DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER (Non-Neurogenic) IN ADULTS: AUA/SUFU GUIDELINE

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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

Note to the Reader:

As of June 28, 2012, B3-agonist class of medications (i.e., mirabegron) has been approved by the FDA for OAB treatment. This class of medications was not reviewed by this guidelines panel, as it has been FDA-approved since the Guideline publication. Prescribing clinicians are advised to educate themselves regarding the cost-benefit and adverse event profile for those pharmaceutical agents they prescribe.

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Purpose: The purpose of this guideline is to provide a clinical framework for the diagnosis and treatment of non-neurogenic overactive bladder (OAB).

Methods: The primary source of evidence for this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment Number 187 titled *Treatment of Overactive Bladder in Women* (2009).[1] That report searched PubMed, MEDLINE, EMBASE, and CINAHL for English-language studies published from January 1966 to October 2008 relevant to OAB. AUA conducted additional literature searches to capture treatments not covered in detail by the AHRQ report (e.g., intravesical onabotulinumtoxinA) and relevant articles published between October 2008 and December 2011. Insufficient evidence was retrieved regarding diagnosis; this portion of the guideline, therefore, is based on Clinical Principles and Expert Opinion. The review yielded an evidence base of 151 treatment articles after application of inclusion/exclusion criteria. These publications were used to create the majority of the treatment portion of the guideline. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low). Additional treatment information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed. See text and algorithm for definitions and detailed diagnostic, management and treatment frameworks.

Guideline Statements

Diagnosis:

1. The clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and exclude other disorders that could be the cause of the patient's symptoms; the minimum requirements for this process are a careful history, physical exam, and urinalysis. *Clinical Principle*
2. In some patients, additional procedures and measures may be necessary to validate an OAB diagnosis, exclude other disorders and fully inform the treatment plan. At the clinician's discretion, a urine culture and/or post-void residual assessment may be performed and information from bladder diaries and/or symptom questionnaires may be obtained. *Clinical Principle*
3. Urodynamics, cystoscopy and diagnostic renal and bladder ultrasound should not be used in the initial workup of the uncomplicated patient. *Clinical Principle*
4. OAB is not a disease; it is a symptom complex that generally is not a life-threatening condition. After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice made by some patients and caregivers. *Expert Opinion*
5. Clinicians should provide education to patients regarding normal lower urinary tract function, what is known about OAB, the benefits vs. risks/burdens of the available treatment alternatives and the fact that acceptable symptom control may require trials of multiple therapeutic options before it is achieved. *Clinical Principle*

Treatment:

First-Line Treatments:

6. Clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first line therapy to all patients with OAB. *Standard (Evidence Strength Grade B)*

7. Behavioral therapies may be combined with anti-muscarinic therapies. *Recommendation (Evidence Strength Grade C)*

Second-Line Treatments:

8. Clinicians should offer oral anti-muscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium (listed in alphabetical order; no hierarchy is implied) as second-line therapy. *Standard (Evidence Strength Grade B)*

9. If an immediate release (IR) and an extended release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. *Standard (Evidence Strength Grade B)*

10. Transdermal (TDS) oxybutynin [patch **(now available to women ages 18 years and older without a prescription)*** or gel] may be offered. *Recommendation (Evidence Strength Grade C)*

11. If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried. *Clinical Principle*

12. Clinicians should not use anti-muscarinics in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention. *Clinical Principle*

13. Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. *Clinical Principle*

14. Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. *Expert Opinion*

15. Clinicians should use caution in prescribing anti-muscarinics in the frail OAB patient. *Clinical Principle*

16. Patients who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist if they desire additional therapy. *Expert Opinion*

Third-line Treatments:

17. Clinicians may offer sacral neuromodulation (SNS) as third line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. *Recommendation (Evidence Strength – Grade C)*

18. Clinicians may offer peripheral tibial nerve stimulation (PTNS) as third-line treatment in a carefully selected patient population. *Option (Evidence Strength Grade C)*

19. Clinicians may offer intradetrusor onabotulinumtoxinA as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. *Option (Evidence Strength Grade C)*

Additional Treatments:

20. Indwelling catheters (including transurethral, suprapubic, etc.) are not recommended as a management strategy for OAB because of the adverse risk/benefit balance except as a last resort in selected patients. *Expert Opinion*

21. In rare cases, augmentation cystoplasty or urinary diversion for severe, refractory, complicated OAB patients may be considered. *Expert Opinion*

Follow-Up:

22. The clinician should offer follow up with the patient to assess compliance, efficacy, side effects and possible alternative treatments. *Expert Opinion*

INTRODUCTION

Section 1: Purpose

This guideline's purpose is to provide direction to clinicians and patients regarding how to recognize non-neurogenic overactive bladder (OAB), conduct a valid diagnostic process and approach treatment with the goals of maximizing symptom control and patient quality of life while minimizing adverse events and patient burden. The strategies and approaches recommended in this document were derived from evidence-based and consensus-based processes. There is a continually expanding literature on OAB; the Panel notes that this document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the individual clinician and patient. As the science relevant to OAB evolves and improves, the strategies presented here will require amendment 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 and treat OAB patients, including those in general practice as well as those who specialize in various branches of medicine.

Section 2: Methodology

The primary source of evidence for this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment Number 187 titled *Treatment of Overactive Bladder in Women* (2009).[1] That report, prepared by the Vanderbilt University Evidence-Based Practice Center (EPC), searched PubMed, MEDLINE, EMBASE and CINAHL for English-language studies published from January 1966 to October 2008 relevant to OAB and excluded non-relevant studies, studies with fewer than 50 participants and studies with fewer than 75% women. AUA conducted an additional literature search to capture articles published between October 2008 and December 2011. In addition, because the Panel wished to consider data for male as well as female patients, studies excluded by the AHRQ report because there were fewer than 75% women participants were extracted and added to the database. Studies that focused primarily on nocturia were also added to the database. Given that the AHRQ report included limited information regarding use of neuromodulation therapies, including sacral neuromodulation (SNS) and peripheral tibial nerve stimulation (PTNS) (also known as posterior tibial nerve stimulation) and limited information regarding the use of intravesical onabotulinumtoxinA to treat non-neurogenic OAB patients, additional searches were performed to capture this literature and relevant data were added to the database. The AUA then performed its own qualitative and quantitative analyses of the extracted data, including meta-analyses as appropriate.

Data from studies published after the literature search cut-off will be incorporated into the next version of this guideline. Preclinical studies (e.g., animal models), pediatric studies, commentary and editorials were eliminated. Review article references were checked to ensure inclusion of all possibly relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only nonredundant information.

OAB Diagnosis. The review revealed insufficient publications to address OAB diagnosis from an evidence basis; the diagnosis portions of the algorithm (see Figure 1), therefore, are provided as *Clinical Principles* or as *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[2] A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other expert clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge and judgment for which there is no evidence.

OAB Treatment. With regard to treatment, a total of 151 articles met the inclusion criteria; the Panel judged that these were a sufficient evidence base from which to construct the majority of the treatment portion of the algorithm. Data on study type (e.g., randomized controlled trial, controlled clinical trial, observational study), treatment parameters (e.g., dose, administration protocols, follow-up durations), patient characteristics (i.e., age, presence of specific symptoms such as urgency, urgency incontinence and/or frequency, detrusor overactivity documented by urodynamics), adverse events, and primary outcomes (as defined by study authors) were extracted. The primary outcomes for most studies were reductions in frequency, urgency incontinence, incontinence and urgency.

Quality of Individual Studies and Determination of Evidence Strength. The quality of individual studies was assessed by the EPC using accepted criteria to determine the quality of internal and external validity. The criteria and rating scheme are described in detail in the published report (see pages 27-30). The same system was used to assess the quality of additional included studies.

The categorization of evidence strength (ES) is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes

consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes and generalizability of samples, settings and treatments for the purposes of the guideline. AUA categorizes evidence strength as Grade A (well-conducted RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies) or Grade C (observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data).

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens.[3] ***Standards*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. ***Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. ***Options*** are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or unclear; ***Options*** may be supported by Grade A, B or C evidence. Options generally reflect the Panel's judgment that a particular decision is best made by the clinician who knows the patient with full consideration of the patient's prior treatment history, current quality of life, preferences and values.

Limitations of the Literature. The Panel proceeded with full awareness of the limitations of the OAB literature. For example, despite the relatively large number of randomized controlled trials (RCTs) with placebo control groups and randomized designs with active controls that assessed pharmacologic OAB treatments, the overwhelming majority of trials followed patients for only 12 weeks. Additional limitations included the use of different inclusion criteria across studies assessing the same treatment, poorly-defined patient groups or use of patient groups with limited generalizability to the typical clinical setting in which OAB patients are seen, lack of consistency in outcome measures and limited outcome measure and adverse event reporting. With regard to measures, although most studies reported urinary frequency and urinary incontinence, many studies did not report other key measures such as urgency, and only a handful reported nocturia data. With regard to adverse events, most pharmacologic studies reported rates of dry mouth and constipation, but few reported on other clinically-relevant issues such as cardiac or cognitive adverse events. The completed evidence report may be requested from AUA.

The Overactive Bladder Panel was created in 2009 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the additional panel members with specific expertise in this area. The AUA conducted a thorough peer review process. The draft guidelines document was distributed to 78 peer reviewers, of whom 31 provided comments. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC. Then it was submitted to the AUA Board of Directors for final approval. Funding of the panel was provided by the AUA and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU), although panel members received no remuneration for their work.

Section 3: Background

Definition. Overactive bladder (OAB) is a clinical diagnosis characterized by the presence of bothersome urinary symptoms. Most studies of OAB, including this guideline, exclude individuals with symptoms related to neurologic conditions. The International Continence Society (ICS) defines OAB as the presence of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of UTI or other obvious pathology."[4] Therefore, OAB symptoms consist of four components: urgency, frequency, nocturia and urgency incontinence. 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 a challenge to interpret the OAB literature related to epidemiology and treatment.

Urgency is defined by the ICS as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer."[4] Urgency is considered the hallmark symptom of OAB, but it has proven difficult to precisely define or to characterize for research or clinical purposes. Therefore, many studies of OAB treatments have relied upon other measures (e.g., number of voids, number of incontinence episodes) to measure treatment response.

Urinary frequency can be reliably measured with a voiding diary. Traditionally, up to seven micturition episodes during waking hours has been considered normal,[5] 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 void.[4] In one study, three or more episodes of nocturia constitutes moderate or major bother.[6] Like daytime frequency, nocturia is a multifactorial symptom which is often due to factors unrelated to OAB (e.g., excessive nighttime urine production, sleep apnea).

Urgency urinary incontinence is defined as the involuntary leakage of urine, associated with a sudden compelling desire to void. Incontinence episodes can be measured reliably with a diary, and the quantity of urine leakage can be measured with pad tests. However, in patients with mixed urinary incontinence (both stress and urgency incontinence), it can be difficult to distinguish between incontinence subtypes. Therefore, it is common for OAB treatment trials to utilize total incontinence episodes as an outcome measure.

Epidemiology. In population-based studies, OAB prevalence rates range from 7% to 27% in men, and 9% to 43% in women.[7-14] No clear differences exist between studies conducted in North America vs. other populations. Some studies report higher prevalence rates in women than men,[7-10] while others found similar rates across genders.[11-14] However, urgency urinary incontinence is consistently more common in women than in men. OAB symptom prevalence and severity tend to increase with age.[11-12, 15] A proportion of OAB cases (37-39%) remit during a given year, but the majority of patients have symptoms for years.[15, 16] To date, no population-based studies have directly examined epidemiologic differences across racial/ethnic groups.

