emptying or urinary retention, especially in patients with concomitant voiding or emptying symptoms. *(Clinical Principle)*

4. Clinicians may obtain a symptom questionnaire and/or a voiding diary in patients with symptoms suggestive of OAB to assist in the diagnosis of OAB, exclude other disorders, ascertain the degree of bother, and/or evaluate treatment response. *(Clinical Principle)*

5. Clinicians should not routinely perform urodynamics, cystoscopy, or urinary tract imaging in the initial evaluation of patients with OAB. (*Clinical Principle)*

6. Clinicians may perform advanced testing, such as urodynamics, cystoscopy, or urinary tract imaging in the initial evaluation of patients with OAB when diagnostic uncertainty exists. *(Clinical Principle)*

7. Clinicians should assess for comorbid conditions in patients with OAB that may contribute to urinary frequency, urgency, and/or urgency urinary incontinence and should educate patients on the role that managing these conditions can have on bladder symptoms. *(Expert Opinion)*

8. Clinicians may use telemedicine for follow-up visits with patients with OAB. *(Expert Opinion)*

SHARED DECISION-MAKING

9. Clinicians should engage in shared decision-making with patients with OAB taking into consideration the patient's expressed values, preferences, and treatment goals in order to help them make an informed decision regarding different treatment modalities or to explore the option of no treatment. *(Clinical Principle)*

NON-INVASIVE THERAPIES

10. Clinicians should discuss incontinence management strategies (e.g., pads, diapering, barrier creams) with all patients who have urgency urinary incontinence. *(Expert Opinion)*

11. Clinicians should offer bladder training to all patients with OAB. *(Strong Recommendation; Evidence Level: Grade A)*

12. Clinicians should offer behavioral therapies to all patients with OAB. *(Clinical Principle)*

13. Clinicians may offer select non-invasive therapies to all patients with OAB. *(Clinical Principle)*

14. In patients with OAB whose symptoms do not adequately respond to monotherapy, clinicians may combine one or more of the following: behavioral therapy, non-invasive therapy, pharmacotherapy, and/or minimally invasive therapies. *(Expert Opinion)*

15. Clinicians should counsel patients that there is currently insufficient evidence to support the use of nutraceuticals, vitamins, supplements, or herbal remedies in the treatment of OAB. *(Expert Opinion)*

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PHARMACOTHERAPY

16. Clinicians should offer antimuscarinic medications or beta-3 agonists to patients with OAB to improve urinary urgency, frequency, and/or urgency urinary incontinence. *(Strong Recommendation; Evidence Level: Grade A)*

17. Clinicians should counsel patients with OAB on the side effects of all oral medication options; treatment should be chosen based on side effect profiles and in the context of shared decision-making. *(Clinical Principle)*

18. Clinicians should discuss the potential risk for developing dementia and cognitive impairment with patients with OAB who are taking, or who are prescribed, antimuscarinic medications. *(Clinical Principle)*

19. Clinicians should use antimuscarinic medications with extreme caution in patients with OAB who have narrow-angle glaucoma, impaired gastric emptying, or a history of urinary retention. *(Clinical Principle)*

20. Clinicians should assess patients with OAB who have initiated pharmacotherapy for efficacy and onset of treatment side effects. *(Expert Opinion)*

21. In patients with OAB who experience intolerable side effects or who do not achieve adequate improvement with an OAB medication, clinicians may offer a different medication in the same class or different class of medication to obtain greater tolerability and/or efficacy. *(Clinical Principle)*

22. In patients with OAB who do not achieve adequate improvement with a single OAB medication, clinicians may offer combination therapy with a medication from a different class. *(Conditional Recommendation; Evidence Level: Grade B)*

MINIMIALLY INVASIVE PROCEDURES

23. Clinicians may offer minimally invasive procedures to patients with OAB who are unable or unwilling to undergo behavioral, non-invasive, or pharmacologic therapies. *(Clinical Principle)*

24. Clinicians may offer patients with OAB, in the context of shared decision-making, minimally invasive therapies without requiring trials of behavioral, non-invasive, or pharmacologic management. *(Expert Opinion)*

25. In patients with OAB who have an inadequate response to, or have experienced intolerable side effects from, pharmacotherapy or behavioral therapy, clinicians should offer sacral neuromodulation, percutaneous tibial nerve stimulation, and/or intradetrusor botulinum toxin injection. *(Moderate Recommendation; Evidence Level: Grade A)*

26. Clinicians should measure post-void residual in patients with OAB prior to intradetrusor botulinum toxin injection. *(Clinical Principle)*

27. Clinicians should obtain a post-void residual in patients with OAB whose symptoms have not adequately improved or have worsened after intradetrusor botulinum toxin injection. *(Clinical Principle)*

28. Clinicians should discontinue oral medications in patients with OAB who have an appropriate response to a minimally invasive procedure but should restart pharmacotherapy if efficacy is not maintained. *(Expert Opinion)*

29. Clinicians may perform urodynamics in patients with OAB who do not adequately respond to pharmacotherapy or minimally invasive therapies to further evaluate bladder function and exclude other disorders. *(Clinical Principle)*

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INVASIVE THERAPIES

30. The clinician may offer bladder augmentation cystoplasty or urinary diversion in severely impacted patients with OAB who have not responded to all other therapeutic options. *(Expert Opinion)*

INDWELLING CATHETERS

31. Clinicians should only recommend chronic indwelling urethral or suprapubic catheters to patients with OAB when OAB therapies are contraindicated, ineffective, or no longer desired by the patient and always in the context of shared decision-making due to risk of harm. *(Expert Opinion)*

OAB and BPH

32. The clinician may offer patients with BPH and bothersome OAB, in the context of shared decision-making, initial management with non-invasive therapies, pharmacotherapy, or minimally invasive therapies. *(Expert Opinion)*

33. Clinicians may offer patients with BPH and OAB monotherapy with antimuscarinic medications or beta-3 agonists, or combination therapy with an alpha blocker and an antimuscarinic medication or beta-3 agonist. *(Conditional Recommendation; Evidence Level: Grade B)*

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INTRODUCTION

Purpose

Overactive bladder (OAB) is defined by the International Continence Society (ICS) 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." The prevalence of OAB and its impact on quality of life (QoL) across the life span is significant. Patients with OAB present to several types of providers including primary care, specialty care, physical therapists, and alternative medicine providers. The purpose of this OAB guideline is to provide evidence-based guidance to all types of clinicians and patients regarding the evaluation, management, and treatment of idiopathic OAB. The guideline informs the reader on valid diagnostic processes and provides an approach to maximizing symptom control and patient QoL through shared decision-making, while minimizing adverse events and burden of disease. The strategies and approaches recommended in this document were derived from evidence-based and consensus-based methods. There is continually expanding literature on OAB; the strategies presented here will require amendments to remain consistent with the highest standards of clinical care. This document was created to serve as a guide for all types of providers who evaluate, manage, and treat patients with OAB, including general practice as well as those who specialize in various branches of medicine and ancillary care.

Methodology

Search and Article Selection

An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases, as well as the Cochrane Library, for systematic reviews and primary studies evaluating diagnosis and treatment of OAB using the PICO elements. During PICO development, panel members submitted landmark studies addressing the Key Questions to the methodologist. These studies were defined as control articles and were compared with the literature search strategy output; the strategy was subsequently updated as necessary to capture all control articles. Databases were searched for studies published from January 2013 through November 2023. In addition to the MEDLINE and EMBASE databases searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

All hits from the OVID literature search were input into reference management software (EndNote 21), where duplicate citations were removed. Abstracts were reviewed by the methodologist to determine if the study addressed the Key Questions and if the study met study design inclusion criteria. For all research questions, randomized controlled trials (RCTs), observational studies, modelling studies with theoretical cohorts, and case-control studies were considered for inclusion in the evidence base. For all Key Questions, studies had to enrol at least 30 patients per study arm. Additionally, the Key Question designed to compare pharmacotherapy regimens was limited to RCTs based on *a priori* knowledge of multiple trials evaluating OAB oral medications. Case series, letters, editorials, *in vitro* studies, studies conducted in animal models, and studies not published in English were excluded from the evidence base *a priori*.

Full-text review was conducted on studies that passed the abstract screening phase. Studies were compared to the PICO criteria. Eight panel members were paired with the methodologist and completed duplicate full-text study selection of 10% of studies undergoing full-text review. The dual review-trained the methodologist, who then completed full-text review of the remaining studies.

Data Abstraction

Data were extracted from all studies that passed full-text review by the methodologist.

Risk of Bias Assessment

Quality assessment for all retained studies was conducted. Using this method, studies deemed to be of low quality would not be excluded from the systematic review; their methodological strengths and weaknesses were discussed where relevant. To evaluate the risk of bias within the identified studies, the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2)[1] tool was used for systematic reviews, the Cochrane Risk of Bias Tool[2] was used for randomized studies, a Risk of Bias in

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Non-Randomized Studies – of Intervention (ROBINS-I) [3] was used for observational studies, and Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2)[4] was used for diagnostic accuracy studies. Additional important quality features, such as study design, comparison type, power of statistical analysis, and sources of funding were extracted for each study.

Determining the Evidence Strength

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[5] system was used to determine the aggregate evidence quality for each outcome informing Guideline Statements. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence is correct. Evidence is categorized as high, moderate, low, and very low. Assessment is based on the aggregate risk of bias for the evidence base, with limitations introduced as a consequence of inconsistency, indirectness, imprecision, and publication bias across the studies.[6] Upgrading of evidence is possible if the body of evidence indicates a large effect or if confounding factors would suggest either spurious effects or would reduce the demonstrated effect.

The American Urological Association (AUA) employs a 3-tiered strength of evidence system to underpin evidence-based guideline statements. Table 1 summarizes the GRADE categories, definitions, and how these categories translate to the AUA strength of evidence categories. High certainty by GRADE translates to A category strength of evidence, moderate to B, and both low and very low to C.

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 2). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence is *likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations can also be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, ***Clinical Principles*** or ***Expert Opinions*** are provided via consensus of the Panel. A ***Clinical Principle*** is a statement about a component of clinical care widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. ***Expert Opinion*** refers to a statement based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature.

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TABLE 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

Panel Formation

The OAB Guideline Panel was created in 2022 by the American Urological Association Education and Research (AUAER), Inc and in collaboration with the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members through an open nomination process. Additionally, the Panel included patient representation. Funding of the Guideline was provided by the AUA; panel members received no remuneration for their work.

Peer Review

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and treatment of OAB. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from SUFU and external content experts. A call for reviewers was placed on the AUA website from November 13 - December 4, 2023, to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and the AUA Public Policy & Advocacy team to open the document further to the patient perspective. The draft guideline document was distributed to 24 nominated peer reviewers, 23 external reviewers (i.e., peer reviewers who responded to the call for comments), and 37 AUA Committee members (PGC, SQC, BOD) and 15 AUA staff. All peer review comments were blinded and sent to the Panel for review. In total, 57 reviewers provided comments, including 17 external reviewers. At the end of the peer review process, a total of 1039 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD and the SUFU Executive Committee for final approval.

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TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

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BACKGROUND

Definitions

The IUGA/ICS joint terminology report[7] defines OAB as "urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of UTI or other obvious pathology." OAB studies have used varying combinations of these symptoms to identify patients for study inclusion and to define treatment response. These methodologic differences across studies make it challenging to interpret the OAB literature related to epidemiology and treatment. Most OAB studies exclude individuals with urinary symptoms related to neurologic conditions or other identifiable causes such as radiation cystitis; therefore, this guideline is focused on the evaluation and treatment of idiopathic OAB.

Urgency is defined by IUGA/ICS[7] as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer." Urgency is considered the hallmark symptom of OAB; however, given its subjective nature, it has proven difficult to precisely define or quantify for research or clinical purposes. Therefore, many studies of OAB treatments have relied upon other measures (e.g., 24-hour urinary frequency, UUI episodes) for inclusion into trials and to measure treatment response.

Increased daytime urinary frequency is defined by IUGA/ICS as the "complaint that micturition occurs more frequently during waking hours than deemed normal."[7] The number of daytime voids can be reliably measured with a voiding diary or by self-report. Traditionally, up to seven micturition episodes during waking hours has been considered normal,[8] but this number is highly variable based upon hours of sleep, fluid intake, comorbid medical conditions, and other factors.

Nocturia is the "complaint of interruption of sleep one or more times because of the need to micturate. Each void is preceded and followed by sleep."[7] Like daytime frequency, nocturia is a multifactorial symptom which is often due to factors unrelated to OAB (e.g., excessive nighttime urine production, fluid intake before bed).

UUI is the "complaint of involuntary leakage of urine associated with urgency (i.e., a sudden compelling desire to void)." Incontinence episodes can be measured reliably with a diary or by self-report, and the quantity of urine leakage can be estimated with pad counts.

Epidemiology

In population-based studies, OAB prevalence rates range from 7% to 27% in men, and 9% to 43% in women.[9-16] No clear differences exist between studies conducted in North America versus other populations. Some studies[9-12] report higher prevalence rates in women than men, while others[13-16] found similar rates across genders. However, UUI is consistently more common in women than in men. OAB symptom prevalence and severity tend to increase with age.[13, 14, 17] A proportion of OAB cases (37-39%) remit during a given year, but the majority of patients have symptoms for years.[17, 18] To date, few population-based studies have been published directly examining epidemiologic differences across racial/ethnic groups and there is even less data on gender diverse groups.[19, 20] Data from the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium's RISE FOR HEALTH Study will be available later this year and will provide contemporary prevalence estimates for OAB and other lower urinary tract symptoms (LUTS) in an ethnically and racially diverse sample of US women aged 18-100 years.[21, 22] It will further inform the concept of bladder health which goes beyond OAB/LUTS to encompass the physical, mental, and social well-being related to the bladder. The study will explore novel risk and protective factors and adaptive behaviors women use to manage their bladders to further advance OAB/LUTS prevention efforts.

This guideline aimed to use "patients with OAB" consistently which is an inclusive term referring to patients of all genders (e.g., cisgender, transgender, genderqueer, nonbinary, etc.) who suffer from OAB. Much of the current literature on OAB provides data only based on patient sex (i.e., only in males or females) and has not collected or reported data on the gender of the people studied. To be factual, any review of prior published data where only sex is specified, or only binary gender was presented, we will use the data as it is presented in the literature with the terms "male," female," "men," and "women" since it is the only information provided in the data. The panel also realizes that many bladder symptoms and condition are affected by anatomical and hormonal differences in patients. Hence, when there is a need to specify

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anatomical or hormonal information, we will use more descriptive terms such as “patients with prostates” or “patients post menopause.”

Patient-Reported Outcomes and OAB

Since OAB is a symptom-based diagnosis, the QoL impact of the symptoms is a critical aspect of the condition. The degree of bother caused by OAB symptoms directly affects OAB care-seeking, treatment intensity, and satisfaction with treatment. Therefore, assessment of patient-reported outcomes (PROs) can be a critical component of OAB management and the most effective means of assessing the patient’s perspective. Numerous questionnaire instruments have been developed to assess symptoms, degree of bother, treatment satisfaction, and health-related QoL in patients with OAB and urinary incontinence. This lack of standardization across the published literature has often limited the comparability and generalizability of outcomes across research studies. To address this, the International Consultation on Incontinence has developed a series of standardized modular questionnaires for pelvic conditions, including OAB.[23] The Lower Urinary Tract Research Network (LURN) developed a comprehensive patient reported LUTS index (LURN-SI-29) for phenotyping that is appropriate for all genders and is available in a short form (LURN-SI-10) for typical clinical use.[24] The Panel encourages the development and utilization of standardized PRO tools in OAB research and clinical practice. The use of validated PRO tools will advance patient-centered comparative effectiveness research and help patients make informed decisions about treatment options.

