American Urological Association (AUA)/ Society of Urodynamics,

Female Pelvic Medicine & Urogenital Reconstruction (SUFU) Guideline

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

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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 the original version of 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. 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 Opinions when insufficient evidence existed. Following initial publication, this Guideline underwent amendment in 2014 and 2019 to pull in literature released since the initial publication of the Guideline. The current document reflects relevant literature published through October 2018. 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 versus 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: Behavioral Therapies

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 pharmacologic management. *Recommendation (Evidence Strength Grade C)*

Second-Line Treatments: Pharmacologic Management

8. Clinicians should offer oral anti-muscarinics or oral β3-adrenoceptor agonists 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 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 or a β3-adrenoceptor agonist may be tried. *Clinical Principle*

12. Clinicians may consider combination therapy with an anti-muscarinic and β3-adrenoceptor agonist for patients refractory to monotherapy with either anti-muscarinics or β3-adrenoceptor agonists. *Option (Evidence Strength Grade B)*

13. 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*

14. 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*

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

16. Clinicians should use caution in prescribing anti-muscarinics or β3-adrenoceptor agonists in the frail OAB patient. *Clinical Principle*

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

Third-line Treatments: PTNS and Neuromodulation

18. Clinicians may offer intradetrusor onabotulinumtoxinA (100U) as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. *Standard (Evidence Strength Grade B)*

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

20. 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)*

21. Practitioners and patients should persist with new treatments for an adequate trial in order to determine whether the therapy is efficacious and tolerable. Combination therapeutic approaches should be assembled methodically, with the addition of new therapies occurring only when the relative efficacy of the preceding therapy is known. Therapies that do not demonstrate efficacy after an adequate trial should be ceased. *Expert Opinion*

Fourth-Line Treatments

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

Additional Treatments

23. 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*

Follow-Up

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

AUA/SUFU Guideline

Overactive Bladder

INTRODUCTION

Section 1: Purpose

This guideline's purpose is to provide direction to clinicians and patients regarding how to recognize non-neurogenic OAB, conduct a valid diagnostic process and approach treatment with the goals of maximizing symptom control and patient quality of life (QOL) 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 the first version of this guideline was the systematic review and data extraction conducted as part of the 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 update literature review process, in which an additional systematic review is conducted periodically to maintain guideline currency with newly-published relevant literature, was conducted in 2014 and 2019. These reviews identified an additional 72 (2014) and 37 (2019) articles relevant to treatment. These articles were added to the database, and AUA's qualitative and quantitative analyses were updated as appropriate. The review panels determined that each update review warranted targeted updates to the document, thereby creating the 2014 and 2019 amendments.

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 associated algorithm, 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 from the original search as well as 72 from the 2014 review, and 37 from the 2019 review processes 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 (DO) 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. The same system was used to assess the quality of additional included studies.

The categorization of evidence strength 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 randomized controlled trials [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 (high level of certainty) or Grade B (moderate level of certainty) 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 (low level of certainty) 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 (high certainty), B (moderate certainty) or C (low certainty) 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 QOL, 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 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 original completed evidence report and the updated literature review evidence report may be requested from AUA.

Table 1: AUA Nomenclature Linking Statement Type to Level of Certainty and Evidence Strength
Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A (high quality; high certainty) or B (moderate quality; moderate certainty) evidence
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C (low quality; low certainty) evidence
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A (high quality; high certainty), B (moderate quality; moderate certainty), or C (low quality; low certainty) evidence
Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature
Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

AUA/SUFU Guideline	Overactive Bladder

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 of the original document. 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 (BOD) 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. AUA's amendment process provides for the amendment of existing evidence-based guideline statements and/or the creation of new evidence-based guideline statements in response to the publication of a sufficient volume of new evidence. The process also provides for the amendment or addition of Clinical Principle and Expert Opinion statements based on consensus among panel members that elements of current practice have shifted such that a new or revised Clinical Principle or Expert Opinion statement is needed. Evidence-based guideline amendments require the agreement of a methodologist and panel members that new evidence is sufficient to change or add evidence-based statements. All guideline amendments require approval of the PGC and BOD.

Section 3: Background

Definition. 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 Urogynecological Association (IUGA) and International Continence Society (ICS) defines OAB as the presence of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), 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 IUGA/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 versus other populations. Some studies report higher prevalence rates in women than men,[7-10] while others found similar rates across genders.[11-14] However, UUI 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

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 IUGA/ICS is the "complaint of sudden compelling desire to pass urine which is difficult to defer."[4,27] 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*

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 PVR is not necessary for patients who are receiving first-line behavioral interventions 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 PVR 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*

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 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 QOL.

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 or β3-adrenoceptor agonists is not invasive and presents the risk of side effects that primarily compromise QOL. Any adverse events are readily reversible with cessation of the medication. Third-line treatment with intradetrusor onabotulinumtoxinA is invasive and presents risks for infection as well as increased PVR and the potential need for self-catheterization, which is not quickly reversible. Various neuromodulation therapies (PTNS, SNS) 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. 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 pharmacologic therapies. Failure and/or the experience of adverse events with one medication should usually be addressed by trying at least one other medication before third-line therapies are considered. In select patients who are unable or unwilling to comply with pharmacologic management, third-line therapies of neuromodulation (PTNS, SNS) 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.