Patient-Reported Outcomes (PROs) and OAB. Since OAB is a symptom-based diagnosis, the quality of life (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. Numerous questionnaire instruments have been developed to assess symptoms, degree of bother and health-related QOL in patients with OAB and urinary incontinence.[17] This lack of standardization has often limited the comparability and generalizability of PROs across research studies. To address this, the International Consultation on Incontinence has developed a series of standardized modular questionnaires for pelvic conditions, including OAB.[18] The Panel encourages the development of such standardized PRO tools which can be used in OAB research and clinical practice.

Impact on Psychosocial Functioning and Quality of Life (QoL). The Panel fully recognizes that OAB constitutes a significant burden for patients. These burdens include the time and effort required to manage symptoms during the course of daily life as well as the resources required to obtain treatments that may be costly and may present logistical challenges (e.g., therapies that require frequent visits to a physician's office). The negative impact of OAB symptoms on psychosocial functioning and quality of life also has been well-documented.[19-22] Carrying out the activities of daily life and engaging in social and occupational activities can be profoundly affected by lack of bladder control and incontinence. Urinary incontinence in particular may have severe psychological and social consequences, resulting in restricted activities and unwillingness to be exposed to environments where access to a bathroom may be difficult. Patients also report negative impact on sexual function and marital satisfaction[23] and OAB symptoms have been linked to depressive illness.[24, 25] This negative impact also is evident among older adults (e.g., ≥ 65 years), resulting in significant impairments in QoL, including high rates of anxiety and depression, with the majority of patients reporting they have not sought treatment.[26]

Successful treatment of OAB symptoms with behavioral approaches, anti-muscarinic medications, neuromodulation therapies, and onabotulinumtoxinA, balanced against adverse events, costs and ultimately patient compliance, all have been reported to improve patient quality of life (see Discussion sections under each treatment type).

Section 4: Patient Presentation

Symptoms. When symptoms of urinary frequency (both daytime and night) and urgency, with or without urgency incontinence, are self-reported as bothersome the patient may be diagnosed with overactive bladder (OAB).[27] Additionally, a caregiver or partner may perceive these symptoms as bothersome and lead the patient to seek care. It is common for patients to have suffered with their symptoms for an extended time before seeking medical advice.

Differentiation. OAB symptoms (frequency, urgency and urgency incontinence) may occur only at night, causing a single symptom of nocturia. The differential of nocturia includes nocturnal polyuria (the production of greater than 20 to 33% of total 24 hour urine output during the period of sleep, which is age-dependent with 20% for younger individuals and 33% for elderly individuals),[28] low nocturnal bladder capacity or both. In nocturnal polyuria, nocturnal voids 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. As such, it is often

age-dependent, increasing in prevalence with aging and with poorer general health.

OAB also must be distinguished from other conditions such as polydipsia. In OAB, urinary frequency is associated with many small volume voids. Frequency that is the result of polydipsia and resulting polyuria may mimic OAB; the two can only be distinguished with the use of frequency-volume charts. In polydipsia, urinary frequency occurs with normal or large volume voids and the intake is volume matched. In this case, the frequency is appropriate because of the intake volume and the patient does not have OAB. Frequency due to polydipsia is physiologically self-induced OAB and should be managed with education, with consideration of fluid management. Similarly, diabetes insipidus (DI) also is associated with frequent, large volume voids and should be distinguished from OAB.

The clinical presentation of interstitial cystitis/ bladder pain syndrome shares the symptoms of urinary frequency and urgency, with or without urgency incontinence; however, bladder and/or pelvic pain, including dyspareunia, is a crucial component of its presentation in contradistinction to OAB. Other conditions also can contribute to OAB symptoms and should be assessed. For example, in the menopausal female patient, atrophic vaginitis can be a contributing factor to incontinence symptoms. There is some evidence for symptom improvement with the use of vaginal (but not systemic) estrogen.[29]

Section 5: Diagnosis

The Diagnostic Approach. Insufficient literature was identified to constitute an evidence base for diagnosis of OAB in clinical practice. For this reason, the section titled *Diagnosis* is based on Clinical Principles or Expert Opinion with consensus achieved using a modified Delphi technique when differences of opinion emerged. This section is intended to provide clinicians and patients with a framework for determining whether a diagnosis of OAB is appropriate; it is not intended to replace the judgment and experience of the individual clinician faced with a particular patient.

Guideline Statement 1.

The clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and exclude other disorders that could be the cause of the patient's symptoms; the minimum requirements for this process are a careful history, physical exam and urinalysis. *Clinical Principle*

Discussion. *History.* The clinician should carefully elicit the patient's bladder symptoms to document duration of symptoms and baseline symptom levels, to ensure that symptoms are not the consequence of some other condition and to determine whether the patient constitutes a complex OAB presentation that may require referral. Questions should assess bladder storage symptoms associated with OAB (e.g., urgency, urgency incontinence, frequency, nocturia), other bladder storage problems (e.g., stress incontinence episodes) and bladder emptying (e.g., hesitancy, straining to void, prior history of urinary retention, force of stream, intermittency of stream). The symptom of urgency as defined by the ICS is the "complaint of sudden compelling desire to pass urine which is difficult to defer."[27] The interpretations of "sudden" and "compelling" are highly subjective and difficult to quantitate. Nevertheless, the clinician can simply ask if the patient has a problem getting to the bathroom in time, assuming the patient has normal mobility.

Bladder function is related to amount and type of fluid intake. Excessive fluid intake can produce voiding patterns that mimic OAB symptoms. For this reason, an inquiry into fluid intake habits should be performed, including asking patients how much fluid and of what type (e.g., with or without caffeine) they drink each day, how many times they void each day and how many times they void at night. Patients who do not appear able to provide accurate intake and voiding information should fill out a fluid diary. Urinary frequency varies across individuals. In community-dwelling healthy adults, normal frequency consists of voiding every three to four hours with a median of approximately six voids a day.[30, 31] Current medication use also should be reviewed to ensure that voiding symptoms are not a consequence of a prescribed medication, particularly diuretics.

The degree of bother from bladder symptoms also should be assessed. If a patient is not significantly bothered by his/her bladder symptoms, then there would be less compelling reason to treat the symptoms. Degree of bother can affect different domains of daily activities related to work and leisure. Patients may avoid certain activities (e.g., travel, situations that do not allow easy access to a toilet) because of their bladder symptoms.

Co-morbid conditions should be completely elicited as these conditions may directly impact bladder function. Patients with co-morbid conditions and OAB symptoms would be considered complicated OAB patients. These co-morbid conditions include neurologic diseases (i.e., stroke, multiple sclerosis, spinal cord injury), mobility deficits, medically complicated/uncontrolled diabetes, fecal motility disorders (fecal incontinence/ constipation), chronic pelvic pain, history of recurrent urinary tract infections (UTIs), gross hematuria, prior pelvic/vaginal surgeries (incontinence/prolapse

surgeries), pelvic cancer (bladder, colon, cervix, uterus, prostate) and pelvic radiation. The female patient with significant prolapse (i.e., prolapse beyond the introitus) also may be considered a complicated OAB patient. Patients with urgency incontinence, particularly younger patients, or a patient with extremely severe symptoms could represent a complicated OAB patient with an occult neurologic condition. A patient who has failed multiple anti-muscarinics to control OAB symptoms could also be considered a complicated OAB patient. If the history elicits any of these co-morbid conditions and/or special situations, then the clinician should consider referring these patients to a specialist for further evaluation and treatment.

Physical Examination. A careful, directed physical exam should be performed. An abdominal exam should be performed to assess for scars, masses, hernias and areas of tenderness as well as for suprapubic distension that may indicate urinary retention. Examination of lower extremities for edema should be done to give the clinician an assessment of the potential for fluid shifts during periods of postural changes. A rectal/ genitourinary exam to rule out pelvic floor disorders (e.g., pelvic floor muscle spasticity, pain, pelvic organ prolapse) in females and prostatic pathology in males should be performed. In menopausal females, atrophic vaginitis should be assessed as a possible contributing factor to incontinence symptoms. The examiner should assess for perineal skin for rash or breakdown. The examiner also should assess perineal sensation, rectal sphincter tone and ability to contract the anal sphincter in order to evaluate pelvic floor tone and potential ability to perform pelvic floor exercises (e.g., the ability to contract the levator ani muscles) as well as to rule out impaction and constipation.

Cognitive impairment is related to symptom severity and has therapeutic implications regarding goals and options. The Mini-Mental State Examination (MMSE)[32] is a standardized, quick and useful assessment of cognitive function. An MMSE should be conducted on all patients who may be at risk for cognitive impairment to determine whether symptoms are aggravated by cognitive problems, to ensure that they will be able to follow directions for behavioral therapy and/or to determine the degree of risk for cognitive decline with anti-muscarinic therapy. In the Panel's experience, the ability of the patient to dress independently is informative of sufficient motor skills related to toileting habits.

Urinalysis. A urinalysis to rule out UTI and hematuria should be performed. A urine culture is not necessary unless indication of infection (i.e., nitrites/leukocyte esterase on dipstick, pyuria/bacteriuria on microscopic exam) is found and may be done at the discretion of the clinician. If evidence of infection is detected, then a culture should be performed, the infection treated appropriately and the patient should be queried regarding symptoms once the infection has cleared. If evidence of hematuria not associated with infection is found, then the patient should be referred for urologic evaluation.

Guideline Statement 2.

In some patients, additional procedures and measures may be necessary to validate an OAB diagnosis, exclude other disorders and fully inform the treatment plan. At the clinician's discretion, a urine culture and/or post-void residual assessment may be performed and information from bladder diaries and/or symptom questionnaires may be obtained. *Clinical Principle*

Discussion. *Urine culture.* Urinalysis is unreliable for identification of bacterial counts below 100,000cfu/ml. In some patients with irritative voiding symptoms but without overt signs of infection, a urine culture may be appropriate to completely exclude the presence of clinically significant bacteriuria.

Post-void residual (PVR). Measurement of the post-void residual (PVR) is not necessary for patients who are receiving first-line behavioral interventions (see Guideline Statement 6 below) or for uncomplicated patients (i.e., patients without a history of or risk factors for urinary retention) receiving anti-muscarinic medications. Because anti-muscarinic medications can induce urinary retention,[33] particularly in complicated patients with retention risk factors, PVR should be assessed in patients with obstructive symptoms, history of incontinence or prostatic surgery, neurologic diagnoses and in other patients at clinician discretion when PVR assessment is deemed necessary to optimize care and minimize potential risks. It should be noted, however, that the occurrence of symptomatic urinary retention or asymptomatic elevations of postvoid residuals after the addition of anti-muscarinic agents occurs in a small proportion of patients; previously undiagnosed poor detrusor function may be unmasked in those individuals.

PVR should be measured with an ultrasound bladder scanner immediately after the patient voids. If an ultrasound scanner is not available, then urethral catheterization may be used to assess PVR. For any patient on anti-muscarinic therapy, the clinician should be prepared to monitor PVR during the course of treatment should obstructive voiding symptoms appear. As there is considerable overlap between storage and emptying voiding symptoms, baseline PVRs should be performed for men with symptoms prior to initiation of anti-muscarinic therapy. Anti-muscarinics should be

used with caution in patients with PVR >250-300 mL.[34] Most randomized trials that evaluated anti-muscarinics for OAB treatment used a PVR of 150-200 mL as an exclusion criterion; the overwhelming majority of participants in these trials were women.