Impact on Psychosocial Functioning and Quality of Life

The Panel recognizes that OAB constitutes a significant physical, emotional, and economic burden for patients. These burdens include the time and effort required to manage symptoms during daily life as well as the resources required to obtain treatments that may be costly and may present logistical challenges (e.g., cost of prescription medication and pads). The negative impact of OAB symptoms on psychological well-being and QoL also has been well-documented.[25-28] Lack of bladder control can profoundly affect an individual’s ability to travel away from home, perform occupational duties, and engage in social activities. Urinary incontinence may have severe psychological and social consequences, resulting in restricted activities, isolation, and unwillingness to be exposed to environments where access to a bathroom may be difficult. Patients also report negative impact on sexual desire, sexual function, and marital satisfaction. OAB symptoms have also been linked to major depressive disorder. [29] [30, 31] This negative impact is most evident among older adults (i.e., ≥ 65 years), resulting in significant impairments in QoL,[32] including high rates of anxiety and depression, with the majority of patients reporting they have not sought treatment. Management of OAB symptoms with behavioral approaches, pelvic floor muscle training (PFMT), medications, neuromodulation, and other therapies, balanced against adverse events, costs, and patient compliance, has been reported to improve patient QoL.

Patient Presentation

Symptoms

The hallmark symptom of OAB is bothersome urgency which may be accompanied by UUI. Often, symptoms of urinary frequency (both daytime and nighttime) are also reported and support a diagnosis of OAB.[33] It is common for patients to have suffered with their symptoms for an extended time before seeking medical advice.[34]

Differentiation from other conditions

A diagnosis of nocturnal polyuria (i.e., the production of greater than 20% to 33% of total 24-hour urine output during the period of sleep) is largely age-dependent: >20% for younger individuals and >33% for elderly individuals.[35] Nocturnal voids associated with nocturnal polyuria are frequently normal or large volume as opposed to the small volume voids commonly observed in nocturia associated with OAB. Sleep disturbances, vascular and/or cardiac disease, and other medical conditions are often associated with nocturnal polyuria.

OAB can be distinguished from other conditions, such as excess fluid intake (more than eight glasses of water per day),[36] with a frequency-volume chart (i.e., a voiding diary). If the patient has urinary frequency because of the high intake volume with normal or large volume voids, then the patient most likely does not have OAB. This can be managed with education and fluid intake management.

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The clinical presentation of interstitial cystitis/bladder pain syndrome (IC/BPS) shares the symptoms of urinary frequency and urgency, with or without UUI; however, bladder and/or pelvic pain, including dyspareunia, is a crucial component of this diagnosis.[37-39]

Other conditions can contribute to OAB symptoms and should be diagnosed since their treatment can improve OAB symptoms. For example, in the patient transitioning through menopause, genitourinary syndrome of menopause (GSM) can be a contributing factor to urgency and incontinence symptoms. There is some evidence for symptom improvement with the use of vaginal (but not systemic) estrogen.[40] Similarly, UTI can have similar symptoms as OAB, but generally is acute in onset, of shorter duration, and accompanied by other clues such as dysuria, or suprapubic discomfort and resolved with antibiotics. LUTS related to neurological conditions such as stroke, Parkinson's disease, and multiple sclerosis are considered neurogenic lower urinary tract dysfunction (NLUTD) and not idiopathic OAB. The diagnosis and treatment are discussed in *The AUA/SUFU Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction: Diagnosis and Evaluation*.[41]

What is new about this Guideline

This guideline is not a revision of *The Diagnosis and Treatment of Overactive Bladder (non-neurogenic) in Adults: AUA/SUFU Guideline*[42] but is rather a new systematic review of the evidence on the diagnosis and management of this condition. Some of the statements have remained relatively unchanged; however, significant changes to this iteration of the Guideline include the incorporation of patients with prostates and a separate analysis of the treatment of men when data was available. Other changes include a focus on the impact of non-urological contributing factors (e.g., medical comorbidity, obesity, constipation, pelvic floor dysfunction), and significant changes in the recommendations for pharmacotherapy with further recognition of the potential harm of antimuscarinic medications.

The evidence base used to support this guideline did not favor the need for a patient with OAB to proceed with treatment in a stepwise manner going from "first" to "second" to "third line therapy," as recommended in previous OAB guidelines. The "step therapy"[43] approach advised that patients cycle through both behavioral and pharmacotherapy before considering advanced therapies. This guideline instead emphasizes the importance of shared decision-making between the clinician and the patient with OAB to select the best therapy or therapies based on the patient's needs, desires, and side effect tolerance. To eliminate the concept of "step therapy," the Panel has grouped OAB treatment options according to their invasiveness (Table 3) rather than putting them in a specific order and will refer to these treatment categories throughout the document.

There are eight treatment categories: 1. Incontinence management strategies, 2. behavioral therapies, 3. optimization of co-morbidities, 4. non-invasive therapies, 5. pharmacologic therapies, 6. minimally invasive therapies, 7. invasive therapies, and 8. indwelling catheters. This new framework provides a menu of options for patients to select from, including the option to select from multiple treatment categories simultaneously to best suit their individual wishes.

Patients with prostates experience OAB nearly as often as those without, but due to the common misconception that all voiding symptoms are attributable to the prostate, they are often underdiagnosed and undertreated for their symptoms. While some patients with prostates experience symptoms of both benign prostatic hyperplasia (BPH) and OAB, others have OAB alone and would benefit from diagnosis specific treatment.

The term "refractory OAB" is used in the urologic literature, but there is no clear definition of what this means. A patient can be refractory to behavioral changes, PFMT, pharmacotherapy, or other modalities. Some studies have used "refractory OAB" to mean refractory to two oral medications for OAB. Given the ambiguity and lack of consensus of this term we have refrained from using it in this guideline.

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Table 3: Overactive Bladder Treatment Options

Treatment category	Description	Examples
Incontinence Management Strategies	Products to better cope with or tolerate urinary incontinence. These do not treat or prevent incontinence, rather they reduce adverse sequalae of incontinence, such as urine dermatitis.	Diapering, pads, liners, absorbent underwear, barrier creams, external urine collection system, condom catheters
Behavioral Therapies	Actions that patients with OAB can perform at home to directly address and improve their OAB symptoms. Can be supported by education or training but are driven by the patient.	Timed voiding, urgency suppression, fluid management, bladder irritant (caffeine, alcohol) avoidance
Optimization of Comorbidities	Medical conditions known to affect the severity of OAB that can be treated or managed.	BPH, constipation, diuretic use, obesity, diabetes mellitus, genitourinary syndrome of menopause, pelvic organ prolapse, tobacco abuse
Non-invasive Therapies	Treatments provided by a nurse or allied health professional that may involve practice or treatments at home.	Pelvic floor muscle training, biofeedback, transcutaneous tibial nerve stimulation, electromagnetic therapy
Pharmacologic Therapies	Prescription medications that are taken to directly treat bladder symptoms.	Beta-3 agonists, antimuscarinic medications
Minimally invasive Therapies	Treatments that are procedural or surgical but with low risk of complication or adverse events.	Botulinum toxin injection of bladder, sacral neuromodulation, percutaneous tibial nerve stimulation, acupuncture, implantable tibial nerve stimulation
Invasive Therapies	Surgical treatments that have higher risks of complications or adverse events.	Urinary diversion, bladder augmentation cystoplasty
Indwelling Catheters	Any urinary catheter left in the bladder as a method to treat incontinence.	Indwelling urethral or suprapubic catheters

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GUIDELINE STATEMENTS

EVALUATION AND DIAGNOSIS

1. **In the initial office evaluation of patients presenting with symptoms suggestive of OAB, clinicians should:**
   a. **Obtain a medical history with comprehensive assessment of bladder symptoms,**
   b. **Conduct a physical examination, and**
   c. **Perform a urinalysis to exclude microhematuria and infection.**
   (Clinical Principle)

2. **Clinicians may offer telemedicine to initially evaluate patients with symptoms suggestive of OAB with the understanding that a physical exam will not be performed and urinalysis should be obtained at a local laboratory (or recent lab results reviewed, if available).** ***(Expert Opinion)***

Medical history and bladder symptom assessment

The clinician's initial assessment of patients with symptoms suggestive of OAB should characterize the patient's symptoms, assess severity and duration, exclude alternative diagnoses, and identify complicated signs or symptoms that may necessitate referral or additional evaluation. Bladder symptom assessment should include questions about typical OAB Symptoms (e.g., urinary urgency, daytime and nighttime frequency, UUI) other urinary storage impairments (e.g., stress incontinence, incontinence without sensation) and evaluation of the ability to empty the bladder (e.g., straining to void, poor force of stream, urinary hesitancy, history of urinary retention, sensation of incomplete emptying). Predominant emptying symptoms can indicate an elevated post-void residual (PVR) and/or bladder outflow obstruction (BOO), especially in patients with prostates. Certain signs or symptoms may suggest a more complicated process that may require further evaluation include abdominal pain, pelvic pain, hematuria, recurrent UTI, sudden onset of severe OAB symptoms, concomitant neurologic symptoms (e.g., blurred vision, limb weakness or numbness), and bowel dysmotility (e.g., fecal incontinence, severe constipation). The presence of incomplete emptying or other complicated symptoms warrants specialist evaluation.

Bladder function is dependent on a number of factors including fluid intake, medications, medical conditions, and surgical history. Therefore, clinicians should inquire about these. Excessive fluid intake and certain medications can contribute to bothersome storage symptoms which mimic OAB. Clinicians should inquire about the volume and type of daily fluid intake (e.g., caffeinated, non-caffeinated, alcoholic beverages) along with the number of daytime and nighttime voids and whether urgency is contributing to the frequency of voiding. Large volume fluid intake will certainly lead to more frequent voiding, but when this occurs in the absence of bothersome or persistent urgency it is not considered pathologic. Current medications should be reviewed with special attention to diuretics and diabetic medications that cause glucosuria (i.e., SGLT2 [sodium-glucose co-transporter 2] inhibitors) as these patients may have urinary frequency. Urinary frequency without persistent urgency can point to polyuria secondary to fluid intake and/or medication rather than OAB.

Co-morbid medical conditions can mimic OAB symptoms, exacerbate symptoms, or limit OAB treatment response. These conditions include recurrent UTI, poorly controlled diabetes, untreated sleep apnea, and prior pelvic surgeries including those for incontinence. Impaired cognition and mobility greatly impact bladder function and toileting resulting in concomitant functional incontinence. Clinicians may use the Mini Mental Status Exam as a standardized, quick, and reproducible means to assess cognitive impairment in patients who are at a high risk. Assessment of a patient's capacity to independently perform activities of daily living and their frailty can provide insight in both areas and may influence treatment planning. The Clinical Frailty Scale (CSF-9) is a visual tool to assess rapidly and objectively assess frailty in a clinical setting.[44] The presence of neurological disorders (e.g., multiple sclerosis, stroke, Parkinson's disease, spinal cord injury) and OAB symptoms are suggestive of NLUTD and should be evaluated according to *The AUA/SUFU Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction: Diagnosis and Evaluation.*[41] A history of pelvic malignancies (e.g., bladder, colon, uterus/adnexa, prostate), history of pelvic radiation, and/or concerns about foreign bodies in the urinary tract (e.g., stones, mesh erosion in the bladder or urethra from prior incontinence or prolapse surgery) warrants additional evaluation to assess for these potential comorbidities.

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Physical examination

There are no findings on physical examination that are specific to OAB. Therefore, a directed physical exam should assess for anatomic factors and/or concomitant conditions that may contribute to OAB symptoms. An abdominal exam should document surgical scars, hernias, palpable abdominal masses, and assess for bladder overdistension/suprapubic fullness or bladder tenderness. The presence of lower extremity edema can be associated with periods of fluid mobilization (as when the patient is supine), often contributing to nocturnal frequency. The genitourinary exam can identify contributory conditions such as signs of estrogen loss (i.e., vaginal atrophy), pelvic organ prolapse (POP), stress urinary incontinence (SUI), as well as the sequalae of urinary incontinence like skin rash, excoriation, or ulceration. It can also identify complicating factors like excessive pelvic floor muscle tone and tenderness and evidence of obstruction from a previous incontinence sling. If performed, rectal exam in patients with prostates should assess for prostate enlargement, nodularity and/or tenderness. Lastly, the ability of all patients to be able to contract their pelvic floor muscles (i.e., perform Kegel exercise) can be ascertained as that may impact treatment and possible referral for pelvic floor muscle training.

Observation of patient's gait and transfers during clinical evaluation may help to identify mobility impairments that can impact symptoms like UUI. The Timed Up and Go (TUG) test measures the time required to transfer from a seated position and walk to and from a point 10 feet away. A time of >12 seconds is associated with an increased risk of falls and may offer objective measure of impaired mobility sufficient to impact toileting.[45]

Urinalysis

Dipstick or microscopic urinalysis should be performed in all patients with symptoms suggestive of OAB to evaluate for other causes of LUTS. Urine culture should be performed in the setting of urinalysis suggestive of infection (e.g., nitrites or leukocyte esterase on dipstick or bacteriuria or pyuria on microscopy) and/or hematuria. Any identified UTI should be treated, and the patient should be instructed to follow up for assessment if symptoms do not resolve. If microscopic hematuria (≥3 RBC/HPF) is identified in the absence of infection, further evaluation should be performed in accordance with the *Microhematuria: AUA/SUFU Guideline*.[46] The presence of glucosuria or proteinuria may be the sequelae of diabetes.

Telemedicine

Telemedicine has become an integral part of patient care for many clinicians. The consensus of the Panel is that telemedicine is a viable option for the initial evaluation of patients with OAB. However, both the clinician and patient should be aware that use of telemedicine will not allow for all elements of the initial in-office OAB evaluation as noted in statement 1. A thorough history can be obtained via telemedicine; however, neither a physical examination nor additional evaluations, such as measurement of a PVR, are possible via telemedicine. As noted in the supporting text for statement 1, urinalysis should be part of the initial evaluation to exclude UTI and hematuria and in the setting of an initial telemedicine visit, can be obtained at a local laboratory or, if available, by review of recent lab results.

Careful monitoring of response to any prescribed treatment is important and this is especially true in the scenario where a physical examination is unable to be performed at the initial telemedicine visit. While the Panel also states that clinicians may use telemedicine to perform follow-up visits for patients with symptoms of OAB (Statement 8), a physical examination is an important part of the OAB evaluation and cannot be ignored. For patients that do not respond to initial therapy after the initial telemedicine evaluation, an in-office visit with a physical examination, along with measurement of PVR and urinalysis as indicated, should be considered. Findings on examination, such as POP and loss of estrogen, may result in symptoms suggestive of OAB.

There are several caveats when considering the use of telemedicine. Certainly, the patient needs to be willing to use telemedicine for the visit and should be technologically able to log on to the telemedicine platform being used. Certain patients prefer in-person visits and may decline the telemedicine option. In addition, clinicians should be aware of the local rules and regulations regarding telemedicine and billing in their community and the state in which the patient resides.

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Table 4: Indications for Additional Evaluation in the Patient Presenting with OAB symptoms

Gross or microscopic hematuria without infection
Palpable prostate nodule
Sudden worsening of symptoms
New neurologic symptoms (i.e., limb weakness or numbness, impaired balance, blurred vision)
Difficulty urinating or urinary retention
Pelvic pain
Abdominal pain of unknown etiology
Prior pelvic cancer treatment (i.e., radical surgery, adiation)
Severe POP

POP: pelvic organ prolapse

3. **Clinicians may obtain a post-void residual in patients with symptoms suggestive of OAB to exclude incomplete emptying or urinary retention, especially in patients with concomitant voiding or emptying symptoms. *(Clinical Principle)***

Incomplete emptying and urinary obstruction can mimic symptoms of OAB, can occur concomitantly with OAB and, if present, can impact outcomes of therapy for OAB. Therefore, it is important to exclude urinary retention in those patients with significant risk factors such as concomitant emptying symptoms, a history of urinary retention, enlarged prostate, neurologic disorders, prior incontinence or prostate surgery, or long-standing diabetes and in those who elect a treatment that may impair emptying. PVR should be performed immediately after voiding with a non-invasive ultrasound bladder scanner. Straight catheterization is acceptable if bladder scanner is unavailable. When elevated PVR is identified, further evaluation with non-invasive uroflow, urodynamics (UDS), and/or cystoscopy may be indicated to help understand the functional bladder volume and voiding efficiency, assess for detrusor underactivity, and evaluate for obstruction. This information is more informative than PVR alone and assists the clinician in developing a safe and effective treatment plan. Clinicians should exercise caution when utilizing certain medications for OAB in those with elevated PVR. It is important to note that there is no accepted volume threshold that defines elevated PVR. Most RCTs in the evidence base that evaluated medication for OAB used a PVR of 150-200 mL as an exclusion criterion. The use of antimuscarinic medications in patients with an elevated PVR may exacerbate incomplete emptying.[47] If a patient has a low functional bladder capacity (<300 mL), clinician can use bladder voiding efficiency (voided volume/bladder capacity) to evaluate for incomplete emptying.