It should be duly noted that, as mentioned above, every patient does not need to proceed through each line of therapy before considering the next. In other words, the lines of therapy, while representing a successive increase in risk or invasiveness, are not intended to represent a strict algorithm. This is specifically relevant with regard to PTNS, as it is the opinion of the Panel that, given the minimally invasive and reversible nature of this therapy, juxtaposed with the potential side effects and cost of medications, PTNS can be considered in drug-naïve patients who opt to forego pharmacotherapy.

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*

Initiating treatment for OAB generally presumes that the patient can perceive an improvement in his or her QOL. 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*

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 QOL, 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 (PFMT) 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, PFMT 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 (Evidence Strength Grade B)*

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 QOL. The literature provides clear support for the effectiveness of bladder training (incremental voiding schedules done with distraction and self-assertions)[41,42] and behavioral training (PFMT with urge suppression techniques).[53] 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 six-month behavioural 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 UUI 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 PFMT 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 pharmacologic management. *Recommendation (Evidence Strength Grade C)*

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] In the Panel's judgment there are no known contraindications to combining pharmacologic management and behavioral therapies. 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 or oral β3-adrenoceptor agonists as second-line therapy. *Standard (Evidence Strength Grade B)*

Anti-muscarinic medications. 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

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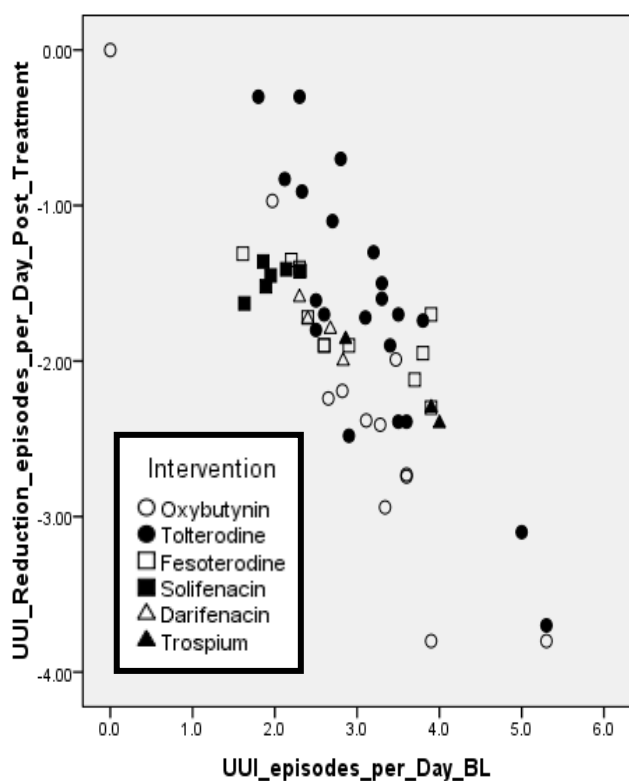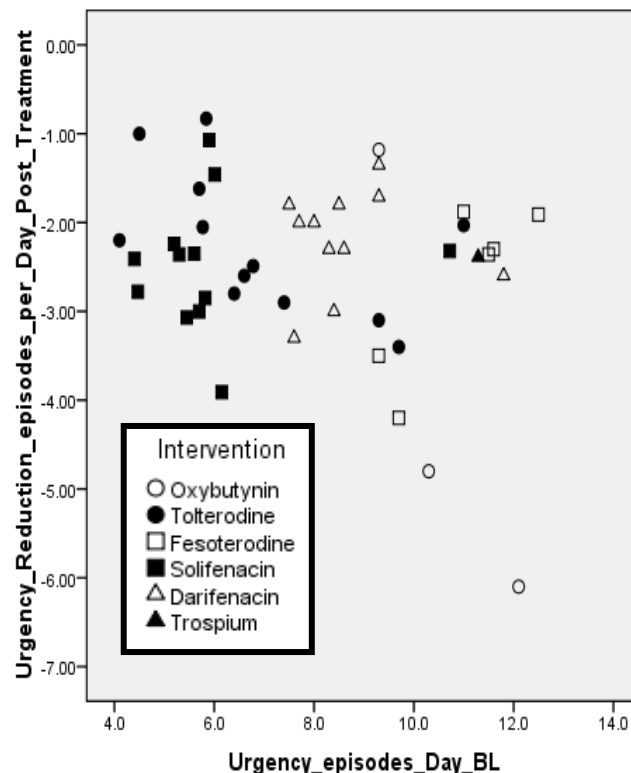
For urgency and nocturia, however, there was no apparent relationship between baseline symptom levels and symptom reduction (See Figure 2 for urgency data).

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.