Bladder diaries. Diaries that document intake and voiding behavior may be useful in some patients, particularly the patient who cannot describe or who is not familiar with intake and voiding patterns. Diaries also are useful to document baseline symptom levels so that treatment efficacy may be assessed.

In particular, self-monitoring with a bladder diary for three to seven days is a useful first step in initiating behavioral treatments for OAB. At a minimum, the patient documents the time of each void and incontinence episode and the circumstances or reasons for the incontinence episode. Rating the degree of urgency associated with each void and incontinence episode also can be useful. Adding measures of voided volumes can provide a practical estimate of the patient's functional bladder capacity in daily life and estimate the amount of overall fluid intake. Recording voided volumes also can be useful to differentiate between polyuria (characterized by normal or large volume voids) from OAB (characterized by frequent small voids). It is more burdensome, however, and is usually completed for only 24 to 48 hours.

The bladder diary is a useful tool for both the clinician and the patient. In the evaluation phase, it provides information that can help the clinician plan appropriate components of intervention, particularly behavioral intervention. Recording the times that the patient voids provides a foundation for determining voiding intervals in bladder training programs. During the course of treatment, it can be used to monitor symptoms to track the efficacy of various treatment components and guide the intervention. For the patient, the self-monitoring effect of completing the diary enhances awareness of voiding habits and helps them recognize activities that can trigger incontinence. Twenty-four hour pad weights also can provide useful information regarding the severity of incontinence symptoms.

Symptom questionnaires. Validated symptom questionnaires have been utilized in OAB clinical trials to quantitate bladder symptom and bother changes with OAB therapies. Among these questionnaires are the Urogenital Distress Inventory (UDI), the UDI-6 Short Form, the Incontinence Impact Questionnaire (II-Q) and the Overactive Bladder Questionnaire (OAB-q).[35-37] The rationale for utilization of these validated questionnaires is to quantitate and follow the patients' responses to OAB treatment as well as to obtain baseline and post-treatment levels of bother.

Guideline Statement 3.

Urodynamics, cystoscopy and diagnostic renal and bladder ultrasound should not be used in the initial workup of the uncomplicated patient. ***Clinical Principle***

Discussion. Urodynamics, cystoscopy and diagnostic renal and bladder ultrasound are not recommended in the initial diagnostic workup of the uncomplicated OAB patient. For complicated patients or refractory patients who have failed multiple OAB treatments, the choice of additional diagnostic tests depends on patient history and presentation and clinician judgment. In some cases, additional information may make clear that the patient has neurogenic OAB rather than non-neurogenic OAB and requires a different treatment plan. Patients with hematuria should be referred for a urologic work up. In the low-risk uncomplicated patient without microscopic hematuria, urine cytology is infrequently associated with atypia requiring further investigation, engendering costs and possibly resulting in morbidity. Urine cytology is not recommended in the routine evaluation of patients with uncomplicated OAB without hematuria who respond to therapy.

Section 6: Treatment

Issues to Consider. It is important to recognize that OAB is a symptom complex that may compromise quality of life (QoL) but generally does not affect survival. Given this context, in pursuing a treatment plan the clinician should carefully weigh the potential benefit to the patient of a particular treatment against that treatment's risk for adverse events, the severity of adverse events and the reversibility of adverse events. The guideline statements in this section are intended to provide a framework to assist the clinician in counseling patients and in developing an individualized treatment plan that optimizes quality of life.

In developing the treatment portion of the algorithm, the balance between benefits and risks/burdens (i.e., adverse events) was considered. The Panel conceptualized risks/burdens in terms of the invasiveness of the treatment, the duration and severity of potential adverse events and the reversibility of potential adverse events. Treatment alternatives were then divided into first-, second-, third-, fourth- and fifth-line groups. This hierarchy was derived by balancing the potential benefits to the patient with the invasiveness of the treatment, the duration and severity of potential adverse events and the reversibility of potential adverse events. Note that the hierarchy was not established based on the number of available studies or on the evidence strength for a particular treatment. For example, first-line treatment with behavioral therapy presents essentially no risks to

patients and should be offered to all patients. Second-line treatment with oral or transdermal anti-muscarinics is not invasive and presents the risk of side effects that primarily compromise quality of life. Any adverse events are readily reversible with cessation of the medication. Third-line treatments of various neuromodulation therapies require active participation by a motivated patient. Sacral neuromodulation is invasive and presents the risk of rare adverse events that may not be quickly reversible, such as infection. Treatment with intradetrusor onabotulinumtoxinA is invasive and presents risks for infection as well as increased post-void residuals and the potential need for self-catheterization, which is not quickly reversible. Additional treatments, such as various kinds of surgery, present the risks of major surgery and are irreversible.

Given that idiopathic OAB is a chronic syndrome without an ideal treatment and no treatment will cure the condition in most patients, clinicians should be prepared to manage the transition between treatment levels appropriately. Treatment failure occurs when the patient does not have the desired change in their symptoms or is unable to tolerate the treatment due to adverse events; lack of efficacy and the presence of intolerable adverse events reduce compliance. The interaction between efficacy, tolerability and compliance is termed clinical effectiveness.[38] To optimize effectiveness, it is critical for patients to have realistic expectations regarding likely treatment effects and adverse events.

Bladder diaries that document voiding behavior can be useful to monitor efficacy and guide treatment. In particular, diaries and validated questionnaires can be helpful to quantify baseline symptom levels and treatment effects so that both the patient and the clinician can assess whether a particular treatment approach is alleviating symptoms and whether the balance between symptom control and adverse events is appropriate for a given patient.

This clinical framework does not require that every patient go through each line of treatment in order. There are many factors to consider when identifying the best treatment for a particular patient, including information regarding allergies, sensitivity to various adverse drug events, patient ability and motivation to comply and availability of and access to specific treatments. Behavioral therapies were selected as first-line therapies because they present essentially no risks to the patient. However, behavioral therapies require an investment of time and effort by the patient to achieve maximum benefits and may require sustained and regular contact with the clinician to maintain regimen adherence and consequent efficacy.[39] In patients who are unwilling or unable to comply with behavioral therapy regimens and instructions, it is appropriate to move to second-line anti-muscarinic therapies. Failure and/or the experience of adverse events with one anti-muscarinic should usually be addressed by trying at least one other anti-muscarinic before third-line therapies are considered (see Guideline Statement 11 below). In select patients who are unable or unwilling to comply with anti-muscarinics, third-line therapies of neuromodulation and intradetrusor onabotulinumtoxinA may be considered. Patients who are felt to be reasonable candidates for third-line therapies who have been treated by nonspecialists will require referral to a specialist. In some cases the specialist may opt to obtain further information with voiding diaries or symptom questionnaires, or may do further testing such as urodynamics to rule out other bladder pathologies or urethral dysfunction. The use of indwelling catheters as a management strategy is not recommended except as a last resort in selected patients. Surgical intervention should be reserved for the rare non-neurogenic patient who has failed all other therapeutic options and whose symptoms are intolerable.

Guideline Statement 4.

OAB is not a disease; it is a symptom complex that generally is not a life threatening condition. After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice made by some patients and caregivers. ***Expert Opinion***

Discussion. Initiating treatment for OAB generally presumes that the patient can perceive an improvement in his or her quality of life. In patients who cannot perceive symptom improvements, treatment may not be appropriate, may be potentially unsafe or may be futile (e.g., in the very elderly or demented patient) except in patients for whom OAB symptoms present a significant health risk (e.g., risk for skin breakdown). It is important for clinicians who treat this problem to recognize this issue and to set feasible therapeutic goals with the patient and/or caregiver. The presence of an overactive bladder frequently accompanies other disorders such as deficiencies in cognition (i.e., dementia) and/or poor mobility, which can complicate treatment. To treat incontinence, optimally the patient must have a desire to be continent or have a desire for symptom improvement. In patients with cognitive deficits, this desire may not be present and family and/or caregivers may have difficulty understanding that simply giving a medication will not correct the problem. The other common situation associated with OAB is severely reduced mobility. Causes can range from dementia, severe arthritis, severe obesity, hemiparesis/plegia, and lower extremity amputations. In these situations, despite receiving an urge to urinate, the patient

physically cannot get from their current position without assistance to a toileting facility. This cannot be corrected pharmacologically and should be recognized by the treating physician.

In certain patients for whom hygiene and skin breakdown are major concerns, treatment may be considered regardless of the patient's perceptions when it is in the patient's best interests. In these patients, behavioral strategies that include prompted voiding and fluid management may be helpful. Pharmacologic treatments and invasive treatments, however, are generally not appropriate for these individuals. The Panel also recognizes that untreated incontinence can result in falls when a patient with compromised mobility attempts to move quickly to a toileting facility. The treating physician, the patient and the caregiver must weigh these risks when making the decision whether and how to treat OAB.

Guideline Statement 5.

Clinicians should provide education to patients regarding normal lower urinary tract function, what is known about OAB, the benefits vs. risks/ burdens of the available treatment alternatives and the fact that acceptable symptom control may require trials of multiple therapeutic options before it is achieved. *Clinical Principle.*

Discussion. Prior to initiating treatment, the clinician should provide patient education regarding normal and abnormal bladder function, including voiding frequency and toileting behavior. Explaining what is normal can help the patient understand how their condition diverges from normal and gives them a comparator (or goal) for judging their own progress in treatment. Education also empowers the patient to engage and participate in their treatment, which is essential when using interventions that rely on behavior change. Patients must understand that voiding is a behavior that can be managed and that successful OAB treatment requires a willing participant who is informed and engaged in the treatment process.

Patients should be informed that OAB is a symptom complex with a variable and chronic course that needs to be managed over time, that it primarily affects quality of life, that there is no single ideal treatment and that available treatments vary in the effort required from the patient as well as in invasiveness, risk of adverse events and reversibility. An effective treatment plan depends on patients having realistic goals for treatment and a clear understanding of the risks and burdens of particular treatments. In this context, it is important to understand the patient's expectations of treatment, not only in terms of its outcome, but regarding what is required of them as well. Expectations are important because they affect motivation and adherence, and they can influence the patient's interpretation of treatment effects and satisfaction with outcomes.

Most OAB treatments can improve patient symptoms but not eliminate them. The available OAB treatments, with the exception of behavioral therapies, present risks for adverse events, some of which are serious. When initiating behavioral interventions, it is crucial that the patient understands that treatment progress and outcomes will depend on their active participation and persistence over time. It is also useful for them to understand several other aspects of behavioral change: progress is usually gradual, change can be irregular with good days and bad days and long-term change in symptoms depends on their long-term change in behavior.

Patients may decide that the symptomatic improvement achieved with a particular therapy (e.g., from 5 incontinence episodes per day to 3 incontinence episodes per day) is not worthwhile given the adverse events associated with that treatment (e.g., dry mouth and constipation associated with anti-muscarinic therapy) and choose to discontinue therapy despite symptomatic improvement. Choosing to forego treatment is a valid decision. It is the opinion of the Panel that patients seeking treatment initially and at any point in the treatment algorithm should be told that they may opt for no treatment with minimal adverse effects on their health and no impact on the success of later management should they choose to pursue treatment in the future.