4. **Clinicians may obtain a symptom questionnaire and/or a voiding diary in patients with symptoms suggestive of OAB to assist in the diagnosis of OAB, exclude other disorders, ascertain the degree of bother, and/or evaluate treatment response. *(Clinical Principle)***

Understanding how a patient's urinary symptoms differ from normal or expected patterns and how they affect daily life is important in treating OAB. Fluid intake and voiding diaries can provide more objective detail about toileting and fluid intake behavior when recall is difficult. Diaries can also provide documentation of baseline symptoms that can serve as a guide for counseling and behavioral modifications. Essential elements of the voiding diary are the time and circumstances for each void and/or incontinence episode. An estimation of the degree of urgency associated with voids/incontinence episodes (or documentation of other reason for incontinence such as cough, exercise, etc.) and documentation of fluid intake provide useful context to help with a diagnosis and identify symptom triggers. Measuring and recording voided volumes provides an estimate of functional bladder capacity and can help to differentiate between OAB and polyuria as well as assist in the diagnosis of nocturnal polyuria, which is treated differently than OAB.[48]

Voiding diary duration can range from 24 to 72 hours and should capture typical behavior. Three-day diaries have demonstrated utility in providing unique symptom information not captured on history or survey instruments.[49]

Validated symptom questionnaires provide a reliable and specific measure of bother related to urinary symptoms. Clinicians may utilize questionnaires to assess baseline bother and monitor treatment response. OAB specific symptoms measures include the Overactive Bladder Questionnaire (OAB-Q), the International Consultation of Continence Questionnaire (ICIQ) and ICIQ Modular Questionnaires, the Primary OAB Symptom Questionnaire (POSQ), the Overactive Bladder Satisfaction Questionnaire (OAB-S) and the Urgency Questionnaire (UQ). Bother and quality of life impact can

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be assessed with the Urogenital Distress Inventory 6(UDI-6), King's Health Questionnaire, the International Prostate symptom Score (IPSS), and the Incontinence Impact Questionnaire 7 (IIQ-7). A more comprehensive assessment of LUTS can be measured with the Bristol Female Lower Urinary Tract Symptoms questionnaire (BFLUTS) or LURN-SI-29 (or the LURN-SI-10 short form) which captures both voiding and storage symptoms as well as incontinence and is valid for all genders.[24]

5. **Clinicians should not routinely perform urodynamics, cystoscopy, or urinary tract imaging in the initial evaluation of patients with OAB.** ***(Clinical Principle)***

6. **Clinicians may perform advanced testing, such as urodynamics, cystoscopy, or urinary tract imaging in the initial evaluation of patients with OAB when diagnostic uncertainty exists.** ***(Clinical Principle)***

As noted in Statement 1, the initial evaluation of patients with symptoms of OAB should include a medical history, physical examination, and urinalysis. Additional components of an OAB evaluation may also include PVR measurement, voiding diary, and a symptom questionnaire. Once the initial evaluation is complete, and the clinician is confident in the diagnosis of OAB, options for therapy can be offered to the patient. There is no need to obtain UDS, cystoscopy, or upper tract imaging in the initial evaluation of a patient with OAB symptoms since these are costly, time consuming, and carry risk to the patient.

However, if diagnostic uncertainty exists, or abnormal findings are obtained, during the initial evaluation, further evaluation with UDS, cystoscopy, and/or urinary tract imaging can be considered to clarify their diagnosis and rule out other lower urinary tract pathology. In addition, further evaluation can also be considered if patients have a suboptimal or unexpected response to standard OAB therapy.

UDS are not beneficial in the initial evaluation of patients with OAB. OAB is a clinical syndrome, therefore, UDS are not necessary to make the diagnosis or guide initial therapy and there are no pathognomonic findings on UDS that confirm OAB.[50] However, there are scenarios where UDS may give the clinician a better understanding of the patient's lower urinary tract dysfunction, resulting in an optimization of the treatment plan. Common examples of when UDS may be helpful are noted in Table 5. There are different components of UDS that may be more applicable to certain patients. For example, a simple uroflow may be an adequate screening tool in a male patient with storage-predominant LUTS; however, if BOO needs to be ruled out definitively, then a pressure-flow study would be required.

Cystoscopy is not helpful to make the diagnosis of OAB. However, there are certainly clinical situations where patients with symptoms suggestive of OAB may benefit from cystoscopy. Those with hematuria on urinalysis at the time of initial (or subsequent) OAB evaluation should undergo evaluation as recommended by the *Microhematuria: AUA/SUFU Guideline*[46] which often calls for cystoscopy and upper urinary tract imaging. In addition, patients with OAB symptoms and a history of recurrent UTI may benefit from cystoscopy as recommended by the *Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline.*[51] Cystoscopy may also be helpful for those patients with both OAB and obstructive voiding symptoms to allow for further evaluation of a potential source of obstruction which may impact decisions for therapy.
Cystoscopy may be helpful in the evaluation of women with symptoms of OAB and a history of a prior sling for SUI. Potential issues would include mesh erosion into the urinary tract or BOO; thus, potential indications would include recurrent UTI, hematuria, and post-sling voiding symptoms.

Urinary tract imaging is not indicated for the evaluation of a patient with OAB. Findings such as recurrent UTI, hematuria, or NLUTD may necessitate upper tract imaging; the indication for imaging in these clinical scenarios is well described in their respective guidelines. Lastly, in men requiring further evaluation for LUTS secondary to OAB versus BPH, especially in those patients under consideration for surgical treatment of BPH, clinicians can consider assessment of prostate size and shape. This can be done with transrectal or abdominal ultrasound, cystoscopy or cross-sectional imaging.[52]

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Table 5: Potential Indications for Urodynamics in Patients with OAB Symptoms

Diagnostic uncertainty
Mixed incontinence or insensate incontinence
Obstructive voiding symptoms (e.g., OAB versus BPH, LUTS after sling)
Neurologic diagnosis/possible NLUTD[41]
Elevated PVR (as part of initial evaluation or found after OAB therapy)
Poor response to therapy

BPH: benign prostatic hyperplasia; LUTS: lower urinary tract symptoms; NLUTD: neurogenic lower urinary tract dysfunction; OAB: overactive bladder; PVR: post-void residual;

7. Clinicians should assess for comorbid conditions in patients with OAB that may contribute to urinary frequency, urgency, and/or urgency urinary incontinence and should educate patients on the role that managing these conditions can have on bladder symptoms. *(Expert Opinion)*

A variety of medical conditions may contribute to urinary frequency, urgency, and/or urgency related incontinence, with or without underlying detrusor dysfunction. This may be secondary to the impact of anatomic changes; mechanical forces on the bladder; bladder obstruction including BPH or prolapse; changes in body fluid physiology, including cardiac or venous insufficiency; urothelial irritation; hormone dysregulation; neurologic input; and/or pelvic floor dysfunction. Addressing these underlying co-morbidities may help to alleviate urinary symptoms that are resultant sequela to OAB or work synergistically with other primary OAB treatments. As such, assessing for these potentially modifiable factors should be considered in the evaluation of patients presenting with OAB symptoms.

Obesity

There is notable evidence supporting an adverse association of obesity with OAB symptoms.[53, 54] The underlying mechanism is not well elucidated, but these may in part be secondary to increased intrabdominal pressures, mechanical stress on the pelvic floor, and metabolic factors. For example, a population-based study including 7949 women demonstrated a significant association of obesity and the rate of OAB, including a dose-dependent relationship.[53, 54]

Similarly, weight loss interventions have been associated with improvement in OAB symptoms. A RCT of overweight and obese women (BMI 25-50 km/m^2) found that an intensive 6-month long weight loss program, which included diet, exercise, and behavioral modification was associated with significant improvement in urinary symptoms compared to a structured education program. Specifically, an 8% weight loss (mean 7.8 kg) resulted in a 47% reduction in overall incontinence (versus 28% in the control group) and a 42% decrease in UUI episodes per week (versus 26% in controls).[55] Likewise, weight loss secondary to bariatric surgery has been associated with significant improvements in OAB symptoms, including UUI.[56]

Constipation

Chronic constipation has been associated with greater prevalence and severity of OAB.[57-59] In a cross-sectional internet-based survey of randomly selected panel members, chronic constipation was more prevalent among women with OAB than those without bladder symptoms (35.9% versus 6.7%).[58] Potential etiologies for this association include anatomic proximity, overlapping neurologic pathways, and impact on the pelvic floor.[60]

Data regarding the effectiveness of treating constipation on the severity of OAB symptoms is limited.[61, 62] In one prospective cohort study of 52 patients with chronic constipation successful treatment of constipation resulted in significant improvements in urinary urgency, frequency, and dysuria.[61] Given the potential QoL benefit from both management of OAB and constipation symptoms, and the typically low-risk nature of initial interventions for constipation (e.g., education regarding diet, fiber intake, fluid intake, and activity levels),[63, 64] strategies for optimization of bowel function should routinely be discussed when counseling about OAB treatment.

Pelvic organ prolapse

POP and OAB symptoms often coexist. This may be secondary to shared risk factors (e.g., age, obesity, constipation), the high prevalence of these conditions, or there may be a causal relationship.[65-67] In community-based studies, OAB is more common among those with POP compared to age-adjusted patients without prolapse. Similarly, previous studies have identified that OAB symptoms may improve following POP repair.[65, 66, 68, 69] Likewise, in a small prospective cohort study (n=63), detrusor overactivity (DO) was demonstrated to resolve in

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74% (14/19) of patients after prolapse surgery (laparoscopic sacrocolpopexy).[70]

Recently, a large prospective population-based cohort of women in Finland (n=2933) reported that baseline urinary frequency was associated with the degree of anterior and apical prolapse and that UUI was associated with the degree of anterior prolapse.[66] Moreover, those who underwent anterior/apical prolapse surgery had a greater degree of OAB symptom improvement than those undergoing isolated posterior compartment surgery. Specifically, among those undergoing anterior/apical surgery, at 24 months, bothersome frequency resolved in 72% of patients (compared to 58% in the posterior repair group) and UUI resolved in 66% of patients (compared to 53% in the posterior repair group).[66]

Limited data are available regarding predictors for resolution of OAB symptoms among patients with anterior and apical prolapse and these have met with conflicting results.[68, 69] One small retrospective study compared urinary frequency and UUI resolution rates at 12 months following surgery between women with stage 1-2 anterior/apical prolapse (n=41) and those with stage 3/4 POP (n=47).[69] Improvement in UUI was reported in 89.7% of patients with lower stage POP and 85% of patients with higher stage POP (p=0.12). On multivariable analysis, higher stage POP was adversely associated with improvement in OAB symptoms (adjusted OR: 0.06; 95% CI: 0.01-0.67). Of note, the women in this study had symptomatic POP in addition to their OAB symptoms.

Hypothetical biologic mechanisms regarding the impact of POP on OAB symptoms include activation of urothelial stretch receptors with bladder descent from POP, BOO from kinking of the urethra, changes in pelvic floor muscle function, and incomplete bladder emptying.[66] However, given the multiple potential pathophysiologic factors that may lead to OAB, POP may variably contribute to urinary symptoms in some patients.

Ultimately, the decision to treat POP (via pessary or surgery) should be in the context of shared decision-making with the patient including consideration of the impact of POP on vaginal, bladder, bowel, and sexual function related symptoms. In many cases, patients have bothersome POP symptoms in addition to urinary symptoms.[71] In this setting, correction of the POP may be beneficial for more than one symptom category. A trial of a pessary to assess symptomatic improvement may be helpful during surgical planning.

Genitourinary syndrome of menopause

GSM refers to the signs and symptoms of decreased estrogen levels on the urogenital tissues.[72] Given shared embryologic origins of the lower urinary and genital tracts, both contain estrogen receptors and may be impacted by hypoestrogenic states.[73] Patients with GSM may present with changes related to estrogen deficiency on physical exam and report vaginal, labial, bladder, and/or urethral symptoms.[73] Urinary symptoms may include frequency, urgency, dysuria, urethral discomfort, recurrent UTI, and/or the presence of a urethral caruncle or urethral prolapse.[73, 74] As such, some GSM symptoms will overlap with the clinical presentation of OAB. Thus, providers should assess for signs of GSM on physical exam during the workup of OAB and consider treatment in shared decision-making with the patient. Regarding bladder and urethral symptoms, the use of topical vaginal estrogen in patients with GSM has been associated with improvements in urinary urgency, frequency, UUI, dysuria, and recurrent UTIs.[74-76]

Glucosuria

Glucosuria can occur when blood glucose levels are elevated, for instance in patients with poorly controlled or undiagnosed diabetes mellitus, and in those taking SGLT2 inhibitors for the management of type 2 diabetes mellitus. SGLT2 inhibitors work by blocking glucose reabsorption in the proximal tubule, thereby decreasing blood levels of glucose and facilitating excretion of excess glucose in the urine.[77]

Glucosuria potentially contributes to urinary symptoms secondary to urothelial irritation and osmotic diuresis. In addition to the impact of glucosuria, undiagnosed or poorly controlled diabetes mellitus may contribute to underlying bladder dysfunction through changes in detrusor muscle pathophysiology, neuronal impairment, and urothelial dysfunction.[78-80] Furthermore, other metabolic changes associated with hyperglycemia can lead to increased thirst and polydipsia, further driving urinary symptoms.

Recognition of glucosuria on urinalysis during the evaluation of OAB should prompt discussion with the patient regarding primary care follow-up to direct any

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other assessment needed and options for serum glucose management.

Obstructive sleep apnea

Obstructive sleep apnea has been consistently associated with worsening of nocturia, potentially secondary to increased bladder filling and sleep disturbance.[81-83] Increased bladder filling is thought to be secondary to physiologic changes surrounding obstructive sleep apnea including creation of negative thoracic pressures from ventilatory effort with an obstructed airway. This negative pressure leads to a false signal of volume overload in the heart which in turn causes atrial natriuretic peptide release and increased urine production.[81] From a urinary symptom standpoint, the degree of obstructive sleep apnea has been correlated with the severity of OAB symptoms.[84] Additionally, treatment of obstructive sleep apnea (e.g., with continuous positive airway pressure) is associated with significant improvements in nocturia, night-time urine volume, and OAB Symptom Scores (OABSS).[85, 86] Clinicians should be aware of this relationship between OAB and obstructive sleep apnea and may consider asking patients about the presence or signs and symptoms of obstructive sleep apnea (e.g., excessive daytime sleepiness, loud snoring, observed episodes of stopped breathing during sleep, etc.) by history or validated questionnaire.

Anxiety/Depression

Multiple studies have identified that anxiety and depression are comorbid conditions that often co-exist in patients with OAB.[87-89] Indeed, a recent systematic review and meta-analysis demonstrates that clinically significant anxiety was more likely among those with LUTS including OAB or IC/BPS, (OR: 2.87; 95% CI: 2.38-3.46; p<0.001). Likewise, LUTS were more likely among those with clinically significant anxiety (OR: 2.87; 95% CI: 1.07-7.74; p<0.001).[89] The biologic mechanism of the interaction between anxiety/depression and OAB is not well elucidated and potentially bidirectional. That is, previous studies have identified that the presence of anxiety is a predictor for the development of incident LUTS and vice versa.[90-92] One hypothesized mechanism regarding the influence of anxiety on OAB symptoms is that it may impact hypersensitivity mechanisms, though further research in this area is needed.[93] Similarly, the impact of treating anxiety on OAB symptom severity is not well studied. Considering the potential impact of diagnosing and treating anxiety/depression on OAB symptoms and the overall health of patients, clinicians may consider asking about the presence of these symptoms through history or validated questionnaires.