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

β3-adrenoceptor agonists: Mirabegron. The 2014 update literature review retrieved a newly-published set of studies that evaluated the benefits and risks/burdens of mirabegron, a β3-adrenoceptor agonist, for overactive bladder. Seven studies evaluated mirabegron in comparison to a placebo group and/or an active control group[130-136] in a total of 9,310 patients; 5,884 of these patients were in the mirabegron groups. For the five studies that used an active control group, the active control was tolterodine ER 4 mg. Five studies were Phase III trials evaluating safety and efficacy. One study was a Phase II proof-of-concept study,[136] and one study was a Phase II dose-ranging trial.[135] Five studies followed patients for 12 weeks. The proof-of-concept study followed patients for four weeks.[136] One of the Phase III trials followed patients for one year.[133] Inclusion criteria were similar across studies, generally requiring patients to have OAB symptoms for ≥ three months, ≥ eight voids/day, and at least three urgency episodes over a three-day period. Patient ages were similar across studies, ranging from mean 55.4 years to mean 61 years. All studies used a two-week single-blind placebo run-in period. Baseline symptom levels were remarkably similar across studies, with baseline voids/24 hours ranging from mean 10.9 to mean 12.3, baseline incontinence episodes ranging from mean 2.4 to 3.6 but with all but one study arm in the 2.4 to 3.0 range, and baseline UUI episodes ranging from 1.7 to 3.5 but with all but one study arm in the 1.7 to 2.7 range. Only two studies measured urgency episodes, and patients ranged from mean 4.1 episodes per day to

mean 6.6 episodes per day.[134,136] The same two studies also reported nocturia outcomes; at baseline patients had mean 1.7 to 2.1 episodes per night.

All studies focused on voids per day and incontinence episodes. Some studies also reported urge urinary incontinence, urgency episodes, and nocturia. Most studies included some measure of QOL (e.g., Treatment Satisfaction-Visual Analogue Scale, Patient Perception of Bladder Condition, OAB-q). In general, most mirabegron doses produced statistically significant symptom reductions for voids per day and incontinence episodes per day compared to placebo. Improvements in UUI, urgency episodes, and QOL measures also occurred but were not as consistently statistically significant. Among studies with an active control group administered tolterodine ER 4 mg/daily, mirabegron generally performed similarly to tolterodine. Higher doses of mirabegron did not produce greater effects.

Pooled analyses and meta-analyses. Nitti Khullar et al.[137] (2013) reported findings from a pre-specified pooled efficacy and safety analysis using data from the USA/Canada Phase III trial,[131] the Europe/Australia Phase III trial,[130] and the Europe/USA/Canada Phase III trial.[132] Mirabegron at doses of 50 and 100 mg once daily significantly reduced incontinence episodes per day (50 mg: -1.49 [95% CI -1.63 to -1.36]; 100 mg: -1.50 [95% CI -1.67 to -1.34]) and number of voids per day (50 mg: -1.75 [95% CI -1.89 to -1.61]; 100 mg: -1.74 [95% CI -1.91 to -1.56] compared to placebo incontinence episodes: -1.10 [95% CI -1.23 to -0.97]; voids per day: -1.20 [95% CI -1.34 to -1.06]) at 12 weeks of treatment. Significant improvements in mean voided volume/micturition, mean level of urgency, mean number of urgency episodes (grade 3 or 4)/day, mean number UUI episodes per day, and mean number nocturia episodes per day also were noted for both doses compared to placebo. The proportion of patients reporting zero incontinence episodes was significantly higher in the mirabegron groups (50 mg: 44.1%; 100 mg: 46.4%) compared to placebo (37.8%). Efficacy in

patients who had used anti-muscarinics compared to treatment-naïve patients was similar across doses. The 25 mg dose significantly reduced frequency and incontinence episodes but generally not other endpoints. The 50 and 100 mg doses also significantly improved ratings on the Treatment Satisfaction-VAS compared to placebo. There was no dose-response gradient for the 50 mg dose compared to the 100 mg dose with both doses producing similar effects. Cui (2014)[138] reported findings from a meta-analysis as standardized mean differences (SMDs) between mirabegron groups collapsed across dose and placebo groups. The SMDs were (statistically significant at p <0.05 unless otherwise noted): number of incontinence episodes per day: -0.44 (95% CI -0.86 to -0.12); voids per day: -0.62 (95% CI -0.89 to -0.25); urgency episodes per day: -0.60 (95% CI -0.85 to -0.36); nocturia episodes per day: -0.12 (95% CI -0.23 to -0.01); TS-VAS: 0.75 (95% CI 0.45 to 1.05; non-significant); OAB-q: -5.34 (95% CI -7.11 to -3.57); PPBC: -0.20 (95% CI -0.33 to -0.07).