First-Line Treatments: Behavioral Therapies

Behavioral treatments are a group of therapies that improve OAB symptoms by changing patient behavior or changing the patient's environment. Most effective behavioral treatment programs include multiple components and are individualized to the unique needs of the patient and his/her unique living situation. There are two fundamental approaches to behavioral treatment for OAB. One approach focuses on modifying bladder function by changing voiding habits, such as with bladder training and delayed voiding. The other approach, behavioral training, focuses on the bladder outlet and includes pelvic floor muscle training to improve strength and control and techniques for urge suppression. Specific components of behavioral treatment can include self-monitoring (bladder diary), scheduled voiding, delayed voiding, double voiding, pelvic floor muscle training and exercise (including pelvic floor relaxation), active use of pelvic floor muscles for urethral occlusion and urge suppression (urge strategies), urge control techniques (distraction, self-assertions), normal voiding techniques,

biofeedback, electrical stimulation, fluid management, caffeine reduction, dietary changes (avoiding bladder irritants), weight loss and other life style changes. In addition, behavioral therapies have the advantage that they can be combined with all other therapeutic techniques. Behavioral therapies are most often implemented by advance practice nurses (e.g., continence nurses) or physical therapists with training in pelvic floor therapy.

Guideline Statement 6.

Clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first line therapy to all patients with OAB. *Standard*

Discussion. *(Evidence strength – Grade B; Benefits outweigh risks/burdens).* Behavioral treatments are designated as first-line treatments because they are as effective in reducing symptom levels as are anti-muscarinic medications, and they consist of many components that can be tailored to address the individual patient's needs and capacities. In addition, they are relatively non-invasive and, in contrast to medications, are associated with virtually no adverse events. They do require the active participation of the patient and/or of the patient's caregiver, however, as well as time and effort from the clinician. Behavioral therapies should be offered to all OAB patients, including OAB patients who require a caregiver; caregivers can be instructed in behavioral techniques in order to optimize patient symptom control (i.e., prompted voiding, timed voiding).

Most of the literature on overactive bladder focuses on the treatment of urinary incontinence, and most studies have been performed with women. Although most patients do not experience complete symptom relief with behavioral intervention, the literature indicates that most patients experience significant reductions in symptoms and improvements in quality of life. The literature provides clear support for the effectiveness of bladder training (incremental voiding schedules done with distraction and self-assertions) and behavioral training (pelvic floor muscle training with urge suppression techniques).[41, 42] Typical mean improvements range from 50% to 80% reduction in the frequency of incontinence. Reductions in voiding frequency have also been documented in men[43] and women.[41, 44, 45]

There is also a good body of literature addressing the effects of weight loss on incontinence specifically. The most definitive trial reported that a 6-month behavioral weight loss intervention resulted in an 8.0% weight loss in obese women, reduced overall incontinence episodes per week by 47% (compared to 28% in the control group) and reduced urgency urinary incontinence episodes by 42% (compared to 26% in controls).[40]

One study evaluated fluid management and reported that a 25% reduction in fluid intake reduced frequency and urgency.[46] The Panel notes that when attempting intake reduction, baseline intake levels must be considered to determine whether reduction is appropriate. There is also evidence from a study of bladder training that reducing caffeine intake results in greater reductions in voiding frequency.[47]

Based on a limited literature, no single component of behavioral therapy appears to be essential to efficacy, and no single type of behavioral therapy appears to be superior in efficacy. In comparing behavioral training that was administered with biofeedback, with verbal feedback or self-administered using a pamphlet, all three approaches had similar effects to reduce incontinence and increase bladder capacity.[48] Patients in the two feedback conditions, however, reported greater treatment satisfaction and better perceptions of symptom control, suggesting that feedback may be important in subjective outcomes. However, in a comparison of pelvic floor muscle training with and without biofeedback, incontinence, pelvic muscle strength and QoL improved more in the group that received feedback.[49] In a study that compared PFMT to bladder training or PFMT in combination with bladder training, patients in the combined group initially had greater incontinence reductions and QoL improvements; however, at 3 month follow-up all three groups had similar improvement levels.[50]

The literature review of comparative effectiveness randomized trials indicated that various types of behavioral treatment were generally either equivalent to[44, 51, 52] or superior to[42, 45, 53] medications in terms of reducing incontinence episodes, improving voiding parameters such as frequency[43, 54, 55] and nocturia[56] and improving QoL. Most studies evaluated oxybutynin (both the IR and the ER formulations).[43, 44, 51-53] One study evaluated tolterodine.[54] One study evaluated flavoxate hydrochloride and imipramine.[42] One study evaluated trospium.[45]

The Panel interpreted these data to indicate that behavioral therapies can result in symptomatic improvements similar to anti-muscarinics without exposing patients to adverse events. Evidence strength is Grade B because although the majority of studies were randomized trials and findings were generally consistent across studies (both randomized and observational), most of the randomized trials were of moderate quality, follow-up durations were short in most studies (12 weeks) and sample sizes were small.

Guideline Statement 7.

Behavioral therapies may be combined with anti-muscarinic therapies. *Recommendation*

Discussion. *(Evidence strength – Grade C; Benefits outweigh risks/burdens).* Behavioral and drug therapies are often used in combination in clinical practice to optimize patient symptom control and QoL. A limited literature indicates that initiating behavioral and drug therapy simultaneously may improve outcomes, including frequency, voided volume, incontinence and symptom distress.[45, 54, 57-59] In patients who are not adequately improved on behavioral or drug therapy alone, there also is evidence that continuing the initial therapy and adding the alternate therapy using a stepped approach can produce additional benefit.[60] Evidence strength is Grade C because of the limited evidence base consisting of relatively few trials, small sample sizes, and limited follow-up durations.

Second-Line Treatments: Anti-Muscarinics

Guideline Statement 8.

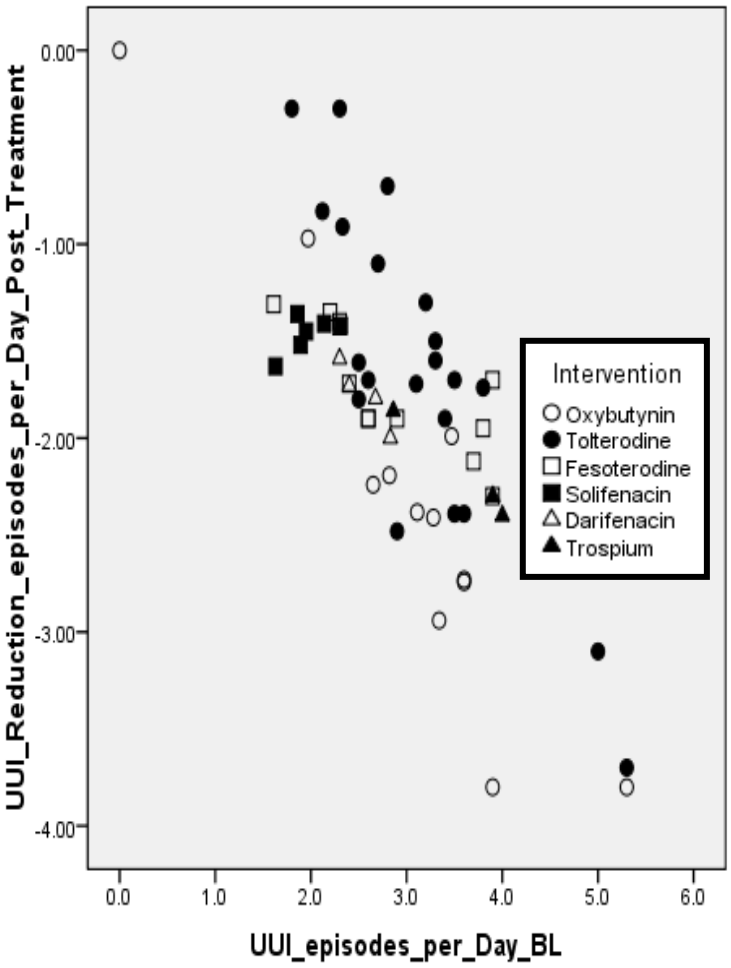
Clinicians should offer oral anti-muscarinics, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium (listed in alphabetical order; no hierarchy is implied) as second-line therapy. *Standard*

Discussion. *(Evidence strength – Grade B; Benefits outweigh risks/burdens).* The choice of oral anti-muscarinics as second-line therapy reflects the fact that these medications reduce symptoms but also can commonly have non-life-threatening side effects such as dry mouth, constipation, dry or itchy eyes, blurred vision, dyspepsia, UTI, urinary retention and impaired cognitive function. Rarely, life-threatening side effects such as arrhythmias have been reported. An extensive review of the randomized trials that evaluated pharmacologic therapies for OAB (including trials with placebo control groups as well as trials with active treatment comparison groups) revealed no compelling evidence for differential efficacy across medications.[44, 51-54, 57, 61-125] This finding is consistent with the conclusions of several published systematic reviews.[126-129]

These data were not suitable for meta-analysis due to of lack of variance information (e.g., standard deviations, variances, standard error of the mean) for outcomes in many studies. Qualitative analysis revealed, however, that for 24-hour frequency, urgency incontinence and incontinence, baseline symptom level was closely related to degree of symptom reduction across medications. Specifically, patients with more severe symptoms, on average, experienced greater symptom reductions. For urgency incontinence and total incontinence episodes, only patients with relatively low baseline symptom levels were likely to experience complete symptom relief.

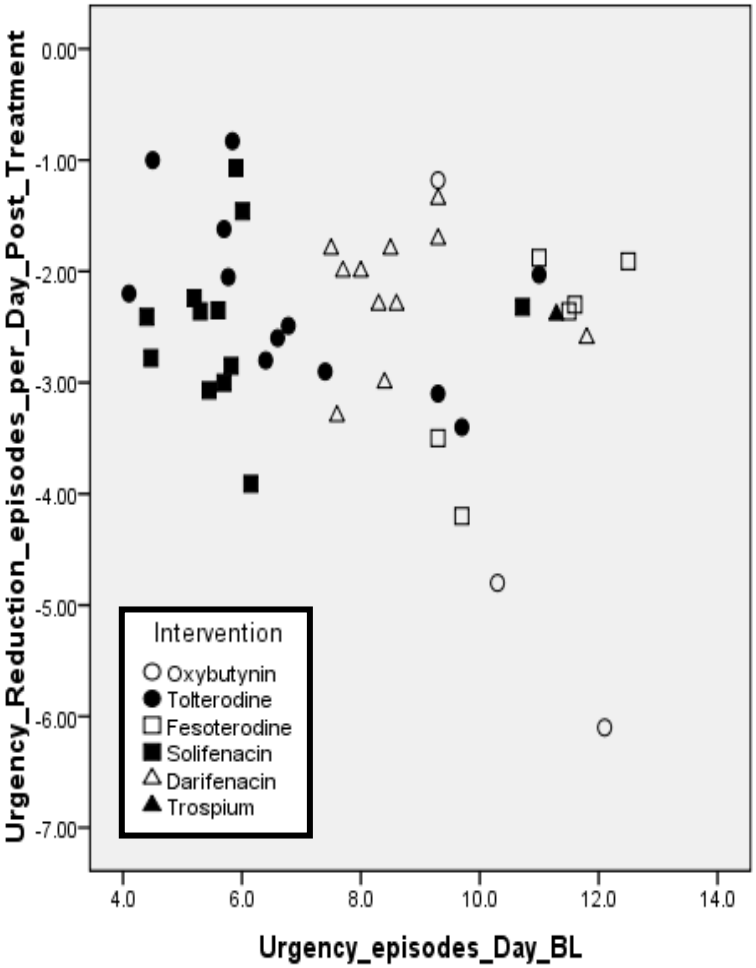
This relationship was evident both within and across medications regardless of study inclusion criteria or dosing regimens (see Figure 1 for urgency urinary incontinence data).