Tobacco cessation

Multiple studies have identified a significant association of tobacco use with OAB symptoms.[94, 95] Several of these studies were performed using web or mailed surveys and noted a higher prevalence of OAB symptoms in current smokers and ex-smokers compared to never smokers, including a dose dependent relationship. For instance, in a web-based survey of 4756 women, current smokers and ex-smokers reported significantly worse OAB Symptom and International Consultation on Incontinence Questionnaire-Short Form scores than non-smokers (p<0.0001 for each comparison). Additionally, the prevalence of UUI was also associated with smoking status.[95] There is a paucity of prospective data on the impact of smoking cessation on OAB symptom resolution. Given the potential benefit on bladder symptoms and the significant other health benefits of smoking cessation (e.g., cardiovascular, oncologic), education on the topic is an important consideration when discussing treatments with patients presenting for OAB.

8. Clinicians may use telemedicine for follow-up visits with patients with OAB. *(Expert Opinion)*

Once a patient has undergone an initial evaluation, the use of telemedicine to follow-up patients with OAB is often an easy and appropriate transition. Assuming there are no clinical changes, in-person evaluation (e.g., examination, urinalysis, PVR assessment) is often unnecessary. Therefore, telemedicine is very effective and convenient for patients when evaluating response to therapy, adjusting or refilling medications and/or considering a change in therapy. If patients are to undergo certain therapies such as intradetrusor botulinum toxin (BTX) injection, percutaneous tibial nerve stimulation (PTNS) or evaluations (e.g., UDS, cystoscopy) then an in-office visit would be required.

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SHARED DECISION-MAKING

Shared decision-making is a process where clinicians and patients balance the best available medical evidence with patients' preferences and values to reach a medical decision.[96] Decision aids are tools (e.g., pamphlets, videos, web-based material) that can help support and facilitate shared decision-making by presenting clear information to the patient about treatment options, potential benefits, and harms. Shared decision-making is not simply providing a patient with decision aids such as pamphlets or telling them the best evidence-based recommendations regarding their condition or treatment choices; nor is it providing a menu of options and abandoning the patient to decide alone. Shared decision-making is an interactive patient-clinician dialogue where the clinician shares information and evidence-based recommendations specific to that patient, taking into consideration their health and social situation. The patient shares their values and preferences to the clinician. Together, once both clinician and patient are informed, they reach a decision on the next best step in care. This approach recognizes the importance of incorporating patient preferences and values in addition to the clinician's recommendation into the decision-making process. This differs from the "informed medical model" which is a passive process by which the clinician informs the patient of all the treatment options but withholds a recommendation, leaving the patient to deliberate and make a decision alone. It also differs from the "traditional medical model" where the healthcare professional provides limited information and options, while making the decision for the patient.[97] Shared decision-making is particularly important in preference-centered health decisions where multiple options exist for the same condition and the clinical outcomes for each decision are relatively equal. In this scenario, the driver of the decision is patient preference. OAB is one such condition hence the emphasis on the use of shared decision-making in this guideline. Decision making for OAB treatment is often driven by symptom severity, patient preferences, and values regarding adverse effects.[98-100]

For OAB medication decision-making clinicians and patients may have diverging decisional priorities and decisional control. The literature is mixed on this topic, in some studies clinicians emphasize benefits whereas patients put more value on minimizing risk and side effects.[101] More recent studies found that clinicians prioritize safety and patients place more emphasis on efficacy.[102] At least two interactive decision-making aids for OAB are under development including OABcare[103] and Streamlined[104] but few validated are freely available for clinical use.[100]

Shared decision-making can lead to increased satisfaction, patient empowerment, and adherence to therapy, all while improving patient outcomes and reducing decisional conflict.[105, 106] Shared decision-making in OAB should involve a collaborative process between clinicians and patients to make informed choices about treatment options.[107]

9. **Clinicians should engage in shared decision-making with patients with OAB taking into consideration the patient's expressed values, preferences, and treatment goals in order to help them make an informed decision regarding different treatment modalities or to explore the option of no treatment.** ***(Clinical Principle)***

Patients with OAB can present with varying symptoms and may not be bothered by them. In such cases, the patient may be seeking an accurate diagnosis to ensure that their condition is not life-threatening, such as a malignancy or urinary retention. Once the correct diagnosis is obtained and other conditions are ruled out, it is appropriate to educate the patient about the nature of OAB and its management. Given that the condition is preference-centered, meaning that no specific treatment has clear superiority, the clinician should engage in shared decision-making regarding the patient's choice of treatments or no treatment at all.

NON-INVASIVE THERAPIES

10. **Clinicians should discuss incontinence management strategies (e.g., pads, diapering, barrier creams) with all patients who have urgency urinary incontinence.** ***(Expert Opinion)***

Patients who present with UUI symptoms should be evaluated and counseled regarding potential management with behavioral therapy, pharmacotherapy, or procedural interventions. In addition to discussing these treatments, clinicians should review potential strategies for managing incontinence with all patients, especially in those who opt for observation of the leakage.

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Incontinence management strategies are differentiated from OAB treatments in that they are not designed to alleviate the leakage episodes, rather they are used to mitigate the impact of leaking on QoL and resultant sequela. Liners, pads, and diapers are commonly used products for leakage containment. Likewise, absorbent washable protective briefs and underwear are also available. Barrier creams can be utilized to prevent incontinence-associated dermatitis and skin breakdown.[108] External catheters may be utilized for urine collection. In one study assessing patient satisfaction with female external catheter use, >80% of responders noted satisfaction, comfort benefits, and likelihood to recommend the product, though >70% noted increased expense compared to diapers.[109] In men, the use of a condom catheter is an additional external management option available. For those with functional limitations and difficulty mobilizing to reach the toilet, bedside commodes or urinals can be considered. It is important to note that no RCTs have compared the clinical or cost effectiveness or patient satisfaction with these strategies despite skin breakdown and urinary dermatitis being significant health problems for people suffering with UUI. Shared decision-making with the patient should include a description, as well as the risks and benefits of these strategies.

11. **Clinicians should offer bladder training to all patients with OAB *(Strong Recommendation; Evidence Level: Grade A)***

12. **Clinicians should offer behavioral therapies to all patients with OAB. *(Clinical Principle)***

Behavioral therapy is a form of conservative therapy (non-surgical and non-pharmacological) that is based on modifying human actions by substituting a new response or set of responses that the individual patient can perform themselves.[110] Such treatment does not require adjunctive measures or instrumentation. Behavioral measures for OAB offer some efficacy, excellent safety, few if any adverse effects, and are generally low to no cost. The risk-benefit ratio of these therapies is excellent with minimal probability of worsening symptoms over time (Table 6).

These therapies have not all been studied equally in the treatment of OAB and therefore the evidence base for these interventions is highly variable. Bladder training has been extensively studied and thus recommended based on strong evidence.[111] Adjuvant measures such as voiding diaries, frequency/volume charts, and mobile electronic apps are often used as an assessment tool in OAB; however their utility in improving the results of bladder training as an OAB treatment is unclear. Review of fluid intake is recommended, and management of these habits may improve OAB symptoms in some individuals.[112, 113] There is some evidence supporting dietary modification (e.g., low fat, high fruit/vegetable, whole grain diet), increasing physical activity, and caffeine reduction in the treatment of OAB, with or without UUI.[114] Similar to bladder training, these interventions are considered very low risk, inexpensive and have few if any adverse effects and therefore can be considered in selected individuals.

There is no general agreement regarding the optimal delivery of behavioral therapy including which to initiate in any given patient or the ideal method of delivery of information to the patient to ensure understanding and compliance (e.g., office counseling, written instructions/pamphlets, on-line learning, individual or group therapy). Patient education, written instructions, and checklists seem to improve outcomes when utilized.[115-117]

Implementation and success of behavioral therapies is highly dependent on patient acceptance, adherence, and compliance. Novel approaches to, and modifications of, the delivery of behavioral therapy are important to potentially improve the historically low success rates with these therapies.[118] It is likely that periodic reinforcement, follow-up office visits, and/or electronic reminders may be helpful tools in maintaining the favorable effects of behavioral therapies.[119, 120]

Patients starting these therapies should be counselled that long term efficacy is dependent on adherence and although short term improvement may be evident following initiation of treatment, long-term cure rates are low without compliance. The underlying reasons for patient dropouts in behavioral therapies, as well as more advanced therapies for OAB, are unclear and need further study.[121]

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Table 6: Behavioral interventions for OAB/UUI*

Bladder training/timed voiding
Fluid management (e.g., fluid restriction at night, avoiding polydipsia)
Caffeine reduction
Physical activity/exercise
Dietary modification (e.g., low fat, high fruit/vegetable, whole grain)
Mindfulness
Bladder training/timed voiding
OAB: overactive bladder; UUI: urgency urinary incontinence **not listed in order of efficacy or recommendation*

13. Clinicians may offer select non-invasive therapies to all patients with OAB. *(Clinical Principle)*

Behavioral therapy is only one category of non-invasive therapy for OAB and is described in Statement 11 above. Non-invasive therapies are conservative therapies for OAB and include a variety of interventions that require participation by the patient, with one or more active external or internal devices, or supervised therapies, but are not pharmacological or surgical (Table7). The definitions of non-invasive and behavioral therapies may have been imprecisely defined in previous literature; however, they are distinct terms and should not be used interchangeably as many forms of non-invasive therapy are not behavioral.

Similar to behavioral therapies, the evidence base across the various non-invasive therapies is highly variable. While the safety profiles are largely excellent across modalities, with few adverse effects and a high risk-benefit ratio. all non-invasive therapies are not considered equivalent with respect to efficacy. Furthermore, these therapies may be expensive since they typically involve participation with an allied health professional or a dedicated device. These are diverse treatments, and it is not expected nor pragmatic for a single practitioner to offer all these interventions or be an expert in the delivery and performance of them. There are no guidelines or generally accepted care pathways directing practitioners and patients toward one or more non-invasive OAB therapies initially or sequentially. Practitioners and patients should opt for those interventions with strong evidence combined with several other factors including cost, convenience, and availability. Most non-invasive therapies require long term patient compliance to maintain a durable effect and patients should be counselled as such before embarking on a course of potentially expensive and lifelong therapy.

PFMT, including urge suppression techniques, should be recommended as therapy for OAB as well as UUI.[114, 122] However, there is considerable variability amongst practitioners in administering PFMT and novel methods of delivery including telehealth[123] and virtual reality[124] have been investigated. The optimal mode of delivery, duration of therapy, and interval for periodic reinforcement are not well defined and are variable across studies,[125] but evidence does support the use of maximal intensity regimens when possible.[126] The addition of behavioral therapy (most notably bladder training) to a regimen of PFMT does appear beneficial.[114] However, the use of biofeedback does not appear to confer additional benefit in patients with OAB undergoing PFMT except in select groups.[114, 127, 128] It is unclear if the efficacy of PFMT, and many other non-invasive and minimally invasive therapies for OAB, is inversely correlated with the severity of the presenting symptoms.

Magnetic stimulation to the pelvic floor is an alternative method of favorably altering pelvic floor function in order to affect a variety of urinary and pelvic conditions including OAB. Magnetic stimulation can be delivered via transcranial and transsacral routes for the treatment of OAB, but these methods are not in widespread use. Compared to sham, pelvic floor magnetic stimulation demonstrated significant reduction in incontinence episodes, frequency, and urgency but no change in OABSS in women with UUI.[129] Magnetic stimulation in addition to bladder training was compared to bladder training alone in 76 women with OAB.[130] Magnetic stimulation in combination with bladder training was superior to bladder training alone in improving nocturia, incontinence episodes and severity, pad use, and QoL, but not urinary frequency.

There are multiple methods of administering electrical stimulation for the treatment of OAB without needles or incisions including vaginally and transcutaneously to peripheral nerves, including the tibial nerve. Therapeutic regimens including length of therapy per session, duration of therapy, and stimulation parameters (e.g., pulse width, frequency, amplitude) are variable across studies and methods making comparisons difficult. Evidence supporting the efficacy of this modality for OAB is generally of low quality. A review of 15 articles indicated

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that transcutaneous tibial nerve stimulation (TTNS) was equivalent to PFMT in the management of OAB; however, it was not as efficacious as pharmacotherapy.[131] A review of seven trials of transvaginal electrical stimulation demonstrated some improvement in a number of OAB outcomes but the evidence was of low quality.[132] The addition of TTNS to Kegel exercises and bladder training demonstrated significant improvements in incontinence episodes, frequency, and nocturia as compared to Kegels and bladder training alone.[133]

It is uncertain whether yoga has a favorable effect on urinary incontinence or OAB. This is due to a poor evidence base related to small numbers of patients and high risk of bias.[134] Hypnotherapy for OAB has not been widely studied and current literature suggests that this treatment confers very little effect on objectively measured symptoms of OAB.[135]

Treatment failure for non-invasive therapy for OAB is generally and pragmatically considered to occur when the patient does not have the desired change in their symptoms or is unable to tolerate the treatment due to adverse events or other reasons.[42] However, the actual definitions of success and failure as well as the time frame for moving onto to more invasive, aggressive or costly therapies is poorly understood.[136]

Table 7: Non-invasive interventions other than behavioral therapy*

PMFT (e.g., urge suppression, muscle strengthening)
Magnetic stimulation
Transcutaneous electrical stimulation
TTNS
Transvaginal electrical stimulation
Yoga
Hypnosis
PFMT: pelvic floor muscle therapy; TTNS: transcutaneous tibial nerve stimulation **not listed in order of efficacy or recommendation*

14. In patients with OAB whose symptoms do not adequately respond to monotherapy, clinicians may combine one or more of the following: behavioral therapy, non-invasive therapy, pharmacotherapy, and/or minimally invasive therapies. *(Expert Opinion)*

Historically, treatment of OAB has followed a stepwise progression of therapies from least invasive to most invasive (i.e., first line-behavioral/non-invasive, second line pharmacologic, third line minimally invasive therapy, major surgery), based on responses to therapy. In day-to-day practice, clinicians may use a layering or combination approach of two or more therapies simultaneously. For example, practitioners may initially offer behavioral therapies individually or in combination. Such therapies are not mutually exclusive. Furthermore, behavioral therapies have been added to other non-invasive,[137] minimally invasive,[138] and pharmacological therapy[139, 140] for OAB with potentially additive favorable effects. To date, there is no significant evidence to support or refute these practices. Notably, there is no general agreement regarding the optimal delivery of combination therapy including when to add on additional therapies or discontinue them. There is a small body of evidence emerging regarding the use of behavioral, non-invasive (e.g., transcutaneous stimulation), and pharmacologic therapies in combination with mixed outcomes.[140, 141 133, 142]

Four recent RCTs were identified that evaluated combination therapy using behavioral, pharmacotherapy, and non-invasive stimulation techniques. Two of the studies looked at adding an additional therapy to behavioral therapy and/or Kegel exercises.[140 133] In both studies, all study arms had varying degrees of improvement relative to baseline and the groups with combination therapy had the highest degree of improvement. TTNS combined with Kegel exercises and bladder training resulted in statistically significant superior improvement in questionnaire scores, micturition frequency, nocturia, and UUI episodes in women. The addition of tolterodine extended release (ER) to PFMT and behavioral changes in male patients demonstrated overall improvement relative to either therapy alone but did not reach statistical significance. Using vaginal stimulation techniques combined with TTNS or topical estrogen had mixed outcomes. Vaginal stimulation with TTNS did not improve the overall outcomes of TTNS.[141] The use of topical estrogen and vaginal stimulation appear to have a synergistic effect with better outcomes in the combination group.[142]

Three prospective trials evaluated combination therapy with antimuscarinic medications and PTNS,[143-145] which demonstrated improvement in outcomes as compared

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with medication and PTNS alone. There is a paucity of data, both RCT and prospective trials, regarding the use of pharmacologic therapies and/or behavioral therapies combined with more invasive therapies such as BTX and sacral neuromodulation (SNM).