Additional useful information is provided by a report from the National Institute for Health and Care Excellence (NICE 2013) that evaluated the mirabegron evidence in preparation for making recommendations to United Kingdom practitioners.[139] NICE performed a mixed treatment comparison analysis – a Bayesian statistical procedure that combines data across trials and compares treatments that were never tested head-to-head. NICE concluded that all medications, including mirabegron, have similar efficacy to reduce frequency. With regard to incontinence episodes, mirabegron and other medications also were similar with the exception of solifenacin (5 and 10 mg), which was statistically significantly more effective. However, NICE notes that the size of differences across medications was small. The Panel interpreted these findings to indicate that, in general, mirabegron has similar efficacy to the anti-muscarinics.

Selected Adverse Events from Pooled Phase III Trials*					
AE	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg
Dry mouth	1.6%	1.6%	0.9%	2.2%	9.5%
Constipation	1.4%	1.6%	1.6%	1.6%	2.0%
Hyperten-sion	4.6%	6.9%	4.7%	3.4%	6.1%
Headache	1.3%	0.9%	2.0%	1.3%	2.2%
UTI	1.8%	4.2%	2.9%	2.7%	2.0%
*from Nitti, Khullar 2013					

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The pooled safety analysis of the three Phase III trials[137] reported that overall rates of treatment-emergent adverse events (TEAEs) were similar across groups (Placebo: 47.7%; 25 mg mirabegron: 48.6%; 50 mg mirabegron: 47.1%; 100 mg mirabegron: 43.3%; tolterodine ER 4 mg: 46.7%) without evidence of a dose-response relationship across the mirabegron groups. The incidence of serious adverse events was similar across groups: placebo -2.1%; mirabegron 25 mg – 1.6%; mirabegron 50 mg – 2.1%; mirabegron 100 mg – 2.8%; and tolterodine ER 4 mg – 2.2%. The proportion of patients withdrawing from the studies for medication adverse events also was similar across groups: placebo – 3.3%; mirabegron 25 mg – 3.9%; mirabegron 50 mg – 3.9%; mirabegron 100 mg – 3.7%; and tolterodine ER 4 mg - 4.4%.

Detailed adverse events are reported in Nitti, Khullar137 (2013) (see table below). Generally, rates of adverse events were similar across groups with the exception of dry mouth, which was higher for the tolterodine ER 4 mg group. Changes in blood pressure and pulse rate were minor and comparable across groups, although pulse rate increases were dose-dependent across the mirabegron groups (from 0.6 to 2.3 beats per minute with increasing dose). In comparison, the tolterodine groups exhibited increases of 1.0 to 2.1 beats per minute. Rates of tachycardia were less than 5% in each group and comparable to placebo rates.

The meta-analysis reported by Cui[138] (2014) indicated that rates of hypertension, cardiac arrhythmias, and urinary retention in mirabegron-treated patients were indistinguishable from rates in placebo groups. Chapple[133] (2013) reported adverse events during a 12-month trial of mirabegron (50 and 100 mg) compared to tolterodine ER 4 mg. Rates of adverse events were generally similar across groups with the exception of dry mouth, which was higher in the tolterodine group. Blood pressure changes were minimal (< 1 mm Hg) as were pulse rate changes (< 2 beats per minute). Below are selected adverse events from Chapple[133] (2013).

Additional useful information is provided by Malik (2012), [140] which reports findings from a randomized, double-blind, placebo- and active-controlled study of mirabegron effects on cardiac repolarization in healthy volunteers. The active control was moxifloxacin. Continuous ECGs were recorded during crossover treatment with once-daily 50, 100, or 200 mg mirabegron or a single 400 mg dose of moxifloxacin (each participant exposed to only one daily dose). Mirabegron did not prolong the QT interval at the 50 mg and 100 mg doses but did result in prolongation at the 200 mg dose in females only (>10 msec from 30 min post-dose to 6 hours post-dose).

The MTC presented by NICE (NICE 2013) further indicates that the probability of dry mouth and constipation were statistically indistinguishable for mirabegron compared to placebo.[139] All of the anti-muscarinics had a significantly higher probability of dry mouth compared to mirabegron 50 mg. Mirabegron was similar to most anti-muscarinics in terms of risk of constipation except for solifenacin (5 mg and 10 mg), fesoterodine (8 mg) and trospium (60 mg), all of which had a higher risk of constipation.

Overall, the Panel interpreted the mirabegron data to indicate that mirabegron appears to be similar in efficacy to the anti-muscarinics and has lower rates of dry mouth than any of these medications. Mirabegron may produce lower rates of constipation than some of

Selected Adverse Events From 12-month mirabegron trial*			
AE	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg
Any AE	59.7	61.3	62.6
Hypertension	11.0	10.1	10.6
Cardiac arrhythmia	3.9	4.1	6.0
Corrected QT interval prolongation	0.4	0.2	0.4
Constipation	2.8	3.0	2.7
Dry mouth	2.8	2.3	8.6
UTI	5.9	5.5	6.4
Dizziness	2.7	1.6	2.6
*From Chapple (2013)			

the anti-muscarinics. This lower incidence of bothersome adverse events may inform the selection of medications for patients who already present with dry mouth (e.g., secondary to Sjogren's syndrome) and/or constipation or for patients who experience efficacy from the anti-muscarinics but cannot tolerate these adverse events.