Figure 1. Baseline Urgency Urinary Incontinence (UUI; episodes/day) and UUI Reduction (episodes/day) for randomized trials by drug.



For urgency and nocturia, however, there was no apparent relationship between baseline symptom levels and symptom reduction (See Figure 2 for urgency data).

Figure 2. Baseline urgency (episodes/day) and urgency reduction (episodes/day) for randomized trials by drug.



Due to the similar efficacy observed for all oral anti-muscarinic medications, the choice of medication for a particular patient depends on the patient's history of anti-muscarinic use, information regarding adverse events experienced in the past, the impact on the patient of adverse events, patient preferences, comorbidities, use of other medications and the availability of and resources to acquire specific medications. In addition, although there was no evidence of differential efficacy across medications, both qualitative analysis and meta-analysis of all randomized trial arms revealed different adverse event profiles for dry mouth and constipation.* This information may be relevant if a patient is particularly sensitive to one of these adverse events.

With regard to dry mouth, meta-analysis revealed that on average 6.90% of placebo patients experienced dry mouth (40 placebo arms; 95% CI: 5.6% to 8.5%). Rates of dry mouth in active drug treatment arms for the newer medications (i.e., darifenacin – 9 arms, fesoterodine – 11 arms, solifenacin – 15 arms) and for trospium (8 arms) ranged from 20.0% to 40.0%. Within each medication, there was no clear relationship between rate and dose. Across medications, rates were statistically indistinguishable with overlapping confidence intervals and derived from relatively few trial arms for each medication; the Panel interpreted these findings as preliminary and descriptive rather than definitive until more data are available.

The majority of the available studies evaluated oxybutynin (25 trial arms) and tolterodine (40 trial arms). The rate of dry mouth for oxybutynin at 61.4% was statistically significantly higher (95% CI: 52.5% to 69.5%) than the 23.7% rate for tolterodine (95% CI: 20.7% to 26.9%) ($p<0.001$). Although there was no clear relationship with dose, there was heterogeneity within each medication based on whether the immediate release (IR) or the extended release (ER) formulation was administered (see Guideline Statement 8 below).

With regard to constipation, on average 3.6% of placebo patients experienced this adverse event (36 placebo arms; 95% CI: 2.7% to 4.8%). Constipation rates in active drug treatment arms for fesoterodine (11 arms), solifenacin (15 arms), and trospium (5 arms) ranged from 7.0% to 9.0%. These rates were statistically indistinguishable with similar 95% confidence intervals spanning 5.0% to 12.0%. The constipation rate for darifenacin (9 arms), however, was significantly higher at 17.0% (95% CI: 13.0% to 21.0%). Within each medication, there was no clear relationship between rate and dose. Since these data were derived from relatively few trial arms, the Panel again interpreted them as descriptive rather than definitive until more data are available.

The majority of the available studies evaluated oxybutynin (21 trial arms) and tolterodine (34 trial arms). The rate of constipation for oxybutynin was 12.1% (95% CI: 7.9% to 18.0%). The rate for tolterodine was statistically significantly lower ($p<0.001$) at 4.9% (95% CI: 4.1% to 5.7%). There were no differences based on dose or between the IR and ER formulations for either medication.

The Panel interpreted the oxybutynin and tolterodine data to indicate that the probability that a patient will experience dry mouth and/or constipation appears to

*Although anti-muscarinic therapy is associated with a range of adverse events deriving from antagonism of the muscarinic receptor across multiple organ systems, most trials reported data only for dry mouth and constipation. As a consequence, there were insufficient data on other adverse events and meta-analysis was not feasible. Meta-analysis of dry mouth and constipation data was conducted using Comprehensive Meta-Analysis ver. 2.0 (Biostat) using a random effects model.

be higher overall with the administration of oxybutynin compared to tolterodine. See Guideline Statement 9 regarding the ER vs. IR formulations. Evidence strength was Grade B because most trials were of moderate quality and follow-up durations were relatively short (i.e., 12 weeks).

Guideline Statement 9.

If an immediate release (IR) and an extended release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. ***Standard***

Discussion. ***(Evidence strength – Grade B; Benefits outweigh risks/burdens).*** A meta-analysis of adverse events indicated that the ER formulations of oxybutynin and tolterodine resulted in statistically significantly fewer patient reports of dry mouth than the IR formulations of both medications. Specifically, the rate for the oxybutynin ER formulation was 40.0% (95% CI: 28.0% to 53.0%) and was statistically significantly lower than the oxybutynin IR rate of 69.0% (95% CI: 60.6% to 76.5%). The dry mouth rate for ER tolterodine was 18.0% (95% CI: 14.8% to 21.4%) and was statistically significantly lower ($p<0.001$) than the IR rate of 28.8% (95% CI: 25.1% to 32.8%). Within each medication, there was no relationship with dose. There were insufficient trospium trial arms to meta-analyze the IR vs. ER formulations; however, a similar pattern was evident. The IR trospium trials reported dry mouth rates that ranged from 19.8% to 41.4% of patients;[45, 82, 102, 108, 123, 130] in contrast, the ER trospium trials reported dry mouth rates of 8.7 to 12.9%.[77, 111]

Because OAB is a chronic condition and treatment with anti-muscarinics generally would be required long-term, optimizing medication tolerability is critical to obtaining patient compliance. Adverse drug events, particularly dry mouth, are the major reasons that patients fail to comply with anti-muscarinic therapy; thus choosing the formulation with the lowest likelihood of adverse events may improve compliance.[131, 132] In addition, compliance with a once-daily treatment has been shown to be greater than with medications that are taken more than once a day.[133] The decision to prescribe an IR vs. an ER formulation, however, should be made in the context of the patient's prior experience with anti-muscarinics and the availability of medications, including insurer constraints, in order to minimize patient burden. Insurer constraints may be such that a patient may need to be prescribed an IR formulation and either have inadequate symptom control or have intolerable side effects prior to obtaining approval to be prescribed an ER formulation. The Panel notes that if a patient has good symptom control and tolerable side effects on an IR formulation, then there is no need to change to an ER formulation.

Guideline Statement 10.

Transdermal (TDS) oxybutynin [patch <u>(now available to women ages 18 years and older without a prescription)*</u> or gel] may be offered. ***Recommendation***

Discussion. ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** Transdermal preparations of oxybutynin may be offered instead of oral anti-muscarinics to patients who are at risk of or who have experienced dry mouth with oral agents. Six randomized trials evaluated transdermal oxybutynin preparations. Four trials that included placebo control groups evaluated the TDS patch.[76, 87, 134, 136] One trial with a placebo control group evaluated oxybutynin chloride topical gel.[135] An additional trial compared the oxybutynin TDS patch to oral oxybutynin.[74] Dmochowski (2002) evaluated three oxybutynin doses administered via TDS patch (1.3 mg, 2.6 mg and 3.9 mg) and reported reductions in incontinence episodes per day (reductions of 2.8 episodes with placebo, 2.7 episodes with 1.3 mg, 2.6 episodes at 2.6 mg and 3.3 episodes at 3.9 mg) and reductions in 24 hour frequency (reductions of 1.7 episodes with placebo, 1.8 with 1.3 mg, 1.8 with 2.6 mg and 2.3 with 3.9 mg); only the reductions with 3.9 mg were significantly different from placebo.[134] A 12-week open-label extension of this study reported larger incontinence episode reductions, ranging from 3.4 to 3.9 episodes. Dmochowski (2003) evaluated only the 3.9 mg dose compared to *r* mg tolterodine ER and placebo in known responders to anti-muscarinics and reported similar findings for frequency for both the TDS and oral medication groups.[76] In addition, in this trial, urgency incontinence episodes were reduced by 2.8 episodes a day using 3.9 mg compared to 3.2 episodes a day with tolterodine and 2.1 episodes a day with placebo. Cartwright (2010) also evaluated 3.9 mg compared to placebo and reported significant reductions in urgency episodes/day (reduction of 1.23 episodes in the 3.9 mg group compared to a reduction of 0.21 episodes in the placebo group) and non-significant reductions in frequency and UI episodes/day.[136] The primary outcome in this trial was patient-selected goals for treatment. A greater proportion of patients in the 3.9 mg group reported goal achievement (41.9%) than in the placebo group (32.2%), but the difference was not significant. The authors note that the relatively low proportions of patients who reported achieving treatment goals may indicate why many patients discontinue anti-muscarinic treatment. Homma and Koyama (2006) compared 2.6 mg, 3.9 mg and 5.2 mg TDS oxybutynin to placebo and reported reductions in incontinence episodes of 1.5 episodes with 2.6 mg, 2.0

episodes with 3.9 mg, 1.6 episodes with 5.2 mg and 1.4 episodes with placebo.[87] Baseline incontinence levels were lower in this trial (average of 3 episodes/ day) than in the Dmochowski (2002) trial (average of 4 episodes/day), which might account for the smaller magnitude of change. In patients known to be responsive to oral oxybutynin, Davila (2001) used 1.3 mg to 3.9 mg TDS oxybutynin or 5 mg to 22.5 mg oral oxybutynin, depending on the patient's prior tolerance for oxybutynin.[74] Reduction of approximately 4.8 incontinence episodes/day occurred in both groups. Staskin (2009) evaluated 1 mg oxybutynin chloride topical gel and reported significant decreases in urgency incontinence (3 fewer episodes/day) and frequency (2.7 fewer episodes/day) compared to the placebo group (2.5 fewer UI episodes/day and 2 fewer frequency episodes/day).[135] Newman (2010) reported on the same patients and noted that treatment with gel improved health-related QoL measures more than did treatment with placebo.[137]

Five trials reported adverse events. Dmochowski (2002) reported dry mouth rates of 8.3% with placebo, 4.6% with 1.3 mg TDS oxybutynin, 6.8% with 2.6 mg and 9.6% with 3.9 mg and constipation rates of 3.0% with placebo, 5.4% with 1.3 mg, 2.3% with 2.6 mg and 0.8% with 3.9 mg.[134] Dmochowski (2003) reported dry mouth rates of 4.1% with 3.9 mg TDS oxybutynin, 7.3% with tolterodine and 1.7% with placebo; constipation rates were 3.3% with 3.9 mg and 5.7% with tolterodine (constipation rate not reported for placebo group).[76] Davila (2001) reported dry mouth rates of 38% in the TDS group compared to 94% in the oral oxybutynin group (constipation rates not reported).[74] Cartwright (2010) reported that 38.2% of patients in the active treatment group experienced erythema or pruritus (compared to 27.1% in the placebo group) and 14.9% experienced at least one systemic adverse event, the most common of which was dry mouth (compared to 12.5% in the placebo group).[136] Staskin (2009) reported dry mouth rates of 6.9% in the oxybutynin gel group compared to 2.8% in the placebo group and rates of other adverse events at 1% or less in both groups.[135]

The Panel interpreted these data to indicate that transdermal oxybutynin (patch and gel) is effective in reducing incontinence episodes, in particular, with dry mouth rates that appear to be less than the meta-analyzed rates of 40.0% for oral oxybutynin ER and 68.0% for oral oxybutynin IR. Because the number of studies evaluating TDS oxybutynin was relatively few with different patient inclusion criteria (i.e., known responders to anti-muscarinic medications in some trials), the body of evidence strength was designated as Grade C.