Practitioners and patients may elect to combine any groups of therapy. When combining therapies, the practitioner should carefully monitor improvement in OAB symptoms and if no improvement is noted, then one or both therapies should be discontinued, and other treatments pursued. If incremental but still unsatisfactory improvement is noted during combination therapy, additional therapies may be initiated. When combining greater than two therapies, the practitioner should proceed in a stepwise fashion, not instituting multiple additions simultaneously thereby allowing the practitioner to determine the individual impact of each therapy on symptoms.

15. **Clinicians should counsel patients that there is currently insufficient evidence to support the use of nutraceuticals, vitamins, supplements, or herbal remedies in the treatment of patients with OAB.** ***(Expert Opinion)***

Nutraceuticals, vitamins, and herbal supplements/remedies have been proposed for the treatment of OAB. While there has been single arm, case series, or underpowered trials published,[146, 147] there are not adequately powered RCTs demonstrating efficacy for any of these agents. Since these agents have not been adequately studied for treatment of OAB, they are not recommended at this time.

PHARMACOTHERAPY

16. **Clinicians should offer antimuscarinic medications or beta-3 agonists to OAB patients to improve urinary urgency, frequency, and/or urgency urinary incontinence.** ***(Strong Recommendation; Evidence Level: Grade A)***

Overall, there is a large body of evidence that supports the use of muscarinic receptor antagonist (i.e., antimuscarinic medications) and beta-3 (β3) adrenergic agonist oral medications for managing symptoms in patients with OAB. Based on these data, all currently available agents, including antimuscarinic medications and β3 agonist medications, demonstrated increased efficacy compared to placebo in RCTs examining the outcomes of urgency urinary episodes, voiding episodes, and UUI.[47, 148-157] However, across the literature, there is considerable variance in estimated magnitudes of effects of OAB medications on symptoms of OAB; the overall effectiveness of OAB medications may be only minimal to modest. [47, 148-156]

When compared to placebo, both antimuscarinic and β3 agonist medications have demonstrated improvement in OAB symptom outcomes. A Cochrane systematic review of 104 randomized or quasi-randomized trials compared antimuscarinic medications alone to placebo and demonstrated that treatment with antimuscarinic medications decreases both the mean number of urgency episodes and micturition episodes per day while patient perception of cure or improvement was improved.[47] Additional RCTs reported similar statistically significant decreases in urgency, UUI, incontinence, and micturition when β3 agonists were compared with placebo.[148, 151-154, 156, 158-160] Although the improvements are statistically significant, these symptom improvements are clinically modest.

Clinical studies have also demonstrated that OAB agents significantly improve other outcomes of interest to patients and clinicians, including overall and condition-specific QoL,[47, 151, 152, 161-163] satisfaction with treatment,[149, 150] and work productivity.[164]

Although outside the scope of the systematic review, the Panel felt it was important to note that the observed placebo effect is very strong in clinical studies. Mostafaei et al. performed a systematic review and meta-analysis of 57 RCTs of oral pharmacotherapy for OAB and reported that placebo agents achieved statistically significant improvements in all outcomes measured (e.g., daily voids, urgency episodes, nocturia, UUI episodes).[165]

Comparability of individual agents

In the past 10 years few studies have been designed to directly compare individual OAB medications. The few studies that have directly compared antimuscarinic medications and β3 agonists demonstrated no OAB symptom control difference across arms,[166] or reported on non-OAB symptom control outcomes, such as cardiovascular safety[167] and medication persistence.[168] More frequently however, RCTs were designed to evaluate a β3 agonists and included an antimuscarinic

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medication arm (tolterodine or imidafenacin) as an active control with both treatment arms only compared to the third placebo arm.[149-151, 153-156, 169, 170] Based on a lack of evidence indicating superiority for either class when evaluating OAB symptoms control, the Panel concluded that the efficacies of antimuscarinic medications and β3 agonists were similar.

In six RCTs that directly compared antimuscarinic medications, two demonstrated non-inferiority of propiverine[171] or imidafenacin[172] when compared with tolterodeine. Of note, neither propiverine nor imidafenacin are currently available in the United States. In the other four studies[173-176] improvements were noted in both arms; however, no significant difference was found between arms. The Panel paired this limited data with evidence from the Cochrane review[47] showing comparable magnitudes of effect for individual antimuscarinic medications when compared with placebo and concluded that it is reasonable to presume that antimuscarinic medications are similarly effective, without superiority among agents.

Similarly, evidence directly comparing β3 agonist agents is limited. A single RCT compared mirabegron and vibegron in female patients, and while OABSS improvements compared to baseline were demonstrated in both groups, there were no significant difference when arms where compared.[177]

Network meta-analyses not included in the evidence base demonstrate minor differences in efficacy between mirabegron and vibegron.[178, 179] Compared to mirabegron (at doses of 25 mg and 50 mg), analyses indicate that vibegron further decreased the mean daily number of total incontinence episodes by slightly less than one episode per day[178] and marginally increased the mean voided volume per void by 10 to 20 mL.[179] Although statistically significant, the Panel concluded that the clinical benefits were so small as to presume each medication is equally effective.

Efficacy by gender

Men and women experience OAB at similar rates according to epidemiologic data, although men report UUI less frequently. There is little to no epidemiological data on the prevalence of OAB in transgender and nonbinary gender groups. Although older studies focused on women, more recent studies examining newer medications have included men in study populations. Even with the addition of men to these studies, studies focused on only male patients and subgroup analyses for both genders are limited. In male patients, subgroup analysis of two older studies that compared fesoterodine to tolterodine as an active control and placebo demonstrated improvements in both micturition rates and urgency episodes in male patients.[180] Similarly, further analyses of male-only arms of mirabegron studies demonstrated that mirabegron was equally as efficacious as solifenacin in improving urinary frequency (24-hour micturition episodes), but not efficacious in reducing urgency episodes or UUI episodes.[181] It is worth noting that these studies included a mix of male patients with and without LUTS associated with BPH and included patients taking alpha blockers. In a study that enrolled male patients and randomized them to mirabegron or placebo for 12 weeks, followed by a 14-week extension phase where both groups received mirabegron, greater reduction in patient reported outcome measures were reported for mirabegron over the initial 12 weeks of the study, while no differences were reported at the 26-week study endpoint.[182]

In female patients, a sub-analyses of women participating in studies on vibegron demonstrated that the magnitude of improvement in efficacy endpoints were similar for women when compared with the entire cohort of both males and females.[151] Additionally, the aforementioned pooled analysis of fesoterodine demonstrated improvement in UUI episodes, micturition frequency, and urgency episodes in a subgroup analysis for female patients.[180] A final post-hoc analysis not included in this evidence base examined pooled data from 10 RCTs studying monotherapy for mirabegron, solifenacin, and tolterodine and determined there were no differences in clinical efficacy outcomes between men and women participating in the studies.[183] Based on review of these data, the Panel concluded that currently available OAB pharmacotherapy agents are equally effective in men and women.

Efficacy by age

The systematic search identified nine studies in older adults[170, 184-191] and the results from these studies suggest that outcomes from OAB therapy are similar when patients are stratified by age or studied in older adults. In a systematic review and network meta-analysis of 20 studies enrolling patients aged ≥65 years, Lozano-Ortega

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et al.[189] reported that efficacy outcomes were similar between antimuscarinic medications and mirabegron compared to placebo, with greatest improvements noted in total number of voids per 24 hours (–0.6 to –1.7 daily episodes), number of urgency voids per 24 hours (–0.5 to –1.9 daily episodes), and voided volume (10 – 32 mL). Total urinary incontinence and UUI episodes per 24 hours were not significantly different from placebo. In additional comparisons between older and younger patients, any statistical differences were small and of little clinical significance, with most studies demonstrating comparable outcomes regardless of age. The Panel therefore concluded that OAB agents are equally effective in patients of any age.

17. Clinicians should counsel patients with OAB on the side effects of all oral medication options; treatment should be chosen based on side effect profiles and in the context of shared decision-making. *(Clinical Principle)*

While efficacy may be similar among OAB medications, side effect profiles differ among agents and between antimuscarinic medications and β3 agonists specifically. Therefore, clinicians should engage the patient in the context of shared decision-making to choose a pharmacologic treatment option that incorporates patient preferences and values. Patients with OAB often prioritize benefits while limiting risks associated with treatments, including pharmacology.[100] Shared decision-making provides opportunity for education, facilitates setting expectations, and allows the clinician and the patient to arrive at treatment plans that align within patients' informed preferences.

Overall, side-effects associated with antimuscarinic medications are well-known, well-recognized, and have been recently reviewed with a high quality meta-analysis.[47] The most commonly reported side-effect of antimuscarinic medications is dry mouth, reported by approximately 25% (for trospium, solifenacin, and tolterodine) to 44% (oxybutynin) of patients.[192] Compared to placebo, antimuscarinic medications is associated with a relative risk of dry mouth of 3.50, (95% CI: 3.26 - 3.75).[47] Constipation is also commonly reported by 8-15% of patients,[192] and is associated with a relative risk (RR) of 2.03 (95% CI: 1.78-2.31) compared to placebo.[47] Voiding dysfunction/incomplete emptying is often one of the most concerning side-effects for clinicians and occurs in approximately 16% (95% CI: 8-27) of women taking oxybutynin.[47] Compared to placebo, antimuscarinic medications are associated with a RR of 3.52 (95% CI: 2.04-6.08) of retention.[47] Blurred vision occurs in up to 11% of patients taking antimuscarinic medications, with a RR of 1.58, (95% CI 1.26 to 1.99) compared to placebo.[47]

Although rare, antimuscarinic medication use can also be associated with palpitations, tachycardia, and QT prolongation, which can lead to the development of torsades de pointes, a potentially fatal ventricular arrhythmia.[193] ER formulations for antimuscarinic medications are superior to immediate release formulations for decreasing side effects and should be used preferentially.[42, 194]

Although not directly compared in studies, β3 agonists appear to have fewer side effects than antimuscarinic medications particularly with lower rates of dry mouth and constipation.[149, 150, 153, 155, 161, 189, 195] β3 agonists likely have less effect on PVR as well, resulting in decreased rates of retention/voiding dysfunction.[151] One of the primary side effect concerns of β3 agonists are potential effects on cardiovascular function, including hypertension, heart rate, and cardiac arrythmias. Initial studies of mirabegron reported mild increases in systolic blood pressure of 1-3mm/Hg. However, pooled analyses of phase 3 RCT on mirabegron suggest no significant differences in the incidence of hypertension between mirabegron, placebo, and tolterodine.[196] It is important to note that the two currently available β3 agonists carry different warnings about use. Mirabegron is not recommended for use in patients with severe, uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180mm/Hg and/or diastolic blood pressure greater than or equal to 110mm/Hg), while vibegron does not have this warning. Overall, the side effect profiles for β3 agonists are similar.

18. Clinicians should discuss the potential risk for developing dementia and cognitive impairment with patients with OAB who are taking, or who are prescribed, antimuscarinic medications. *(Clinical Principle)*

There is mounting evidence to suggest an association between antimuscarinic medications and the development of incident dementia. A meta-analysis of 11

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cohort studies and three case-control studies with a total of 1,564,181 subjects found that antimuscarinic medications use were associated with increased risk of all-cause dementia (RR: 1.20; 95% CI: 1.15-1.26) and Alzheimer's disease (RR: 1.18; 95% CI: 1.11-1.25).[197] The increased risk of dementia was noted in both low and high antimuscarinic medication drug exposures. In a subgroup analysis that included only three studies of OAB antimuscarinic medications, the risk of all-cause dementia was retained, and when compared to other categories of antimuscarinic medications, were among the antimuscarinic medications with the highest risk.[197]

There may also be a cumulative and dose-dependent effect of antimuscarinic medications over time. One notable population-based cohort study of 3,434 older adults found that higher cumulative antimuscarinic medication use was associated with increased risk of dementia over a mean of 7.3 years of follow up.[198]

One population-based matched cohort study using administrative data from Canada matched 47,324 new users of antimuscarinic medications to 23,662 new users of a β3s agonist (mirabegron). This study found that there was an increased risk of dementia among antimuscarinic medication users compared to β3 users (HR: 1.23; 95% CI: 1.12-1.35), suggesting increased effect with antimuscarinic medications compared to β3.[199]

The risk may not be the same for all OAB antimuscarinic medications, as some may have more of an effect on cognition than others. This variability can depend on blood brain barrier permeability, physiochemical factors such as lipophilicity, molecular weight, the charge of individual OAB antimuscarinic medications, and affinity for active transport mechanisms such as P-glycoprotein (P-gp) to selectively move certain OAB antimuscarinic medications (5-HMT [the active metabolite of fesoterodine], darifenacin, and trospium out of the brain. Based on these drug characteristics, it is believed that fesoterodine, darifenacin, and trospium are likely to have lower permeability across the blood brain barrier and therefore theoretically carry lower risks of cognitive side effects.[199]

Based on these and other studies, a SUFU White Paper advises that chronic use (>3 months) of antimuscarinic medications is likely associated with increased risk of new-onset dementia and that clinicians should consider potential cognitive risks in all patient populations when prescribing these medications for chronic use. Additionally, the paper advises that when pharmacotherapy is indicated for OAB, a trial of a β3 agonists is typically preferred before antimuscarinic medications.[200]

19. Clinicians should use antimuscarinic medications with extreme caution in patients with OAB who have narrow-angle glaucoma, impaired gastric emptying, or a history of urinary retention. *(Clinical Principle)*

Clinicians should prescribe antimuscarinic medications with extreme caution in patients with narrow angle glaucoma and in consultation with a treating ophthalmologist. Use of these medications can affect the cholinergic receptors on the ciliary muscle and the sphincter pupillae in the eyes, potentially causing increases in intraocular pressures.[201] Since muscarinic receptors are also present throughout the gastrointestinal tract, clinicians should also use caution in prescribing these medications in patients with any conditions that affect gastric emptying. Of note, antimuscarinic medications are relatively contraindicated in those who are taking oral potassium supplementation since reduced gastric motility caused by antimuscarinic medications may cause prolonged potassium retention, resulting in intestinal irritation and ulceration.[193] Additional considerations in prescribing antimuscarinic medications should be given in patients with diabetes, prior abdominal surgery, narcotic use, scleroderma, hypothyroidism, Parkinson's disease, multiple sclerosis, and any other conditions that may impact gastric emptying. To this effect, an additional thorough review of medications should also be performed to identify any medications that may cause delays in gastric emptying, including GLP-1 receptor agonists and its analogs, in addition to those that may interact with antimuscarinic medications in other ways. Consultation with a gastroenterologist may be helpful in these situations. If a patient has a history of urinary retention or is at risk for retention, a PVR should be obtained and careful consideration and weighing of risks and benefits should be considered and discussed with the patient in terms of the potential for worsening of bladder emptying.

20. Clinicians should assess patients with OAB who have initiated pharmacotherapy for efficacy and

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for onset of treatment side effects. *(Expert Opinion)*

The Panel recommends that patients should be assessed within 4 – 8 weeks after initiating OAB pharmacotherapy for efficacy of the treatment as well as the onset of side effects. Most clinical studies included assessments of efficacy and/or side-effects at 4 weeks and most were able to demonstrate medication effects by that time.[151-154, 156] In a few cases, clinical studies reported earlier outcomes, which suggest that some agents may have earlier onset of efficacy. For example, vibegron demonstrates improvements in symptoms by as soon as 2 weeks.[153, 154]

Assessment may be performed either in-person or remotely via telemedicine, in select patients. Efficacy can be assessed by patient self-report, standardized PRO measures, or even by bladder diary. Side-effects similarly can be assessed by patient self-report. To assess for voiding dysfunction or urinary retention, PVR may be considered in certain patients (e.g., those with elevated pre-treatment PVRs, those initiating antimuscarinic medications, elderly patients). Those at risk for cognitive impairment may warrant specific cognitive assessment.