The body of evidence strength for the benefits and risks/burdens of mirabegron is Grade B. The available RCTs appear to have been well-conducted and evaluated large numbers of patients. However, follow-up in most studies is limited to 12 weeks, the magnitude of symptom reductions is relatively modest, and the patients in most trials cluster on the lower end of OAB symptomatology. These limitations result in uncertainty regarding long-term use of mirabegron in broader patient populations, particularly those with more severe OAB symptoms. In addition, there are no data on the use of mirabegron in patients with significant comorbidities, such as cognitive impairments, glaucoma, or uncontrolled hypertension. Clinicians should be cautious in management of these potentially vulnerable patient groups and engage in regular monitoring for adverse events. Further, there is no information regarding whether patients are more likely to adhere to mirabegron than to the anti-muscarinics.

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 (Evidence Strength Grade B)*

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 versus 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, 141] 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.[142, 143] 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 versus 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 or gel) may be offered. *Recommendation (Evidence Strength Grade C)*

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, 145, 147] One trial with a placebo control group evaluated oxybutynin chloride topical gel.[146] 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.[145] 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.[147] 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).[146] Newman (2010) reported on the same patients and noted that treatment with gel improved health-related QOL measures more than did treatment with placebo.[148]

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.[145] 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).[147] 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.[146]

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 or a β3-adrenoceptor agonist may be tried. *Clinical Principle*

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[149-151] or oxybutynin[151, 152] reported better efficacy and/or more acceptable adverse event profiles with fesoterodine,[149] solifenacin[150, 152] or darifenacin.[151] 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. Further, clinicians may also switch patients to a β3-adrenoceptor agonist (e.g., mirabegron) given an efficacy profile that appears similar to the anti-muscarinics and a relatively lower adverse event profile.

Guideline Statement 12.

AUA/SUFU Guideline

Overactive Bladder

Clinicians may consider combination therapy with an anti-muscarinic and β3-adrenoceptor agonist for patients refractory to monotherapy with either anti-muscarinics or β3-adrenoceptor agonists. *Option (Evidence Strength Grade B)*

The 2019 update literature review uncovered a number of studies looking at combination therapy for the treatment of OAB. Typical pharmacotherapy options for the management of OAB include both anti-muscarinics and β3-adrenoceptor agonists. While these therapies have different mechanisms of action, co-administration appears to have no noticeable effects on pharmacokinetics.[153] Further, studies have demonstrated improved efficacy with combination therapy without any significant effect on the safety profile when compared to monotherapy. While the strongest evidence for combination therapy comes from the SYNERGY I/II[154,155] and BESIDE[156] trials, which utilized solifenacin (5 mg) and mirabegron (25 or 50 mg), additional combinations utilizing various other drug classes and dosing schedules have been tested and are discussed below. At this time, the Panel feels that such data are less robust; as such, more data will be required before such additional combinations can be recommended.

In the 18-week SYNERGY trial, Herschorn et al. (2017) [154] randomized 3,398 wet OAB patients (77% women) to solifenacin (5 mg) plus mirabegron (25 mg), solifenacin (5 mg) plus mirabegron (50 mg), placebo, mirabegron (25 mg) monotherapy, mirabegron (50 mg) monotherapy, or solifenacin (5 mg) monotherapy in a 2:2:1:1:1:1 ratio. While the solifenacin/mirabegron 50 mg group was superior to solifenacin monotherapy for mean adjusted difference in UI episodes per 24 hours (-0.20, 95% CI -0.44 to 0.04, P= 0.033), statistical superiority was not seen versus mirabegron 50 mg monotherapy (-0.23, 95% CI -0.47 to 0.01, P= 0.052). In secondary analyses, all active treatment groups showed greater improvements in UI episodes per 24 hours versus placebo (nominal P values all <0.05). Effect sizes for the combined therapy groups (solifenacin/mirabegron 25 mg: -0.70; solifenacin/mirabegron 50 mg: -0.65) were higher than those obtained with monotherapy (range -0.37 for mirabegron 25 mg to -0.45 for solifenacin 5 mg). All active treatment groups had greater improvements in the mean numbers of micturitions per 24 hours versus placebo, with effect sizes for the combined therapy groups (solifenacin/mirabegron 25 mg: −0.85; solifenacin/mirabegron 50 mg: −0.95) higher than with mirabegron monotherapy (25 mg: −0.36; 50 mg: −0.39) and solifenacin 5 mg (−0.56). Researchers noted that the combined solifenacin/mirabegron 50 mg group was statistically significantly superior to both monotherapies at end of treatment for UUI episodes, urgency episodes and nocturia, with effect sizes that

appeared to be additive. Adverse events including dry mouth, constipation, and dyspepsia, were slightly increased in the combination therapy groups compared to monotherapies. Additionally, events indicative of urinary retention were reported more frequently in the combination groups compared to monotherapy and placebo.