Guideline Statement 11.

If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried. ***Clinical Principle***

Discussion. In the Panel's experience, patients who experience inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication may experience better symptom control and/or a more acceptable adverse drug event profile with another anti-muscarinic. In addition, in some patients, dose modification (i.e., reducing dose or reducing dose and combining medication with behavioral techniques) may achieve a better balance between efficacy and adverse drug events. A small literature composed of observational studies supports this experience, particularly when switching from an older medication to a newer medication. Patients who had prior unsatisfactory symptom control and/or unacceptable adverse events with tolterodine[138-140] or oxybutynin[140, 141] reported better efficacy and/or more acceptable adverse event profiles with fesoterodine,[138] solifenacin[139, 141] or darifenacin.[140] Based on the Panel's clinical experience and this limited literature, the Panel advises that clinicians should not abandon anti-muscarinic therapy if trial of one medication appears to fail or produces an unacceptable adverse event profile.

There is no literature that addresses combination therapy of anti-muscarinics with each other or with other classes of medication such as tricyclics to manage non-neurogenic OAB.

Guideline Statement 12.

Clinicians should not use anti-muscarinics in patients with narrow angle glaucoma unless approved by the treating ophthalmologist and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention. ***Clinical Principle***

Discussion. Clinicians should not use anti-muscarinics in patients with narrow angle glaucoma unless the treating ophthalmologist approves and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention, carefully weighing the benefits vs. the significant risks. If the patient is at risk for or has a history of gastric emptying problems, then the patient should be seen by or receive clearance from a gastroenterologist. If the patient has a history of or is at risk of urinary retention, then urology consultation should be strongly considered. It is useful to obtain a post void residual in any patient the clinician suspects has a higher than normal risk of urinary retention. Anti -muscarinics are also contraindicated in patients using

solid oral forms of potassium chloride, as the reduced gastric emptying potentially caused by the anti-muscarinics may increase the potassium absorption of these agents. If these patients can be switched to alternative forms of potassium chloride, then anti-muscarinic therapy may be possible with caution. In weighing the risks of anti-muscarinic therapy in high-risk patients, it is important to remember that OAB may compromise quality of life, but it is not a life-threatening condition. Clinicians, therefore, should exercise extreme caution in using treatments that may present life-threatening risks.

Guideline Statement 13.

Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. ***Clinical Principle***

Discussion. One of the main limitations of anti-muscarinic therapy is that the majority of patients discontinue after a few weeks or months.[131, 133] Although there may be several factors involved in this decision, side effects are commonly cited as the reason for discontinuation.[132] One way clinicians can help patients benefit from anti-muscarinic therapy is to proactively monitor for and manage common side-effects. Even before initiating anti-muscarinic therapy, patients should be educated about the possible effects of medication on bowel function and the roles of adequate dietary fiber and fluid, psyllium-based fiber supplements, regular exercise and normal bowel habits. Preparing for 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. When dosing options are available, dose reduction can provide relief from side-effects while retaining some therapeutic effects. In older patients who may metabolize drugs differently, it is often advisable to start with a minimal dose and then increase it if it is tolerated well. With multiple drugs available for OAB, trying alternate anti-muscarinics may identify a medication that the patient can more easily tolerate.

Guideline Statement 14.

Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. ***Expert Opinion***

Discussion. The concurrent use of other medications with anti-cholinergic activity may potentiate the side effects of the anti-muscarinic class of OAB medications. These medications include tricyclic antidepressants, those used in the treatment of Parkinsonism and other extra-pyramidal diseases and of Alzheimer's disease, and include benzotropine, biperiden HCl, galantamine, rivastigmine and trihexyphenidyl HCl. Certain anti-nausea medications and those with atropine-like properties, such as trimethaphan, methscopolamine bromide and ipratropium, may also potentiate these side effects. Providers also should exercise caution in patients who are prescribed acetycholinesterase inhibitors such as donepezil. This list is not intended to be exhaustive; prescribers should be aware of precautions and contraindications for these medications.

In addition, most clinical studies of OAB medications have been conducted on relatively narrow patient populations and provide only short-term data (i.e., 12 weeks) on adverse drug events. In the absence of long-term data on patients neither eligible for nor included in clinical trials, the prevalence and severity of adverse drug events is largely unknown.

Guideline Statement 15.

Clinicians should use caution in prescribing anti-muscarinics in the frail OAB patient. ***Clinical Principle***

Discussion. In frail patients, defined as patients with mobility deficits (i.e., require support to walk, have slow gait speed, have difficulty rising from sitting to standing without assistance), weight loss and weakness without medical cause and who may have cognitive deficits[142] (PR 37, 98, 315), the use of OAB medications may have a lower therapeutic index and a higher adverse drug event profile. OAB medication studies generally are not conducted in the frail elderly, resulting in a lack of data in this group. In the Panel's experience, however, adverse drug events in addition to the typically reported events of dry mouth and constipation may occur, including impaired thermoregulation that can cause dangerous core temperature elevation. Clinicians should begin with the lowest possible dose and increase doses slowly while carefully assessing for the balance between symptom control and adverse events. The use of transdermal anti-muscarinics should be monitored to ensure that the skin where the medication is applied remains intact.

Cognitive deficits, particularly memory difficulties, have been reported in response to anti-muscarinics,[143-145] and clinical experience suggests that elderly patients may be particularly prone to these adverse effects. There is some suggestion that the newer agents (e.g., darifenacin) are less likely to produce cognitive deficits in elderly patients than are the older agents, but the literature is limited and the two-week drug administration period in these studies is not long

enough to yield definitive conclusions.[146, 147] Kay (2006) notes, however, that patients may not recognize that memory deterioration has occurred, making it essential for the clinician, family members and caregivers to monitor for these effects.[147] In addition, polypharmacy is common in community dwelling patients who are frail,[148] placing them at higher risk for adverse drug events, including impaired cognition. In dementia patients, anti-muscarinics should be used with extreme caution or may be contraindicated entirely depending on the level of cognitive impairment. The clinician should consider these possibilities in prescribing anti-muscarinics to frail patients and reassess the balance between benefits and risks/ burdens with the patient, caregiver and/or family on a regular basis and/or when functioning appears to change. In patients who cannot tolerate anti-muscarinics or for whom these medications are not appropriate, behavioral strategies that include prompted voiding and fluid management may be helpful.

Guideline Statement 16.

Patients who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist if they desire additional therapy. *Expert Opinion*

Discussion. The Panel defines the refractory patient as the patient who has failed a trial of symptom-appropriate behavioral therapy of sufficient length to evaluate potential efficacy and who has failed a trial of at least one anti-muscarinic medication administered for 6 to 12 weeks. Failure of an anti-muscarinic medication may include lack of efficacy and/or inability to tolerate adverse drug effects. The Panel notes that this definition is a minimum definition; individual clinicians and patients may decide that it is in the best interests of the patient to persevere with behavioral and/or anti-muscarinic therapy for longer periods, to combine behavioral and anti-muscarinic therapies to achieve better efficacy, or to try alternate anti-muscarinics before judging that a patient is refractory.

Behavioral therapies present no risks to patients and anti-muscarinics present risks that cease when the medication is stopped. The remaining treatment levels present increasing risks to patients that must be balanced with potential efficacy. Before a patient is exposed to these therapies, a comprehensive evaluation should be conducted to ensure that the patient's symptoms are attributable to OAB and not to some other disease process that requires other kinds of treatment and the patient's desire for further treatment should be ascertained.

Third-Line Treatments: In the patient who has failed behavioral and anti-muscarinic therapy or who is not a candidate for these therapies, neuromodulation or onabotulinumtoxinA therapy may be offered. The Panel also notes that use of these third-line therapies requires careful patient selection and appropriate patient counseling. Clinicians may offer the third-line treatments in any order and may offer alternate third-line treatments if a patient is refractory to the initial treatment choice. The Panel notes that there is no literature that addresses using these therapies in combination.

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Guideline Statement 17.

Clinicians may offer sacral neuromodulation (SNS) as third-line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. ***Recommendation***

Discussion. ***(Evidence strength – Grade C; Benefits outweigh risks/burdens).*** Thirteen studies, predominantly single-group observational designs, evaluated sacral neuromodulation in patients with severe refractory OAB symptoms, many of whom had failed multiple other therapies.[149-161] In general, patients were characterized by extremely severe levels of baseline incontinence, ranging from 5.0 to 11.6 episodes per day, by severe frequency (most studies reporting baseline levels of more than 13 episodes per day) and by pad use of more than 4 per day at baseline in most studies. This group of studies is characterized by much longer follow-up durations than in other OAB studies, with follow-up ranging from 24 weeks to 260 weeks and most studies following patients for more than a year. In general, studies reported that all measured parameters, including QoL and subjective improvement, show improvement with treatment and that improvement dissipates if treatment ceases. Siegel (2000), Janknegt (2001) and van Kerrebroeck (2007) evaluated the same groups of urgency incontinence patients compared to urgency-frequency patients and reported that at 5 years post-surgery greater than a 50% improvement was reported by 68% of the UI group and 56% of the urgency-frequency group.[152, 157, 160] Groen (2011) reported that treatment success (defined as ≥ 50% decrease in the number of daily incontinence episodes or pads used) was 87.0% of patients at one month post-surgery with a decline to 62.0% at five years.[150] An additional study reported on urodynamics outcomes for patients evaluated by Schmidt (1999) and noted that patients with UI, with and without detrusor overactivity, had similar improvements in urodynamic parameters.[156, 162] Leong

(2011) assessed long-term satisfaction with SNS and reported that 90% of 207 patients surveyed reported being satisfied with the treatment (median post-implant interval of 77 months).[154] In an effort to reduce adverse events and possibly limit nervous system adaptation and diminished efficacy that may occur with continuous stimulation, Oerlemans (2011) tested an on-demand protocol in which patients turned the apparatus off for several hours a day.[155] Approximately 63% of patients were able to maintain symptom improvement by using the on-demand procedure during the two-week test.

In contrast to PTNS studies (see discussion under Guideline Statement 18), SNS studies reported frequent adverse events, including pain at the stimulator site (3.3 to 19.8% of patients), pain at the lead site (4.5 to 19.1% of patients), lead migration (2.2 to 8.6% of patients), infection/irritation (2.2 to 14.30% of patients), electric shock (5.5 to 7.9% of patients) and need for surgical revision (6.25 to 39.5% of patients). In most studies, the need for surgical revision occurred in greater than 30% of patients. There is some evidence that newer, less invasive surgical procedures and tined devices may be associated with fewer adverse events.[159] Leong (2011) reported that although 90% of patients reported satisfaction with SNS, 56% reported adverse events, particularly pain at the stimulator site and when the stimulator was turned on and daily life limitations, such as difficulty passing through airport metal detectors and inability to undergo magnetic resonance imaging (MRI).[154]

The Panel interpreted these data to indicate that in carefully selected patients, SNS is an appropriate therapy that can have durable treatment effects but in the context of frequent and moderately severe adverse events, including the need for additional surgeries. The Panel notes that patients should be counseled that the device requires periodic replacement in a planned surgical procedure and that the length of time between replacements depends on device settings. Patients also must be willing to comply with the treatment protocol because treatment effects typically are only maintained as long as the therapy is maintained and have the cognitive capacity to use the remote control to optimize device function. In addition, patients must accept that the use of diagnostic MRIs is contraindicated in individuals with the device implanted. Given the negative effects on quality of life associated with severe incontinence and frequency, the Panel judged that benefits of SNS in the appropriate patient outweighed the risks/burdens and notes that patients should be carefully counseled regarding the risks/burdens. Evidence strength is Grade C because of the predominance of observational designs, the small sample sizes, the limited number of unique patient groups (i.e., there are multiple reports on the same patient groups followed over time) and limited information regarding the protocols used by patients to maintain symptom control.