As noted previously, side-effects occur frequently and are generally minor, although side effects can potentially be quite bothersome and drive treatment withdrawal and discontinuation. In a meta-analysis of 30 clinical trials reporting on adherence and persistence to OAB pharmacotherapy, the 1-year persistence was 12%–25% for antimuscarinic medications and 32%–38% for mirabegron.[202] The median time to discontinuation was <5 months for antimuscarinics and 5.6–7.4 months for mirabegron. The report identified determinants of persistence and adherence included being female, older age group, use of ER formulation and treatment experience.

Many side-effects can be managed effectively, and clinicians can help patients benefit from OAB pharmacotherapy by proactively monitoring and managing common side-effects. Even before initiating OAB pharmacotherapy, patients should be educated about the possible effects of medication on bowel function and the roles of adequate dietary fiber and fluid intake, psyllium-based fiber supplements, regular exercise, and normal bowel habits. Management of dry mouth might include advice on oral lubricants, avoiding mouthwashes with alcohol, taking small sips of water, sucking on sugar-free hard candies, and chewing sugar free gum.

The Panel felt assessment after initiating OAB therapy was important to avoid medical "purgatory," in which patients remain in a state of none to minimal improvement or significant side-effects. Those who do not achieve appropriate improvement should be offered change in therapy.

21. **In patients with OAB who experience intolerable side effects or who do not achieve adequate improvement with an OAB medication, clinicians may offer a different medication in the same class or a different class of medication to obtain greater tolerability and/or efficacy. *(Clinical Principle)***

Overall, there are limited data that support substituting one agent for another, especially in the same class of medication (e.g., one antimuscarinic medication for another antimuscarinic medication). In one study that surveyed patients with OAB who were enrolled in a regional medical group, 65% of the study population used only one antimuscarinic medication, while 35% used ≥ two antimuscarinic medications during the follow-up period.[203] Among those who switched to a different agent, none reported improvement in their frequency of UUI episodes. Because β3 agonists appear to have lower rates of common side-effects, such as dry mouth or constipation as compared to antimuscarinic medications, switching to a β3 agonist may be more tolerable for patients while maintaining efficacy.[204]

22. **In patients with OAB who do not achieve adequate improvement with a single OAB medication, clinicians may offer combination therapy with a medication from a different class. *(Conditional Recommendation; Evidence Level: Grade B)***

While patients are often started on a single OAB medication, many may not experience the benefit that they desire. One option is for clinicians to offer combination therapy with both an antimuscarinic medication and a β3 agonist by adding a medication from a different drug class. While the two large studies evaluating combination therapy are limited to two drugs

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(the BESIDE and SYNERGY studies evaluating solifenacin and mirabegron, respectively), the Panel felt that the principle of combination therapy is likely generalizable to other medications within these classes of drugs.

The BESIDE study evaluated the efficacy, safety and tolerability of combination solifenacin and mirabegron versus solifenacin monotherapy, among OAB patients who remained symptomatic after 4 weeks of solifenacin alone. Combination therapy was found to be superior to solifenacin 5 mg, but not to solifenacin 10 mg for improvements in incontinence and frequency,[205] as well as health-related QoL and symptom bother.[206, 207]

The SYNERGY study evaluated the combination of solifenacin 5mg with either mirabegron 25 mg or 50 mg in a Phase 3 RCT of 3,527 subjects. The study demonstrated superiority of solifencacin 5 mg plus mirabegron 50 mg over solifenacin 5 mg alone, with the combination showing consistent improvements in efficacy compared to either drug alone across most outcome parameters with a generally additive effect, supporting the use of combined therapy treatment.[208]

The SYNERGY II RCT evaluated the safety and efficacy of solifenacin 5 mg in combination with mirabegron 50 mg versus monotherapy in 1,794 subjects over 12 months. Adverse events were found to be slightly higher in the combination group (49%) compared to the mirabegron and solifenacin monotherapy groups (41% and 44%, respectively).[195] Combination therapy was significantly superior to mirabegron and solifenacin alone for the number of incontinence episodes and micturitions.[195]

MINIMIALLY INVASIVE THERAPIES

23. Clinicians may offer minimally invasive procedures to patients who are unable or unwilling to undergo behavioral, non-invasive, or pharmacologic therapies. *(Clinical Principle)*

A tenet of OAB is that every patient has an individualized experience with the symptom complex and its impact on that individual person's life. However, an empiric treatment strategy is commonly utilized for OAB wherein all patients are initially started on the least invasive, least expensive intervention ("first line therapy") and then, if ineffective, are progressed to more invasive and expensive options. In this paradigm, individuals with OAB are not initially offered more invasive options. While the prior framework was based on medical evidence and treatment characteristics, it was incomplete as it did not incorporate patient preferences.[100] Patient adherence with selected therapies is multifactorial and include establishment of realistic treatment goals, affordability, tolerability, side effect profile, and ease of intervention.[209]

Behavioral therapy and pharmacotherapy have been the first two lines of treatment based on risk/benefit relationships and degree of invasiveness; however, long-term compliance with these measures is poor resulting in high rates of failure[210, 211] and patient frustration. As a result, many patients fail to move on to more invasive therapies which have the potential for therapeutic success.[212] Many patients may not desire the time commitment and effort required for behavioral interventions or the need for long term medication management and its associated cost and potential adverse effects. At the same time, patients may still desire relief from their OAB.

Minimally invasive treatment options for OAB including PTNS, implantable tibial nerve stimulation, BTX, and SNM have all been associated with high success rates, durable efficacy, and excellent patient satisfaction; however, the patient populations that have been studied are largely patients who have not had an adequate response to behavioral measures and medication management.[213]

Acupuncture has been studied as a minimally invasive therapy for OAB. There are various methods in administering acupuncture which makes analysis of this treatment modality challenging. Nevertheless, one meta-analysis concluded that the evidence supporting acupuncture is uncertain as compared to no treatment or sham treatment in OAB, but low-certainty evidence suggests that acupuncture results in similar improvements to pharmacotherapy in treatment naïve patients with respect to reduction in UUI episodes, nocturia, and urinary frequency.[214]

Both laser and radiofrequency as thermal therapies have not been well studied in OAB. What evidence exists is of poor quality and thus these measures cannot be recommended at this time.[215]

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These interventions would offer considerable therapeutic benefits for naïve patients who do not want to or cannot pursue behavioral or pharmacological treatment options. There is a paucity of data in treatment naïve patients utilizing minimally invasive interventions. The lack of these studies should not preclude the practitioner from offering these interventions in the properly selected and counselled patient. Such studies however are needed.

24. Clinicians may offer patients with OAB, in the context of shared decision making, minimally invasive therapies without requiring trials of behavioral, non-invasive, or pharmacologic management. *(Expert Opinion)*

The advantages and disadvantages of minimally invasive OAB therapies can have a wide range of implications for individual patients. Integrating patient preferences and values enables providers to craft personalized treatment plans aligned with patient goals, potentially enhancing the effectiveness of OAB management. In addition to clinical efficacy and side effects, the mode and frequency of administration (e.g., daily oral therapy versus injection every 6 months versus weekly treatments for 3 months + maintenance versus an implantable device) varies among these therapy options, creating various levels of treatment burden, and further highlights the importance of individualized therapy approaches in OAB. In a non-interventional cross-sectional study of pharmacotherapy and minimally invasive therapy in treatment-naïve patients with OAB symptoms, the method of drug delivery (oral versus injections), decreased daytime urination, and out-of-pocket expenses emerged as the most important therapy characteristics.[216]

The published data demonstrates comparable clinical efficacy across the various OAB treatment modalities. For example, data comparing “first-line” and “second-line” therapy in 164 OAB-wet women, randomized to anticholinergic pharmacotherapy, bladder training, PFMT, or combined pelvic floor rehabilitation (bladder training + PFMT + behavioral education), demonstrated no significant outcome differences (UUI episodes, urinary frequency, dry rates, and QoL) among the four comparator groups at 4 year follow up.[217] However, antimuscarinic medications had the lowest adherence rate at 3 months follow up (antimuscarinic medications = 64% versus bladder training =85%, combined pelvic floor rehabilitation = 95%, and PFMT = 90%; p=0.01). A 2014 Cochrane review noted better subjective outcomes with antimuscarinic medications as initial OAB therapy in combination with bladder training compared to bladder training alone.[218] However, dry mouth was the most commonly reported side effect among antimuscarinic medications users, occurring in approximately one-third of patients. These findings underscore the importance of considering efficacy, tolerability, and adherence rates in therapy decision making.

Existing data suggests comparable clinical efficacy among certain pharmacological and interventional therapies. The ABC trial was a randomized, placebo- and sham-controlled trial that randomized 249 women to antimuscarinic medications or 100 units of BTX. Study findings demonstrated a comparable reduction in mean daily episodes of UUI.[219] However, women randomized to BTX were significantly more likely to report complete resolution of symptoms (27% versus 13%; p<0.01), less likely to report dry mouth, but more likely to experience a UTI or need short-term intermittent catheterization.

PTNS is the only minimally invasive therapy that has been studied in OAB therapy naïve patients. In a prospective, multicenter, single-arm study of treatment naïve patients with OAB, the authors observed statistically significant improvements in UUI episodes (2.4 +/- 2.1; p<0.01) and a reduction in urinary frequency (1.7 +/- 2.5 voids/day; p<0.01) after 12 sessions. The most common adverse event was site pain (3.3%).[220]

Overall, the data suggests that OAB therapy decisions require a nuanced approach that considers the delicate balance between efficacy, adverse effects, and individual preferences rather than adherence to a prescriptive one-size-fits all, stepwise model.

25. In patients with OAB who have an inadequate response to, or have experienced intolerable side effects from, pharmacotherapy or behavioral therapy, clinicians should offer sacral neuromodulation, percutaneous tibial nerve stimulation, and/or intradetrusor botulinum toxin injection. *(Moderate Recommendation; Evidence Level: Grade A)*

Sacral neuromodulation

SNM involves the placement of a neurostimulator that delivers electrical pulses to the sacral nerves through an

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implanted electrode. Clinicians may consider SNM as a therapy option for patients who have not achieved satisfactory outcomes with other OAB therapies. SNM has shown effectiveness in patients refractory to behavioral therapy and pharmacotherapy.[221-223] High quality data evaluating the impact of SNM settings are lacking; however, a secondary analysis of a large RCT found that maximal intraoperative responses in the more distal electrodes predicts better SNM outcome.[224] Adverse events reported with SNM include surgical revision for pain or infection, device discomfort, and lead migration.

Sacral neuromodulation versus antimuscarinic medications

In one prospective RCT, Seigel et al. compared SNM to antimuscarinic medications in OAB-wet and OAB-dry patients who did not have an adequate response to pharmacotherapy.[223] Eighty-six percent of OAB patients randomized to SNM were responders. At 6 months, 61% in the SNM group and 42% in the antimuscarinic medication group met criteria for therapeutic success, with superior continence rates in the SNM group (39% versus 21%, respectively; p=0.06). The SNM group also demonstrated higher QoL scores, with 86% of SNM reporting improved or greatly improved urinary symptom interference, while only 44% of the antimuscarinic medication group reported similar improvement ($p < 0.001$). At one year, device related adverse events included undesirable change in stimulation (12%), implant site pain (7%), and implant site infection (4%). Overall permanent explant rate was 5%.

Sacral neuromodulation versus intradetrusor botulinum toxin

The Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment (ROSETTA) trial, a multicenter study, evaluated 364 OAB-wet women who were refractory to >1 behavioral therapy and >2 or more antimuscarinic medications, and randomized them to SNM or 200U of BTX. OAB outcomes were reported at 6-month and 24-months.[221, 222] Eighty-four percent of participants randomized to SNM after a successful first stage were responders (>50% improvement in UUI episodes). The study demonstrated a greater reduction in UUI episodes/day in the BTX arm over the SNM arm (-3.9 versus -3.3; p=0.01) at 6 months;[222] however, at 24 months the reduction in UUI episodes were similar between groups (-3.88 versus -3.50; p=0.15).[221] Treatment satisfaction and endorsement were greater in the BTX group compared to the SNM arm at 6 months and 2 years.[221, 222] UTI risk at 6 months (35% versus 11%; p<0.001); recurrent UTI at 2 years (24% versus 10%; p<0.01), and risk for catheterization at 1 month and 6 months post procedure (8% and 2% respectively) were greater in the BTX group. Of note, the recommended starting dose for idiopathic OAB is 100U.

Sacral neuromodulation after intradetrusor botulinum toxin

SNM has also shown effectiveness in patients who have an inadequate response to or cannot tolerate BTX. A meta-analysis by Yang et al.[225] evaluated four studies that included patients with OAB refractory to behavioral therapy, pharmacotherapy, and BTX. Analysis demonstrated no significant difference in success rates for BTX failures versus naïve patients (RR: 0.96; 95% CI: 0.72–1.26; p=0.74). In a large retrospective cohort study of BTX failures versus naïve subjects (n=263), Reekmans et al. found that SNM had high immediate (66.7% versus 72.9%, respectively) and long-term success rates (86% versus 82.9%), defined as >50% improvement.[226] These results highlight the strong evidence supporting SNM as a therapeutic option for individuals with inadequately controlled OAB symptoms despite prior treatment failures.

Percutaneous tibial nerve stimulation

PTNS refers to electrical neuromodulation applied to the posterior tibial nerve; this nerve shares innervation with the sacral plexus that controls the bladder. The treatment protocol for patients with OAB is based on the Study of Urgent PC vs Sham Effectiveness in Treatment of Overactive Bladder Symptoms Trial (SUmiT), a large, multicenter, sham-controlled RCT involving placement of a 34-gauge needle in the area of the posterior tibial nerve and application of a current of 0.5-9mA at a frequency of 20Hz, for 30 minutes once a week for 12 weeks.[227] SUmiT, which was published prior to our systematic review study period, found that 55% of participants were moderately or markedly improved after 12 weeks of therapy compared to 21% in the placebo group (p<0.01).[227] In a 2020 meta-analysis of both randomized and non-randomized studies, PTNS shows a reduction of about 2 voids/day, 1-2 episodes of nocturia, and 1-2 episodes of urinary incontinence per day when compared with baseline.[228]

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Percutaneous tibial nerve stimulation versus antimuscarinic medications

In the OrBIT RCT, which was published prior to our systematic review period, PTNS demonstrated objective outcomes comparable to tolterodine, with similar mean reductions in voids/day (-2.4 ±- 4.0 versus -2.5 ± 3.9; p =0.44) and UUI episodes (-1.0 ± 2.2 versus -1.7 ± 3.8; p-value not reported), respectively.[229]

Percutaneous tibial nerve stimulation versus intradetrusor botulinum toxin

Comparative trials of PTNS and other minimally invasive therapies are lacking. In two studies that compared PTNS to BTX, reported outcomes carried a low certainty of evidence. The TROOP study is a multicenter, prospective cohort, non-inferiority study comparing outcomes of BTX and PTNS at 3 months in women who failed >2 OAB treatments. Of the 160 patients required to detect non-inferiority of PTNS, only 97 of the 161 enrolled patients who completed the study were included in the final analysis. The patients were enrolled in the study after they had already decided on treatment with BTX or PTNS. Furthermore, the BTX group had more severe symptoms at baseline than the PTNS group. Details such as BTX dose were not reported. The primary outcome was success based on a composite score that included PGII and OABq Symptom Severity Scale (OABq-SSS). BTX subjects demonstrated a greater improvement in OABq-SSS for both urgency and UUI symptoms compared to PTNS but no difference in success was observed (50% of BTX group versus 44% of PTNS group; p=0.57) and both groups experienced improvements in their urinary QoL.[230] However, the study was underpowered.[230]

In another study, Sherif and colleagues randomized 60 patients to PTNS or BTX and followed them for 9 months. Details of randomization, sample size calculation, or the primary outcome were not reported. The authors observed statistically significant improvements in micturition rate, UUI, and OABSS in both PTNS and BTX therapies. However, the BTX group exhibited greater durability in symptom improvement at 9 months, albeit with 6.6% catheterization rates, which was recommended to all patients with a PVR >200 mL (with or without symptoms related to incomplete bladder emptying), and 6.6% UTI rate in the BTX group. [231]

Percutaneous tibial nerve stimulation versus transcutaneous tibial nerve stimulation

In a systematic review of studies comparing PTNS to TTNS, Yang et al. found that both modalities had similar efficacy in terms of reduction in voiding frequency, nocturia, number of urgency episodes, and number of incontinence episodes among people who had an inadequate response to other OAB therapies.[225] Specific to QoL, both PTNS and TTNS significantly improve the QoL of people with OAB after 12 weeks of therapy; however, there was no significant difference in the QoL improvements between these two treatment modalities.[232]

Implantable tibial nerve stimulation

One limitation of PTNS is the necessity for individuals to undergo repeated in-office treatments. To address this, two implantable tibial nerve stimulators have been developed and approved by the FDA.[233] The first is a fully implantable, nickel-sized device that is placed by the tibial nerve and delivers adjustable stimulation every 3 days for 18 weeks, and then every 4 days.[234] A single arm, open-label study of 137 people experiencing OAB and UUI unresponsive to previous medical or interventional treatments found that mean UUI episodes decreased by 2-3/day from baseline, 68% had a ≥50% reduce in UUI at 48 weeks, and 20% were dry after tibial nerve stimulator placement.[234]

The second FDA approved implantable device is a small linear stimulator that is secured under the skin to the fascia over the tibial nerve. An external cuff is worn to power the device during at home treatment sessions.[235] A single arm study of 36 patients with OAB that had failed behavioral and medical therapy found that, incontinence episodes decreased by 2-3/day at 6 months, 24% had a ≥50% improvement in incontinence, and 28% were dry.[235] Complications with these systems were generally minor, and included implant site pain/swelling, device infection, and device migration; they generally resolve at 1-2 weeks, and in rare cases required explantation of the device. The literature on implantable tibial nerve stimulators is limited by a lack of studies providing a direct comparison to other OAB treatment modalities or placebo, and therefore a recommendation specific to these implantable systems is not provided.