In the follow up SYNERGY II trial, Gratzke et al. (2018) [155] evaluated the safety and efficacy of combination therapy over 12 months. The trial randomized 1,829 wet OAB patients (80% women) to combination 5 mg solifenacin plus 50 mg mirabegron, solifenacin monotherapy, mirabegron monotherapy, or placebo. The primary objective was safety as measured by TEAEs; additionally, efficacy was measured as the change from baseline to the end of treatment in the mean number of incontinence episodes and micturitions per 24 hours. Adverse events were reported more frequently in the combination group (49%) than in the mirabegron group (41%) or solifenacin group (44%), with dry mouth being the most commonly reported TEAE. Combination therapy was statistically superior to mirabegron and solifenacin monotherapy for decreasing number of incontinence episodes (mirabegron, p<0.001; solifenacin, p=0.002) and micturitions (mirabegron, p<0.001; solifenacin, p=0.004).

Drake et al. (2016)[156] in the BESIDE trial evaluated the efficacy, safety, and tolerability of combination therapy (solifenacin 5 mg plus mirabegron 50 mg) versus monotherapy (solifenacin 5 or 10 mg) in a 1:1:1 randomized trial for OAB patients remaining incontinent after 4 weeks of solifenacin 5 mg. A total of 2,174 patients were randomized (83% women). At end of treatment, combination therapy was found to be superior to solifenacin 5 mg, with significant improvements in daily incontinence (p = 0.001), daily micturitions (p < 0.001), and incontinence noted in a 3-day diary (p = 0.014). Combination was noninferior to solifenacin 10 mg for key secondary end points, including a change from baseline to end of treatment in the mean number of micturitions per 24 hours and number of incontinence episodes noted in a 3-day diary at end of treatment. Combination was superior to solifenacin 10 mg for improving daily micturitions.

One RCT by Kosilov et al. (2018)[157] and one prospective cohort study by Kosilov et al. (2013)[158] evaluated combination solifenacin and trospium in women with OAB. The Panel notes that the doses of solifenacin and trospium utilized in the Kosilov et al. studies are higher than the standard recommended doses. The RCT randomized 312 women (60-83 years of age) to high dose solifenacin (20 mg/day) plus high dose trospium (60 mg/day), or a lower dose of solifenacin (10 mg/day) plus a lower dose trospium (30 mg/day), or placebo.[157] Following treatment, QOL parameters in

terms of the functional state of the lower urinary tract were improved compared with placebo, but with no differences between the higher dose and lower dose combination groups (p<0.05). The prospective cohort study was designed in two phases and included 229 women (65-77 years of age).[158] In the first phase all women received 60 mg trospium and 40 mg solifenacin daily, while in the second phase, defined as the maintenance phase, women were allocated to additional trospium plus solifenacin treatment, electrical stimulation of detrusor muscle, laser puncture using a helium-neon laser applied to acupuncture points, or placebo for one month. The study reported that maintenance with the combination therapy resulted in effective maintenance of clinical and urodynamic results for at least seven months, while electrical stimulation was less effective, and laser puncture was inefficient.

Another RCT by Ellington et al. (2016) evaluated combination tolterodine and intravaginal estradiol cream in 58 menopausal women.[159] Women were randomized to either oral tolterodine or estradiol cream for 12 weeks and then offered addition of the alternative therapy with follow-up at week 24 and week 52. Both monotherapies resulted in decreased symptom bother scores at 12 weeks when compared with baseline values. Following addition of the alternate therapy at the 12 week time-point, within group OAB symptom severity and HRQL scores remained improved significantly at 24 and 52 weeks from baseline, though it should be noted that only addition of tolterodine at 12 weeks to the estradiol group resulted in further significant improvement in the OAB-q symptom bother score and the HRQL scores above the single therapy effect noted at 12 weeks.

Finally, an RCT by Rovner et al. (2018)[160] compared a 3 month combination of oral desmopressin 25 µg plus 4 mg tolterodine with 4 mg tolterodine monotherapy in 106 women. When evaluating the overall population, combination therapy resulted in a non-significant reduction in nocturnal voids over monotherapy (p=0.112). In a subgroup of patients with nocturnal polyuria, combination therapy resulted in improved nocturnal void volume (p=0.034) and time to first nocturnal void (p=0.045).

Guideline Statement 13.

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*

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 versus 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 PVR 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 QOL, 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 14.

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*

One of the main limitations of anti-muscarinic therapy is that the majority of patients discontinue after a few weeks or months.[142, 144] Although there may be several factors involved in this decision, side effects are commonly cited as the reason for discontinuation.[143] 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 15.

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

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 16.

Clinicians should use caution in prescribing anti-muscarinics or β3-adrenoceptor agonists in the frail OAB patient. *Clinical Principle*

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[161] 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,[132-152,157,161-164] 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.[165, 166] 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.[166] In addition, polypharmacy is common in community dwelling patients who are frail,[167] 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 Panel further notes that presently there are no data on the use of β3-adrenoceptor agonists (e.g., mirabegron) in the frail patient, the patient with significant comorbidities, or the patient on multiple medications. The clinician should consider these possibilities in prescribing anti-muscarinics or β3-adrenoceptor agonists 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 pharmacologic management is not appropriate, behavioral strategies that include prompted voiding and fluid management may be helpful.