Guideline Statement 18.

Clinicians may offer peripheral tibial nerve stimulation (PTNS) as third-line treatment in a carefully selected patient population. ***Option***

Discussion. ***(Evidence strength – Grade C; Balance between benefits and risks/burdens uncertain).*** Eight studies reported in ten publications assessed the efficacy of PTNS to treat OAB symptoms.[103, 109, 163-170] The majority of studies were single-group observational designs that evaluated patients with refractory OAB symptoms. Patients in these studies are characterized by having moderately severe baseline levels of incontinence (ranging from 2.2 to 9.8 episodes per day) with most studies assessing patients with more than 3 episodes a day. Patients had moderately severe frequency symptoms at baseline, ranging from 11.8 to 16.5 episodes per day. Most trials report improvements in all measured symptoms, including incontinence (typical reductions of 1 to 3 episodes/day), frequency (reductions of 2 to 5 episodes/day), nocturia (reductions of 1 to 2 episodes/night) and quality of life. The most common protocol was the application of 30 min of stimulation once a week for 12 weeks (the trial duration; for continued benefit, weekly stimulation would have to continue). Peters (2009) compared PTNS to tolterodine ER 2-4 mg daily and reported similar improvements in both groups in voiding parameters but a greater proportion of patients in the PTNS group indicating subjective improvement.[103] Sancaktar (2010) compared tolterodine ER 4 mg daily with and without PTNS and noted that the combined treatment group improved more than did the tolterodine alone group.[109] Two reports followed patients for long periods of time (44 weeks in Klingler 2000; 52 weeks in MacDiarmid 2010 – a long-term report on patients initially evaluated in Peters 2009) and indicate that improvements were maintained as long as the treatment was maintained.[103, 163-165] Additional studies did not report raw voiding data but reported improvements in symptoms and quality of life with treatment[171, 172] that ceased when treatment ceased.[171] The validity of PTNS treatment responses is supported by Peters (2010), which compared a PTNS group to a sham-PTNS group and found that only the active treatment group exhibited improvements in frequency, nocturia and urgency incontinence. Adverse events were relatively uncommon and mild.

The Panel interpreted these data to indicate that PTNS can benefit a carefully selected group of patients characterized by moderately severe baseline

incontinence and frequency and willingness to comply with the PTNS protocol. Patients must also have the resources to make frequent office visits in order to obtain treatment because treatment effects dissipate once treatment ceases. As a group, the PTNS studies constitute Grade C evidence because of the predominant observational designs, varying patient inclusion criteria and short follow-up durations for most studies.

Newly FDA-Approved Since the Publication of This Guideline

Guideline Statement 19.

Clinicians may offer intradetrusor onabotulinumtoxinA as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. *Option*

Discussion. *(Evidence strength – Grade C; Balance between benefits and risks/burdens uncertain).* The Panel designated intradetrusor onabotulinumtoxinA treatment as an option because although most studies reported improvements in measured parameters, rates of adverse events that could compromise quality of life or lead to serious illness were extremely high in some trials, making the balance between benefits and risks/ burdens unclear. The available literature on intravesical use of onoabotlinumtoxinA is reviewed below; the Panel focused this treatment Option on injections into the detrusor specifically because most studies assessed this injection location. There is insufficient evidence at present to comment on the relative efficacy of injections into other intravesical locations.

Four randomized trials with placebo control groups (reported in five papers), two randomized trials without placebo control groups and 15 observational studies without control groups evaluated the effects of onabotulinumtoxinA in patients with non-neurogenic OAB who had inadequate symptom control with anti-muscarinics or intolerable side effects.[173-194] All studies reviewed evaluated onabotulinumtoxinA (BoTox R, Allergan, Inc., Irvine, CA) except for one[180] which evaluated abobotulinumtoxinA (Dysport TM, Medicis Pharmaceutical Co., Scottsdale, AZ). Studies varied in onabotulinumtoxinA dose and in injection location. Doses of onabotulinumtoxinA are not equivalent to doses of abobotulinumtoxinA.

The four RCTs with placebo control groups evaluated injections into the detrusor of 200 U onabotulinumtoxinA,[173, 176] 200-300 U onabotulinumtoxinA,[175] or 50-300 U onabotulinumtoxinA.[174, 189] The randomized trials without placebo control groups injected 100 U onabotulinumtoxinA into the suburothelial space, the detrusor or the bladder base[178] or injected 100 U onabotulinumtoxinA into the bladder body, bladder body and trigone or bladder base and trigone.[179] Significant reductions in incontinence episodes[173, 175, 179] and in urgency[176, 178, 179] were reported in active treatment groups (but not in placebo controls where included). Frequency data were less clear with reductions occurring in most active treatment groups (except for patients injected in the suburothelial space in Kuo 2007 who experienced increased frequency) but with a large range of reductions (e.g., from a non-significant 1.3 episodes per day in Flynn 2009, to 6.1 episodes per day in Sahai 2007, to 14.2 episodes per day in Kuo 2007 in the detrusor injected group).[175, 176, 178] To some extent this range may be related to the inclusion of patients with different baseline frequency levels (e.g., patients in Flynn 2009 had baseline 24-hour frequency of 10.5 episodes per day compared to patients in Kuo 2007 who had 24-hour frequencies ranging from 17.8 to 29.8 episodes per day),[175, 178] but the largest reductions were reported in Kuo (2007),[178] which is the trial with the lowest onabotulinumtoxinA dose (100 U). Flynn (2009) also reported reductions in nocturia (0.5 fewer episodes/night) and in pad use (2.2 fewer pads/day) at six weeks post-injection.[175] In addition, Sahai (2007) reported improvements in a variety of urodynamic parameters and improved scores on the IIQ-7 and the UDI-6 in onabotulinumtoxinA patients but not in placebo patients.[176] Two additional papers reporting on the same group of patients noted improved scores in onabotulinumtoxinA patients on the King's Health Questionnaire during the randomized trial as well as during an open-label extension study[195] and that quality of life improvements and improved urodynamic parameters were restored in patients who required repeat injections.[196] In Kuo (2007), three months after injection of 100 U onabotulinumtoxinA, the proportion of patients reporting a status of excellent or moderately improved was 93% of the detrusor group, 80% of the suburothelial space group and 67% of the bladder base group.[178] These proportions dropped to 67% (detrusor), 47% (suburothelial space) and 13% (bladder base) at 6 months and to 20% (detrusor), 20% (suburothelial space) and 6.7% (bladder base) at 9 months. Dmochowski (2010) compared responses across a wide range of onabotulinumtoxinA doses (50 to 300 U) and reported that doses of 100 U or greater were sufficient to reduce urgency incontinence episodes and improve QoL measures but without clear dose-response effects such that doses above 150 U did not contribute additional clinically-relevant symptom improvement.[174] Additional information on the same patients was provided by Rovner (2011).[189] This paper reported that doses of ≥ 100 U all resulted in significant improvement of OAB

symptoms (i.e., reductions in UI episodes and frequency) without clear dose-response effects. Findings also were broken out between patients with and without detrusor overactivity (DO); similar improvements were reported in both groups.

The observational studies injected doses of onabotulinumtoxinA ranging from 100 – 300 U. Most studies injected into the detrusor except for two studies, which injected into the detrusor and sphincter[191, 192] and two studies,[184, 185] which injected into the submucosa of the bladder wall. Jeffery (2007) injected 500 U of abobotulinumtoxinA into the detrusor.[180] As a group, the observational studies reported reductions in frequency, nocturia, pad use and incontinence; improvement in urodynamics parameters and improvement in quality of life measures. Follow-up durations ranged from 1.5 weeks to 145 weeks. In the longer studies, improvements diminished over time and repeat injections were required to restore improvements. Gamé (2010) reported that in patients who had up to five repeat injections to maintain improvement, QoL improved after each injection.[197]

These outcomes occurred, however, in the context of high rates of adverse events in the active treatment groups in some studies. Rates of UTIs were reported in 13 studies and ranged from 3.6% to 44.0% with two of the RCTS[173, 176] reporting rates of 44.0% and Dmochowski (2010) reporting that rates generally increased with dose with rates ranging from 33.9% to 48.1% across active treatment groups.[174] The definition of elevated post-void residual (PVR) varied across studies from 100 ml to 400 ml with most studies defining an elevated PRV as 100 - 150 ml. It should be noted, however, that that the highest rates of urinary retention were not necessarily reported in studies that used the lowest PVR thresholds. Rates of urinary retention were reported in six studies and ranged from 0% to 43% with rates of 43.0% and 30.0% reported in one RCT (elevated PVR defined as 200 cc)[173] and one observational study (elevated PVR defined as 250 cc),[177] respectively. Rates of PVR increase were reported in 11 studies and ranged from 0% to 75% with half of these studies reporting rates of 43.0% or higher[173, 177, 179, 180, 184, 187] The proportion of patients who needed to perform self-catheterization was reported in 16 studies and ranged from 0% to 43% with six studies reporting rates higher than 20.0%.[173, 174, 176, 180-183] Increased PVRs and the need for self-catheterization persisted for six to nine months in some patients.[177, 180, 190] It should be noted, however, that Kessler (2009) examined QoL outcomes in women who had to perform self-catheterization post-onabotulinumtoxinA treatment compared to those who did not and found no differences in UDI-6 and IIQ-7 scores.[182] Bauer (2011) focused more broadly on side effects and interviewed patients (n = 56) who had been administered onabotulinumtoxinA (100, 150 or 200 U) or abobotulinumtoxinA (500 U) regarding the occurrence of gross hematuria, dry mouth, dysphagia, speech problems, impaired vision and weakness of the eyelids, arms, legs, torso and/or whole body.[198] Approximately 54% of patients reported at least one side effect, including urinary retention (8.9%), gross hematuria (17.9%), UTI (7.1%), dry mouth (19.6%), dysphagia (5.4%), impaired vision (5.4%), eyelid weakness (8.9%), arm weakness (8.9%), leg weakness (7.1%) and torso weakness (5.4%). The authors note that symptoms other than urinary retention and UTI were transient and resolved without the need for further treatment. These data indicate, however, that patients may experience neurological adverse events in addition to the more commonly reported events of urinary retention and UTIs.

The Panel interpreted these data to indicate that, although onabotulinumtoxinA injections can improve symptoms, the risk of adverse events that could require secondary intervention is substantial (e.g., an untreated UTI, undiagnosed urinary retention). Patients considering onabotulinumtoxinA treatment must be counseled regarding the possible need to perform self-catheterization for long periods (or to have a caregiver perform catheterization) and should be willing to accept this possibility. OnabotulinumtoxinA treatment also may require access to a clinician who can measure PVR on a periodic basis if necessary. Further, effects diminish over time for most patients; therefore, patients also should be informed that repeat injections are likely to be necessary to maintain symptom reduction. The Panel also believes that this procedure should be performed by experienced personnel familiar with intravesical injection techniques.