Intradetrusor botulinum toxin

There is strong evidence that 100U intradetrusor BTX injection improves OAB symptoms in male and female patients who have had an inadequate response to, or have experienced intolerable side effects from

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antimuscarinic medications [221, 236-239] and/or β3 agonist medications.[240]

In four RCTs that compared BTX injection with placebo,[236, 238-240] all demonstrated statistically significant decreases in both incontinence episodes and micturition rates (range of mean change of incontinence episodes from baseline to 12 weeks: -2.5 to -3.6 episodes/day in the treatment arm versus -0.9 to -1.6 in placebo; range of mean change of micturition rates from baseline to 12 weeks: -1.9 to -2.8 voids per day in the treatment arm versus -0.4 to -1.1 in placebo).

Three studies also reported on UUI and demonstrated statistically significant decreases in the number of episodes per day (range of mean change from baseline to 12 weeks: -2.8 to -3.5 in the treatment arm versus -0.82 to -1.7 in placebo).[236, 238, 240] PRO and QoL scores were also improved with BTX.

Given the benefits of BTX and its low side effect profile,[236, 238-240] if a patient does not achieve symptom relief while on β3-agonist therapy, it would be reasonable to bypass antimuscarinics and move directly to BTX injections in those patients who cannot take, or do not wish to try, these agents.[240] Likewise, BTX may be offered to patients who have declined oral pharmacotherapy.

BTX should be offered with caution to patients who have primarily nocturnal symptoms. Although studies demonstrated statistically significant decreases in nocturia in comparison to placebo (range of mean change from baseline to 12 weeks: -0.3 to -0.7 in the treatment arm versus 0.03 to -0.4 in placebo), this change has marginal clinical significance. [236, 238-240]

The most common adverse effects following injection with 100U were UTI, incomplete bladder emptying requiring clean intermittent catheterization (CIC), and gross hematuria.[236, 238-240]

Intradetrusor botulinum toxin and urinary tract infection

Given that patients with a history of UTI are at higher risk of UTI post-procedure they should be counselled that their rate of UTI may increase post injection.[241] Presence of an active UTI is a contraindication of the procedure until it is treated. A symptom assessment and urinalysis +/- a culture can be done pre-procedure to rule out UTI.

Intradetrusor botulinum toxin dosage

Men and women with inadequate response to BTX 100U and minimal side effects may be offered BTX 200U, but should be monitored for and counseled regarding the potential for increased risk for adverse effects such as incomplete bladder emptying requiring CIC and UTI.[242] A small study compared injection of 200U with injection of 100U distributed among 20 injection sites to patients who were refractory to antimuscarinic medications.[242] Patients in the 200U arm experienced significantly higher continence rates, a greater decrease in daytime voids, and improved urgency rates at 9 months when compared to patient receiving the 100U injection. However, patients receiving the 200U injection also appeared to have numerically higher rates of UTI, although no statistical analysis was conducted.[242]

Intradetrusor botulinum toxin injection techniques

The evidence suggests that BTX injection techniques that either spare or include the trigone are effective in treating OAB symptoms. A small RCT that randomized OAB patients to a trigonal-sparing technique or a trigonal-involved technique compared symptoms and OABSS and demonstrated a significantly lower incontinence rate and UUI rate at 6-months post injection in the trigonal-sparing arm; however, there was no difference in urgency rates, nocturia rates, or total OABSS at any time point.[244] In studies comparing BTX injection and placebo, the trigone-sparing technique was the technique used in the RCTs used to form the evidence base for this statement.[236, 238-240]

The decision to undergo BTX should be made in the context of shared decision-making. The patient should be given appropriate counseling regarding the adverse effects associated with BTX including UTI, incomplete bladder emptying requiring CIC, gross hematuria, as well as the long-term need for repeat injections (typically every 3-12 months).

26. Clinicians should measure post-void residual in patients with OAB prior to intradetrusor botulinum toxin therapy. *(Clinical Principle)*

Patients should have a PVR measured prior to BTX injection and counseled about the risk of incomplete bladder emptying, which may necessitate CIC following the procedure. RCTs included in the evidence based used a PVR $\geq$ 100-200 mL exclusion criteria[222, 236, 239] leading

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the Panel to conclude that caution should be used when performing BTX injection in patients with a PVR ≥ 100-200 mL, taken in context of their voided volumes and voiding symptoms.

27. Clinicians should obtain a post-void residual in patients with OAB whose symptoms have not adequately improved or worsened after intradetrusor botulinum toxin injection. *(Clinical Principle)*

Clinicians should evaluate patients approximately two weeks after the initial BTX injection to assess symptom improvement and to rule out potential urinary retention, which is highest at two weeks post-procedure.

If a patient does not have symptom improvement following BTX injection, a PVR, urinalysis, and if positive, a urine culture should be obtained since UTI or incomplete emptying may be the reason for these symptoms. If the PVR is elevated with respect to their voided volume (i.e., PVR 100-300 mL), the clinician may decide to start the patient on CIC based on voiding/emptying symptoms or the presence of UTI. If the patient has findings suggestive of an acute UTI, it should be treated based on the *Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline.*[51] If a patient empties well after their first BTX injection, it is optional to check PVR post-procedure for subsequent injections since the rate of retention after a prior history of good emptying is rare.

Patients who have good symptom relief of their OAB after BTX injection and do not have any signs or symptoms of UTI or incomplete bladder emptying can opt for a telemedicine visit with the understanding that PVR and urinalysis cannot be easily obtained.

28. Clinicians should discontinue oral medications in patients with OAB who have an appropriate response to a minimally invasive procedure but should restart pharmacotherapy if efficacy is not maintained. *(Expert Opinion)*

Limited evidence examined the effect of discontinuing oral medications following BTX injection, SNM, or tibial nerve stimulation. The Panel recommends that if a patient has a good treatment response to a treatment modality, there is likely no added benefit continuing OAB medications, but there is the risk of polypharmacy, added cost and potential side effects. If discontinuation results in symptom recurrence, then these agents could be restarted.

29. Clinicians may perform urodynamics in patients with OAB who do not adequately respond to pharmacotherapy or minimally invasive therapies or procedures to further evaluate bladder function and exclude other disorders. *(Clinical Principle)*

OAB is a clinical diagnosis predicated on the presence of urinary urgency; therefore, UDS are not required to make the diagnosis of OAB. However, in patients that present with atypical symptoms, or those with an inadequate response to treatment, UDS can be considered. It is important to note that the presence or absence of DO is not required for the diagnosis of OAB. DO can be seen in 20% of asymptomatic patients. In addition, it is seen in about 50% of women with OAB and the urodynamic presence of DO does not predict the success of medical therapy for OAB.[245, 246] Cohort studies have suggested there are some UDS parameters that may predict response rates and adverse events with interventional therapies; however, the results are heterogenous. Except for cases where OAB symptoms coexist with elevated PVR requiring further management, no urodynamic parameter is an absolute contraindication to an interventional therapy trial.[247, 248]

UDS may be particularly helpful when a physician is suspicious of other diagnoses, such as BOO, SUI, or an acontractile or underactive detrusor that presents with OAB symptoms. The urodynamic assessment and diagnosis of these conditions may add additional relevant non-OAB therapy options. In patients with mixed urinary incontinence where it is difficult to define a predominant type of incontinence, or those with unaware incontinence, UDS in combination with a voiding diary may provide clues regarding bladder sensation, presence and characteristics of DO, volume at which incontinence occurs, and stress leak point pressure which may be used to guide further incontinence therapy. UDS should be considered in patients with OAB and suspicion of poor bladder compliance; these patients may not respond as well to medical or interventional OAB therapy and may need surgical procedures, such as bladder augmentation, to achieve symptom resolution. Finally, prior research has suggested that DO may represent a different phenotype

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of OAB patient, as DO correlates with worse symptoms and a greater impairment of QoL, and therefore it's presence may help in patient counseling.[249, 250]

INVASIVE THERAPIES

30. The clinician may offer bladder augmentation cystoplasty or urinary diversion in severely impacted patients with OAB who have not responded to all other therapeutic options. *(Expert Opinion)*

There is a very small subset of patients with OAB who, despite trials of numerous medical and interventional therapies, experience persistent and substantial impairment in their QoL due to inadequately controlled OAB symptoms. In these patients, invasive surgical procedures may be considered by experienced physicians following a comprehensive discussion of the potential risk, benefits, and alternatives. The patient must weigh the significant risks, including short and long-term surgical morbidity, need for CIC (for continent diversions or bladder augmentation), and the absence of data on QoL outcomes.[251]

INDWELLING CATHETERS

31. Clinicians should only recommend chronic indwelling urethral or suprapubic catheters to patients with OAB when OAB therapies are contraindicated, ineffective, or no longer desired by the patient and always in the context of shared decision-making due to risk of harm. *(Expert Opinion)*

When OAB therapies are contraindicated, ineffective, or no longer desired by the patient, providers may recommend, or patients may request, indwelling catheterization. Before deciding on this form of bladder management, it is essential to counsel the patient on the potential long-term risk, benefits, and alternatives.

Chronic indwelling urethral catheters can cause urethral trauma, including erosion and, in severe cases, urethral loss, significant urinary incontinence, and need for reconstructive surgery. Therefore, individuals opting for urethral catheterization should be counseled on the importance of regular follow-up to detect and address potential signs of urethral trauma.

Patients encountering incontinence related to catheter bypassing or leakage around the catheter should be made aware that increasing the catheter size or balloon volume is not the recommended solution. Such adjustments may potentially exacerbate damage to the urethra and its sphincters. Optimal management involves comprehensive evaluation by a trained health care provider to identify the underlying cause of the leakage and guide management.

Suprapubic tubes (SPT) are the preferred chronic indwelling catheter option due to the reduced likelihood of urethral damage. They may also be preferred by individuals seeking to maintain their capacity for sexual activity or those experiencing urethral discomfort associated with the urethral catheter. While SPTs are less likely to cause urethral complications, SPT placement is associated with potential risks, such as bowel perforation or vascular injury. Some of this risk can be mitigated with routine use of ultrasound guided SPT placement. Other SPT associated complications include development of granulation tissue, bleeding, catheter site erosion, and loss of access during catheter changes.

Complications common to both urethral catheters and suprapubic tubes, are catheter associated UTI, bladder calculi, catheter obstruction, bladder spasms, pain, diminished bladder capacity, and urine leakage.[252, 253] A retrospective cohort study identified almost 37,000 patients who were long term indwelling catheter users and found that these patients had a significantly increased hazard ratio of 4.8 (95% CI: 4.26 - 5.42) for bladder cancer compared to matched controls, and bladder cancer specific death, though rare (0.3% over a median of ~ 9 years), was 8.7-fold higher than controls.[254] Long term use of both catheterization methods is associated with a small but increased risk of squamous cell bladder carcinoma that is thought to be secondary to chronic inflammation.

BPH and OAB

32. Clinicians may offer patients with BPH and bothersome OAB, in the context of shared decision-making, initial management with non-invasive therapies, pharmacotherapy, or minimally invasive therapies. *(Expert Opinion)*

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Clinicians may offer bladder outlet reduction surgeries for patients who present with LUTS and BPH. There is an increasing number of surgical therapies that have been utilized to treat BPH and range from minimally invasive to invasive therapies, with some procedural considerations specific to the size and shape of the prostate. Many studies of these technologies have retrospectively evaluated the efficacy of these therapies among subgroups of men with OAB predominant LUTS and BPH. For example, a recent retrospective analysis of men with OAB predominant LUTS and BPH underwent either transurethral resection of the prostate, holmium laser enucleation of the prostate or photovaporization of the prostate. In all groups, there were significant improvements in Qmax, PVR, and presence of DO on UDS from baseline to 6 months postoperatively (all $p<0.001$). There was also significant improvement in the subjective parameters of International Prostate Symptom Scores, frequency, urgency, nocturia, and urinary incontinence from baseline to both 3 and 6 months postoperatively in each of the three studied groups.[255] Similarly many newer therapies including robotic waterjet treatment,[256] temporary implantable nitinol baskets,[257] drug-coated balloon,[258] water vapor thermal therapy, and prostatic artery embolization[259] have the potential to treat OAB predominant LUTS and BPH. Shared decision-making regarding the choice of surgical therapy and their potential side effects should be conducted in accordance with BPH guidelines.

For those opting for procedural interventions, clinicians should discuss that some patients may experience de novo or worsening OAB symptoms after BPH surgical interventions, among other potential adverse events. The frequency, timing, and persistence of OAB symptoms may vary based upon the type of surgical therapy offered. For example, up to 44% of men may experience transient urge incontinence at 1 month after HoLEP.[260] Likewise, a previous multicenter RCT comparing photoselective vaporization of the prostate to transurethral resection of the prostate demonstrated that a significantly higher number of men reported significantly worse OAB symptoms in the first 3-, 6- and 12-months of the study in the photoselective vaporization of the prostate arm as measured by OABq-SF questionnaires.[261] While some studies have recently considered simultaneous treatment of OAB symptoms in the setting of BPH surgery with either medications[262] or BTX injection,[263] this is currently considered investigational. However, persistent or de novo bothersome OAB symptoms should be addressed accordingly after surgical treatment. The timing and type of interventions should be made based upon clinical situation, patient preference and shared decision-making.

33. Clinicians should offer patients with BPH and OAB monotherapy with antimuscarinic medications or beta-3 agonists, or combination therapy with an alpha blocker and an antimuscarinic medication or beta-3 agonist. *(Conditional Recommendation; Evidence Level: Grade B)*

The diagnosis of BPH is significantly more common among men with LUTS than isolated OAB (61.5% versus 25.8%).[264] Patients with a prostate who present with OAB predominant LUTS should be evaluated to assess for the relative contribution of BOO secondary to BPH. As such, clinicians should follow the clinical workflow outlined in *Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia (BPH): AUA Guideline Amendment 2023*[52] which considers assessing the presence and severity of urinary symptoms using standardized questionnaires, PVR, prostate volume determination, and measurement of flow rate. Those who are found to have obstructive symptoms (e.g., weak stream, difficulty initiating a stream, intermittency) should follow algorithms outlined in the AUA Guideline.