Guideline Statement 17.

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

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 4 to 8 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 pharmacologic therapy for longer periods, to combine

behavioral and pharmacologic therapies to achieve better efficacy, or to try alternate medications before judging that a patient is refractory.

Behavioral therapies present no risks to patients and medications 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: PTNS and Neuromodulation

In the patient who has failed behavioral and pharmacologic therapies or who is not a candidate for these therapies, onabotulinumtoxinA therapy, PTNS, or neuromodulation may be offered. The Panel 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 the alternate third-line treatment 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.

FDA-Approved

Guideline Statement 18.

Clinicians may offer intradetrusor onabotulinumtoxinA (100U) as third-line treatment in the carefully-selected and thoroughly-counseled patient who has been refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. *Standard (Evidence Strength Grade B)*

The Panel designated intradetrusor onabotulinumtoxinA treatment as a Standard in the thoroughly-educated and carefully-counseled patient with moderate to severe OAB symptoms because a body of moderate-quality evidence indicated sustained improvements in voiding and QOL outcomes and rates of adverse events that could compromise QOL or lead to serious illness were less likely to occur with use of the FDA-approved dose of 100U. The available literature on intravesical use of onoabotlinumtoxinA is reviewed below; the Panel focused its deliberations 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.

The original literature searches retrieved 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 that evaluated the effects of onabotulinumtoxinA in patients with non-neurogenic OAB who had inadequate symptom control with anti-muscarinics or intolerable side effects.[168-189] All studies reviewed evaluated onabotulinumtoxinA (BoTox R, Allergan, Inc., Irvine, CA) except for one[175] 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,[168,169] 200-300 U onabotulinumtoxinA,[170] or 50-300 U onabotulinumtoxinA.[169,184] The randomized trials without placebo control groups injected 100 U onabotulinumtoxinA into the suburothelial space, the detrusor or the bladder base[173] or injected 100 U onabotulinumtoxinA into the bladder body, bladder body and trigone or bladder base and trigone.[174] Significant reductions in incontinence episodes[168, 170, 174] and in urgency[171, 173, 174] 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).[170, 171, 173] 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),[170, 173] but the largest reductions were reported in Kuo (2007),[173] 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.[170] 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.[171] 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[190] and that QOL improvements and improved urodynamic parameters were restored in patients who required repeat injections.[191] 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.[173] 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.[169] Additional information on the same patients was provided by Rovner (2011).[184] 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 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[176,186] and two studies,[179, 180] which injected into the submucosa of the bladder wall. Jeffery (2007) injected 500 U of abobotulinumtoxinA into the detrusor.[175] As a group, the observational studies reported reductions in frequency, nocturia, pad use and incontinence; improvement in urodynamics parameters and improvement in QOL 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.[192]

The 2014 update literature review retrieved 27 new studies, including five randomized trials with placebo control groups,[131,193-196] two randomized trials with active control groups (Kuo 2011 – compared 100U in three different injection sites; AlTaweel 2011 – compared 100U to 200U in the detrusor),[197] and 20 observational studies.[198-217] Patient selection criteria were similar to those in the prior evidence (e.g., patients with moderate to severe baseline levels of UUI, incontinence, frequency, and urgency) and, in aggregate, the new randomized trials reported on

responses of 887 patients treated with BTX-A – more than double the number of patients in the active treatment groups from the prior randomized trials. The lack of long-term follow-up remains, with the largest trials reporting outcomes at 12 weeks. A few trials reported additional outcomes at longer intervals (e.g., AlTaweel 2011 – nine months; Denys 2012 – 6 months);[194,197] the general pattern is of diminishing effectiveness. With the exception of Kuo (2011) who compared injection sites, most studies injected into the detrusor.[208] In contrast to prior evidence, the most commonly used dose was 100U rather than 200U.

In general, most trials reported statistically significant improvements in measured voiding outcomes (UUI, incontinence, frequency, urgency, nocturia, pad use) and in QOL outcomes compared to placebo groups. Fowler (2012)[218] reported QOL data from the Dmochowski (2010)[169] dose-finding trial and noted that the I-QOL and KHQ exhibited significant improvement compared to placebo for all groups administered 100U or greater. Studies that measured urodynamics parameters also reported improvements (e.g., in maximum bladder capacity). Denys (2012)[194] compared placebo to 50U, 100U, and 150U; at three months post-procedure, >50% improvement in urgency and UUI was reported by 30% of placebo patients, 37% of the 50U patients, 68% of 100U patients, and 58% of 150U patients (sample sizes were <30 in each group; only the 100U group was statistically significantly different from placebo). The 100U and 150U groups exhibited significantly reduced frequency compared to placebo and this reduction persisted for 30 days in the 100U group and was still significant at 60 months for the 150U group. The number of patients who achieved complete continence at three months was significantly greater in the 100U group (55%) and the 150U group (50%) compared to the placebo group (11%). At five months post-treatment, these differences were maintained. Kuo (2011) compared injection of 100U into the bladder body, bladder body plus the trigone, and the bladder base plus the trigone and found no differences across injection sites in success rates (70 to 74% of patients in each group) or in reductions in urgency or UUI episodes.[208]