Evidence strength is Grade C because follow-up durations were short in the best-designed studies (ranging from 4 to 12 weeks for the RCTs), most of the available studies were observational designs without control groups, doses and injection sites varied across studies, adverse event reporting was extremely variable and the total number of patients evaluated in the randomized trials was small (approximately 400).

Additional Treatments

Guideline Statement 20.

Indwelling catheters (including transurethral, suprapubic, etc.) are not recommended as a management strategy for OAB because of the adverse risk/benefit balance except as a last resort in selected patients. ***Expert Opinion***

Discussion. In situations where the medical management of burdensome OAB, as outlined above, is not feasible, effective nor recommended, as in the

patient with severe cognitive deficits or mobility issues, then other management options may need to be considered. Management with diapering and absorbent garments is always preferred to indwelling catheterization because of the high risk of indwelling catheter-associated UTIs, urethral erosion/destruction and urolithiasis. Intermittent catheterization may be an option when concomitant incomplete bladder emptying is present leading to overflow incontinence; however, this approach generally requires either patient willingness and ability or significant caregiver support. As a last resort, an indwelling catheter may be considered when urinary incontinence has resulted in the development and progression of decubiti, during the management of those decubiti, or rarely, where urinary incontinence is the predominant disability affecting activities of daily living and therefore may result in institutionalization.

Guideline Statement 21.

In rare cases, augmentation cystoplasty or urinary diversion for severe, refractory, complicated OAB patients may be considered. ***Expert Opinion***

Discussion. In general, surgery is not recommended for OAB patients except in extremely rare cases. The vast majority of case series that document the effects of augmentation cystoplasty and diversion focus on neurogenic patients. Little is known regarding the impact of these procedures on non-neurogenic OAB patients and, particularly, on their quality of life. There are substantial risks to these procedures, however, including the likely need for long-term intermittent self-catheterization and the risk of malignancy.[199] In the Panel's judgment, therefore, a surgical approach to OAB treatment is appropriate only in the extremely rare patient.

Follow-Up

Guideline Statement 22.

The clinician should offer follow up with the patient to assess compliance, efficacy, side effects and possible alternative treatments. ***Expert Opinion***

Discussion. The purpose of follow-up is to assess compliance with treatment protocols, query patients regarding symptom improvements and any adverse events and present information about possible alternative treatments to patients who have insufficient symptom improvement and/or intolerable adverse events. There are many ways to measure symptom changes, including voiding diaries with or without frequency-volume charts and patient-rated global response scales for urgency, urgency incontinence, incontinence, frequency and nocturia. In addition, validated OAB-specific instruments may be used to assess the impact of OAB symptoms on quality of life. Ideally, clinicians should obtain baseline measures using the same instruments in order to chart progress. Patients should be encouraged to persist with a particular treatment for four to eight weeks; this time period will identify the majority of responders.[61]

Clinicians and any clinical personnel engaged in follow-up should be aware that the various treatment options for OAB have different requirements for efficacy and different adverse event probabilities and severities. For example, the efficacy of some treatments (e.g., behavioral therapies, neuromodulation) depends greatly on treatment compliance, and the efficacy must be balanced against possible adverse events. For other treatments, such as the use of anti-muscarinics, adverse events are common but vary in severity across patients. Patients should be informed about and subsequently queried regarding dry mouth and its severity (i.e., sufficient to impair alimentation), constipation, fecal retention and any possible central nervous system (CNS) effects. Queries of the patient and caregiver regarding CNS effects are particularly important in elderly or frail patients; clinical experience suggests that CNS effects can be severe enough to cause loss of independent living skills in some patients. Non-responders to anti-muscarinics should be tried on at least one other anti-muscarinic and/or dose modification attempted to determine if a better balance between efficacy and adverse events occurs. If adverse events are severe enough to compromise patient quality of life, then strategies to manage specific adverse events, such as ameliorating constipation with appropriate bowel management, should be implemented before abandoning anti-muscarinic treatment.

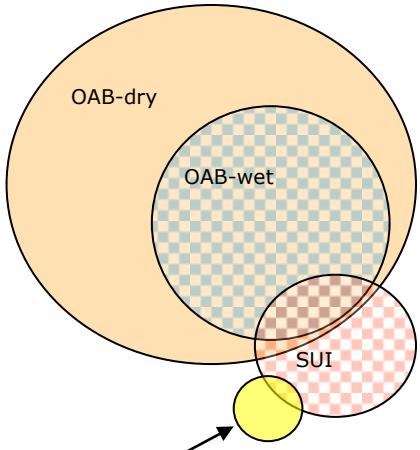
For therapies collectively labeled as neuromodulation, including sacral neuromodulation and peripheral tibial nerve stimulation, pre- and post-therapy measures are essential to assess efficacy. The before-and-after evaluation should include baseline assessment with a voiding diary and assessment of urgency as well as a global response assessment. Adverse events such as pain and collateral stimulation should be assessed, and sacral neuromodulation wound complications should be evaluated.

Patients treated with intradetrusor onabotulinumtoxinA should be followed for the possibility of increased PVRs and the need for self-catheterization. Patients who have undergone surgical treatments (e.g., augmentation cystoplasty with or without sling, supravesical diversion) or permanent or semi-

permanent catheter placements also should be followed regularly for symptom level, QoL and any complications. Patients who are using incontinence pads, regardless of whether or how they are being treated, should be followed for appropriate skin care and skin integrity.

Section 7: Research Needs and Future Directions

Better Stratification of OAB. OAB, because it is a symptom complex, is primarily a diagnosis of exclusion. Treatments are aimed at relieving symptoms and not necessarily at reversing pathophysiologic abnormalities. Understanding the pathophysiology and the risk factors for development of OAB is needed both to treat the syndrome as well as to prevent it. Future research will need to address the entire spectrum of research endeavors including epidemiology, QoL measurements, treatment modalities and basic bladder physiology including sensory and motor signaling. Within the field of OAB, research sometimes is dichotomized between OAB/lower urinary tract symptoms or LUTS (e.g., OAB-dry) versus OAB/urgency incontinence (OAB-wet). However, this type of compartmentalization highlights our lack of understanding of OAB. In other words, are OAB-dry and OAB-wet pathophysiologically related? Is OAB-dry a milder manifestation of the OAB condition which progresses to OAB-wet over time? Or are OAB-dry and OAB-wet two different conditions with different pathophysiologic mechanisms? How can we better objectively measure bladder symptoms? In addition, particularly in females, stress urinary incontinence (SUI) symptoms may exist concomitantly with OAB-symptoms (dry or wet). Further, isolated nocturia is a separate symptom entity, requiring different evaluation and management strategies. This overlap in bladder symptoms is captured in the Venn diagram below with their potential to be concomitantly present. This Venn diagram will appear different based on the gender and age of the population depicted; the diagram included here is intended to provide a point of reference for discussion. Therefore, the phenotype of bladder symptoms should be carefully considered and declared in all research to clarify the particular patient group being studied.



While not specifically understood.

Textured circles – incontinent subjects

Non-textured circles – continent subjects

Epidemiology. Studies assessing how OAB develops and its natural history and progression are required. The timing and circumstances around which OAB develops and associated risk factors are not yet well-targeting epidemiology of OAB, there are large community-based studies that assess prevalence of lower urinary tract symptoms and urinary incontinence.[200, 201] By longitudinally studying these community cohorts, these investigators have developed a new hypothesis that lower urinary tract symptoms are likely related to other systemic diseases/conditions.[202, 203] Continuation of these types of studies could lead to potential preventive interventions for OAB symptoms and/or utilization of treatments that target the associated systemic conditions rather than the bladder. Epidemiologic studies provide a better cross sectional estimation of the overall population impact of OAB-type symptoms.[204]

Clinical Research. As discussed previously, several validated OAB-symptom and OAB-symptom bother tools have been developed. However, objective measures of the "cornerstone" OAB-symptom of urgency[205] remains poorly assessed. As defined by the International Continence Society,[27] "urgency is the complaint of a sudden compelling desire to pass urine which is difficult to defer." Investigators have tested urgency questionnaires to assess for validity and reliability;[206-208] however, no single measure is used consistently across trials, making it difficult to compare findings.

Clinical studies should use validated standardized measures to report subjective outcomes. Objective outcomes should include frequency, nocturia, urgency, incontinence episode frequency and reporting of the variance for each of these measures. Furthermore, the

Guideline Panel's meta-analytic efforts were hampered by lack of consistent reporting of variance information (e.g., standard deviations, standard errors of the mean) for baseline and post-treatment measurements.

The effect of treatment of OAB on the elderly, the very frail and those with pre-existing cognitive deficiencies needs further research. These include measures of cognitive side effects from anti-muscarinic treatments.

Basic Science / Translational Research. The finding of a biomarker for OAB would advance the pathophysiologic understanding of OAB. Investigated biomarkers which have been published include nerve growth factor,[209] corticotrophin releasing factor,[210] prostaglandins[211] and inflammatory factors such as C - reactive protein.[212] Another approach to find potential relevant biomarkers is to utilize high throughput DNA array profiles, using subtractive techniques to identify uniquely expressed genes in OAB (as compared to controls).[213] However, this approach is non-targeted and may result in selection of many spurious, non-OAB specific candidate biomarkers.

Functional MRI (fMRI) has provided an imaging tool to ascertain the roles of the central nervous system (brain/cerebrum) in mediating bladder symptoms and whether there are visible abnormalities in subjects with OAB-symptoms. Different investigative groups have reported findings of alterations in brain processing of bladder sensory signals in OAB subjects.[214, 215]

Sensory (afferent) signaling from the bladder and urethra has been studied with various methodologies. The ideal sensory testing for the lower urinary tract that will have clinical impact in evaluation and management of OAB is not known. Use of current perception thresholds (CPT) electrophysiologic testing as a research tool has been described both in asymptomatic and OAB individuals.[216-218] A recent review has also highlighted the potential interaction of the bladder urothelium, suburothelium and interstitial cells with the sensory afferent pathways.[219] The urothelium has been proposed to be a "sensor-transducer" cellular compartment with urothelial cells able to release and respond to neurotransmitters, thus able to communicate with the afferent nerve endings that terminate within the urothelium.[220] The bladder suburothelium and detrusor muscle compartments are purported to contain "pacemaker-like" cells, similar to interstitial cells of Cajal found in the gut, which can modulate bladder contractility, rhythmicity and/or overactivity.[221] A more complete understanding of sensory mechanisms could lead to novel OAB therapies.

Finding other drug targets besides the muscarinic receptor represents an advance in treatment of OAB. ~~Recently, β3-agonist class of medications (i.e., mirabegron) has shown promise in OAB treatment.[222] These lines of research focus on the bladder and present a unique opportunity to advance bladder-targeted diagnostics and therapeutics.~~ **As of June 28, 2012, B3-agonist class of medications (i.e., mirabegron)[222] has been approved by the FDA for OAB treatment. This class of medications was not reviewed by this guidelines panel as it has been FDA-approved since the Guideline publication. Prescribing clinicians are advised to educate themselves regarding the cost-benefit and adverse event profile for those pharmaceutical agents they prescribe.***

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This document was written by the Overactive Bladder Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2009. The Practice Guidelines Committee (PGC) of the AUA selected the panel chair. Panel members were selected by the chair. Membership of the panel included urologists and other clinicians with specific expertise on this disorder. The mission of the committee 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 guideline 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.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines are not intended to provide legal advice about use and misuse of these substances.

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.
For this reason, the AUA does not regard technologies or management which are too new to be addressed by these guidelines as necessarily experimental or investigational.