Clinicians may consider pharmacologic interventions among patients with predominant OAB symptoms and who happen to have BPH. The pharmacologic options to treat OAB symptoms in this setting include antimuscarinics, β3 agonists, alpha adrenergic antagonists, 5-alpha-reductase inhibitors, and phosphodiesterase-5 inhibitors. Antimuscarinics and β3 agonists are effective in treating OAB in this population as monotherapy, and while antimuscarinic medications may increase PVR volumes slightly, they do not appear to be associated with a significant increased risk of urinary retention among groups of patients with co-existing BOO secondary to BPH.[265] A discussion of the risk of retention should occur when discussing these medications with those presenting with elevated PVR values.[180, 182, 266] While a consistent PVR threshold has not been defined as concerning before medication initiation, the effects of these medications among those with residual volumes greater than 200 mL are not well studied.

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There is no strong evidence or agreed upon order in which monotherapy or combination therapy should be initiated for the treatment of OAB predominant LUTS with the presence of BPH. Randomized studies of individual antimuscarinic medications and β3 agonists demonstrate efficacy for each among men with predominant OAB symptoms.[180, 182, 181] For example, in a multi-institutional trial of 464 men with OAB symptoms were randomized to 50 mg of mirabegron (n=310) versus placebo (n=154).[182] Those who received mirabegron demonstrated significant improvements in the number of micturition episodes and OAB symptoms compared to placebo. Similarly, Ginsberg et al. published a randomized trial data comparing monotherapy with 8 mg fesoterodine or 4 mg ER tolterodine to placebo.[180] This trial showed significant improvements in OAB symptoms and UUI rates with pharmacologic therapy. Urinary retention rates for antimuscarinic medications were low (fesoterodine 2%, ER tolterodine <1%, no statistical comparison performed).

Several other studies, including two meta-analyses and four RCTs, have recently evaluated cohorts of patients with OAB predominant LUTS and concomitant BPH and compared combination therapy with an alpha adrenergic antagonist and either antimuscarinic medications or β3 agonist to monotherapy with an alpha adrenergic antagonist alone.[267-270] While the evaluation and outcome metrics vary based upon study design and investigational medication, results suggest that combination therapy improves OAB symptoms to a significantly greater extent than monotherapy. For instance, a meta-analysis, included three randomized studies, evaluated outcomes following mirabegron with tamsulosin versus tamsulosin alone.[271] Combination therapy was associated with significant improvements in frequency and urgency symptoms. There was a statistically significant difference in PVR favoring combination therapy, though this was a mean difference of 12.02 mL (95% CI: 6.01-18.04; p<0.0001).

FUTURE DIRECTIONS

OAB is a symptom-based diagnosis that is made after clinical evaluation has excluded other causes. Although the diagnosis is typically straightforward, the ideal treatment remains elusive, and management rather than cure is the goal.

There is no gold standard therapy for OAB since no single treatment is universally effective. This is because OAB is multifactorial, and we lack information on all the etiologies and the pathophysiologic mechanisms contributing to the symptom complex. Experts in bladder health have difficulty consolidating the root causes of the condition[272] and localizing whether it lies inside the bladder itself or in the pathways between the brain and the bladder or both.

Use of a multidimensional approach to care addresses the multifactorial nature of OAB

There are many proposed pathophysiological mechanisms including: afferent or efferent nerve dysfunction; detrusor muscle disease; detrusor mucosal hypersensitivity; pelvic floor dysfunction; other pelvic organ anatomic distortion; the microbiome; and alterations in the central nervous system. It is also possible that OAB is simply a precursor of other aging conditions, such as cognitive decline due to loss of frontal cortex inhibition. Several receptors both in the mucosa (urothelium) and the muscle (detrusor) have been implicated in OAB. We currently target muscarinic receptors and β3 receptors with our existing two classes of pharmacotherapy (antimuscarinic medications and β3 agonists, respectively), but there remains untapped potential of other mechanisms including cannabinoid and purinergic receptors.[273] Future drug development will yield more effective medical therapy for OAB with greater tolerability and less financial toxicity.

There exist many known risk factors for OAB but those that are most obvious such as age and sex assigned at birth are not modifiable.[274] For others such as obesity and smoking, we need to educate the general public on their association OAB and strategies for weight control and smoking cessation. The PLUS research consortium is a transdisciplinary approach aiming to promote bladder health and prevent LUTS such as OAB in women across the lifespan. They are working towards defining the construct of “bladder health” as well as measures to assess this. Their RISE FOR HEALTH study[21] will focus on the prevalence of bladder health in women and assess risk and protective factors that may exist, and this information will be used for educational strategies to improve bladder health promotion and well-being across the life course. The scientific community anxiously awaits results for this study.

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Independent researchers are making strides towards better understanding of OAB. LURN was formed to improve the understanding of patients with LUTS through deep phenotyping and longitudinal study of a large cohort of one thousand patients of all genders with LUTS.[275] This first study (LURN1) improved our knowledge on the overlap of various LUTS conditions, central nervous system differences, and treatment outcome, and provided clustering analysis to better define novel symptom complexes.[272] A second cohort (LURN2) is underway solely recruiting patients with OAB given that this disorder was the most enigmatic. We expect even deeper phenotyping results with more information on the impact of behavior, sleep, physical activity, consumption, and longitudinal symptom change. We hope that there will be actionable results to improve patient care.

Knowledge regarding the pathophysiology of OAB that is refractory to current treatment options is also lacking. Why do some patients respond to medical therapy, yet others do not? Which will respond to neuromodulation or neurotoxins? Are there potential urinary or serum biomarkers that would predict resistance to pharmacotherapy and guide the practitioner directly to more advanced therapy? Are there patient factors such as concomitant diseases or physical exam findings that can provide clarity? Will MRI, fMRI, or other central nervous system assessments help with diagnosis or treatment selection? Our current diagnostic tools including UDS have not been able to predict response to medical therapy nor to any of the minimally invasive treatments. There has been nascent work to predict response to antimuscarinic medications using machine learning algorithms, but these tools have not been widely adopted.[276] Although UDS are very helpful at identifying other LUTS such as stress incontinence or BOO in patients with confusing presentations, in patients with only OAB they often reveal no objective abnormalities or distinguishing characteristics to guide therapy. There are no pathognomonic findings on UDS to diagnose OAB, though many patients report early sensations of fullness or sensory urgency and a subset will experience DO. A normal study is relatively common especially among women[50]and UDS parameters do not correlate with symptom severity or patient reported symptoms scores.[277] There are clearly functional issues of the lower urinary tract implicated in OAB and further refinement of UDS and other diagnostic modalities will hopefully shed some light on how we can use this valuable tool better.

Research needs for treatment

Behavioral modifications and non-invasive treatments have been well studied and are relatively effective particularly in milder cases. Unfortunately, many of these are time consuming or difficult to implement for patients, particularly if trying to implement more than one. Adherence is limited by self-efficacy and discipline. Should they limit caffeine, or would pelvic floor physical therapy be more effective, or do they need to change the rate of their fluid intake? Having individualized recommendations to give a patient that would be more effective in their particular situation would likely be more accepted by patients and be less burdensome than trying a long list of therapies. Phenotyping our patients for both the biological components of their OAB and their psychological attributes as a patient will allow us to deliver personalized care, optimizing and expediting outcomes.

Medical therapy

Medical therapy has been extensively studied yet important question remain unanswered. Many insurance providers mandate step therapy trialing one or more antimuscarinic medications before other therapies will be approved. The assumption, since most trials of minimally invasive therapies enroll participants with OAB who had an inadequate response to medical therapy, is that medications must be trialed and failed in order to move to other treatments. Scant evidence exists on success of these more advanced therapies in the treatment-naïve patient and this question should be answered since many patients do not want to take a series of potentially harmful or costly medications for the rest of their lives and would rather move to non-pharmacologic means.[43] Given the lack of evidence we need to provide better choices for our patients and engage in shared decision-making not make them trial medications they have no intention of continuing. Patients unwilling to take medications are being lost to follow up, and not being given the choice of advanced therapies, thus choosing nothing and continuing to experience their OAB symptoms.

A key question created by the Panel that could not be answered with the available literature was: at what timepoint (in hours or days) after administration of OAB pharmacotherapy is maximum symptoms control achieved? Most studies assessed patient response at twelve weeks of follow-up but given that these medications achieve steady state serum concentrations within days it does not seem reasonable to expect a

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patient to take a medication for three months before assessing efficacy. Patients already wait excessively long periods of time before progressing to more effective treatment and long delays in decision-making lead to patient frustration and most discontinue on their own and stop seeking care for their problem. More granular studies on exactly when efficacy peaks and side effects of medications stabilize would help patients progress to other treatments if these fail.

Minimally invasive treatment

A difficulty barrier in patients with OAB undertaking minimally invasive therapies is the discordance between research defined success of a procedure, which is currently 50% improved and what patients with OAB are seeking. It is difficult to counsel patients with data being focused on such a low bar for treatment success. This is perhaps a sign that we have much work to do to better define this problem.

A key question that the Panel could not find sufficient evidence to provide a statement was on the comparative efficacy of minimally invasive treatments. It is a logical solution to progress to BTX when oral agents fail. Unfortunately, just as there is no equipoise with pharmacotherapy, there remain no testing or clear patient factor that will guide choices of what was previously termed "third line" therapy since there is equivocal or absent data on effectiveness between options.[278] No RCTs compare tibial stimulation to any "third-line" therapy, and the only study on BTX compared to SNM was exclusively in women and utilized a higher dosage (200U) of BTX that is not FDA approved for idiopathic OAB (ROSETTA).[221, 222] Unless a patient has comorbid conditions such as fecal incontinence or incomplete bladder emptying on top of OAB where neuromodulation can have dual benefits, this remains a preference sensitive decision. As such, decision making often rests on avoidance of side effects or complications since no data on comparative efficacy exists.

A key question of how the severity of OAB symptoms impacts the success of minimally invasive procedures could also not be answered. Although this is a simple parameter to measure with symptoms scores, voiding diaries and/or pad weights/counts, providers have no clear guidance on which treatments to recommend for the most severe patients. This is a critical research question since these severe patients should not have their treatment strategy picked nearly at random but should start with the most effective modality.

Another significant dilemma facing clinicians is how to proceed when a minimally invasive option fails. It is easy to simply try whatever option that has not been tried as the next step, which is a "kitchen sink approach" to this problem but data is sparse on the effectiveness of this strategy and chances of success diminish with each failed attempt.[279] The data suggests that SNM after failed BTX is relatively successful,[226] but the reverse is not true[279] and no data exists on PTNS failures or its ability to treat SNM or BTX failures.

Many groups of patients with OAB remain poorly studied: men, racial and ethnic minorities, and older adults. Older adults, and in particular the frail older adults, have a high prevalence of OAB and suffer disproportionately with the consequences of OAB including a higher risk of falls, skin breakdown, higher risk of nursing home admission[280] and are more sensitive to side effects from all of the treatments offered. This population also suffers disproportionately from detrusor underactivity and are at risk of poor emptying. There is also emerging evidence on widespread disparities in care across racial and ethnic minorities and treatment disparities are particularly evident in access to minimally invasive treatments for OAB.[19]

Emerging data on the potential cognitive effects of antimuscarinics and their association with dementia have been highly publicized in the lay press and are well known to patients.[199, 281] These associations need validations and further study both in younger patients who may be taking such medications for long periods and in older frail adults who may be the most vulnerable to cognitive decline. Older adults are often excluded from research studies due to the inherent challenge in including people with comorbidities and at higher risk of side effects. This is precisely the reason this group needs to be included in research since these patients are often the most in need of these therapies in the real world.

The evidence for success of minimally invasive treatments is emerging for older adults but requires much more effort to better counsel these more vulnerable patients with OAB. A large systematic review on the success of botulinum toxin for OAB on the elderly did not identify results by age.[282] Where information does exist, it suggests that greater age and functional comorbidity are

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both associated with reduced likelihood of 50% improvement and less patient satisfaction with this therapy.[283] There is also concerns about retention being more common and more prolonged in older women.[284-286] The RELIEF study Reduced-dose BTX for urgency Incontinence among Older Females (RELIEF study Clinical Trial Registry Number: NCT05512039; Unique Protocol ID: STUDY02001338) is an ongoing randomized controlled trial that will compare treatment of UUI among women ≥ 70 years of age with low-dose (50 unit) versus standard-dose (100 unit) bladder BTX injection to assess if this lower dose is more appropriate in older women. This study will also include analysis of heterogeneity of treatment effect by frailty status.

Men have remained almost unstudied on their response to minimally invasive treatments. Medical therapies including combinations of BPH and OAB therapies and behavioral therapies combined with medical therapy have been well studied and are included in the systematic review for this guideline, however the literature on more advanced treatments is sparse.

In a recent systematic review of OAB therapy in men the entirety of the literature that stratified results to separate data between men and women found that for PTNS there is only data on 187 men total (7.6% of the populations studied). None of the papers included had more than 20% of men in their population and most had <5% or zero and none presented sub analysis of success in men.[228, 287] For SNM the data on men remains equally sparse with only 10% of the studied population being male among nine studies (n=1181) that reported results of the testing or implantation.[288] Studies do suggest that while men respond symptomatically during test phase similarly to women[289] they are less likely to proceed to SNM implantation. It is not that men are not receiving this therapy since in population studies using the California Office of Statewide Planning and Development ambulatory surgery database 23% of SNM trials were in men (n=630) and male gender was a predictor of failure.[290] With such small numbers it is unclear why men fare poorly with this therapy and more importantly how can we do better.

BTX bladder injections have actually been studied in men with one study exclusively in men receiving BTX showed robust improvement in 62% of men but 69% of the cohort declined to receive a second injection.[291] Compared to women, men receiving BTX also had a greater elevation in PVR and a higher incidence of need to CIC.[241]

The diagnosis and management of OAB is complex, research has not identified a unifying pathophysiology nor has diagnostic testing lead to reliable patterns that can guide treatment. Nascent research has focused on phenotyping OAB and identifying predictors of treatment outcomes. Incorporating these elements into the shared decision-making model can help clinicians and patients select the best treatment modality and improve patient outcomes. Each step presents an open opportunity for additional research. One thing is certain, we should strive for upfront and clear communication with patients regarding OAB as a poorly understood and chronic syndrome, with interventions designed to mitigate symptoms, rather than to ‘treat or resolve’ an underlying condition. This may help reinforce the multi-modal symptom management strategy that may cycle through treatments throughout the life course. Shared decision-making should include a plan of care with emphasis on multiple modalities that are acceptable to the patient to optimize response.

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ABBREVIATIONS

AUA	American Urological Association
AUAER	American Urological Association Education and Research
β3	Beta-3
BMI	Body mass index
BOD	Board of Directors
BOO	Bladder outlet obstruction
BPH	Benign prostatic hyperplasia
BTX	Botulinum toxin
CIC	Clean intermittent catheterization
CSF	Clinical frailty scale
DO	Detrusor overactivity
ER	Extended release
GSM	Genitourinary syndrome of menopause
ICS	International Continence Society
IC/BPS	Interstitial cystitis/bladder pain syndrome
IUGA	International Urogynecological Association
LURN	The Lower Urinary Tract Research Network
LUTS	Lower urinary tract symptoms
NLUTD	Neurogenic lower urinary tract dysfunction
OAB	Overactive bladder
OABSS	Overactive bladder symptom score
OR	Odds ratio
PGC	Practice Guidelines Committee
PICOTS	Patient interventions comparison outcome time setting
PLUS	Prevention of Lower Urinary Tract Symptoms
PMFT	Pelvic floor muscle training
POP	Pelvic organ prolapse
PRO	Patient reported outcome
PTNS	Percutaneous tibial nerve stimulation
PVR	Post-void residual
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SQC	Science and Quality Council
SNM	Sacral neuromodulation
SPT	Suprapubic tube
SUI	Stress urinary incontinence
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
TTNS	Transcutaneous tibial nerve stimulation
TUG	Timed Up and Go
UDS	Urodynamic studies
UTI	Urinary tract infection
UUI	Urgency urinary incontinence

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THE AUA/SUFU GUIDELINE ON THE DIAGNOSIS AND TREATMENT OF IDIOPATHIC OVERACTIVE BLADDER

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Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the diagnosis and treatment of overactive bladder.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

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Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

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