These outcomes occurred, however, in the context of high rates of adverse events in the active treatment groups in some studies. Rates of UTIs ranged from 3.6% to 54.5% with four of the RCTS reporting rates of >40.0% and Dmochowski (2010) reporting that rates generally increased with dose with rates ranging from 33.9% to 48.1% across active treatment groups.[169] The definition of elevated 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 10 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)[168] and one observational study (elevated PVR defined as 250 cc),[172] respectively. Rates of PVR increase were reported in 14 studies and ranged from 0% to 75% with half of these studies reporting rates of 43.0% or higher (Kuo 2011);[168,172,174,175,179,182,208] The proportion of patients who needed to perform self-catheterization was reported in 20 studies and ranged from 0% to 43% with six studies reporting rates higher than 20.0%.[168, 169, 171, 175-178] Increased PVRs and the need for self-catheterization persisted for six to nine months in some patients.[172, 175, 185] 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.[177] 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.[219] 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.

Additional useful information regarding efficacy and adverse events is provided by the large group of observational studies.

Diabetic patients. Wang (2013) reported on 48 type II diabetes mellitus (DM) patients compared to 48 non-diabetic age-matched control patients. These patients were older, on average, than in the randomized trials (DM patients mean age 73 years; non-DM patients mean age 72 y).[217] All patients had UDS-verified DO. Patients received 100U BTX-A in the suburothelial space and were followed at three and six months. At three months, frequency, UUI episodes, and PPBC scores had improved similarly in both groups; urgency episodes were reduced in both groups but not significantly. Success rates (defined as PPBC score improvement of two or more points) were statistically similar at 56% for DM patients and 61% for non-DM patients and remained at 6 months. DO disappeared in 56.3% of DM

patients and 47.8% of non-DM patients. After the six months point, success rates began to decrease. However, the DM patients had significantly higher rates of large PVR volumes (60.4%) and general weakness (10.4%) compared to the non-DM patients (large PVR – 33.3%; general weakness – 0%).

BTX-A in the frail elderly patient. Liao & Kuo (2013) reported on 166 patients, including 61 frail elderly (mean age 75.8 years), 63 elderly without frailty (mean age 75.7 years), and 42 younger patients (mean age 44.6 years).[206] Frailty was defined as age >65 years and three or more of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, low physical activity. Frail patients averaged 1.6 comorbidities, and 5.7 medications per day. All patients had idiopathic DO refractory to medications and persistent UUI/urgency. Patients received 100U of BTX-A injected into the suburothelial space. At three months, significant improvement had occurred in UUI and PPBC scores for all three groups and CBC and PVR also had increased significantly for all three groups. Success rates (defined as improvement of two or more points on the PPBC) were similar at three months (frail elderly – 83.4%; elderly – 91.2%; younger – 88.9%) and at six months across groups (frail elderly – 44.9%; elderly – 52.1%; younger – 49.4%). By 12 months post-injection, however, success rates among frail elderly were significantly lower at 6.82% then rates for elderly (22.3%) and younger patients (23.1%) and cumulative success rates (Kaplan-Meier analysis) also were significantly lower at follow-up to 15 months post-injection. Rates of acute urinary retention (AUR), straining to void, and hematuria were similar across groups. Frail elderly, however, were more likely to have a PVR >150 mL (60.7%) compared to elderly (39.7%) and younger patients (35.7%). Although the difference in AUR rates was not significant, the recovery period to spontaneous voiding was longer in frail elderly (median 3.5 months) compared to one and 0.5 months for elderly and younger patients respectively. Frail elderly also were more likely to report generalized weakness (6.6%) compared to elderly (0%) and younger patients (0%). Interestingly, the highest rates of UTI occurred among younger patients (28.6%) with lower rates among frail elderly (13.1%) and elderly (9.5%).

Long-term follow-up. Kuo (2011), Chen (2012), and Ke (2012) reported on the same group of 174 patients with idiopathic DO and UUI who received 100U BTX-A using various injection sites (e.g., detrusor or suburothelial injection in bladder body and/or bladder base including the trigone). Improvements of at least 2 points on the PPBC were designated as successes.[208,210,211] At three months, success rates were similar for males (79%) and females (80%), for patients aged 75 or older (80%) and younger patients (79%), and similar across different injection sites.

Patients were monitored for adverse events for up to 24 months. Adverse events included: AUR in 6.9%; PVR >150 mL in 46.6%; straining to void in 42%; gross hematuria in 9.8%; UTI in 15.5%; and general weakness in 3.4%.

Okamura (2013) reported on 17 patients (mean age 67 years) who received one injection of BTX-A 100U submucosally and were followed every month for one year.[212] Urgency episodes, UUI, and daytime frequency were significantly decreased up to 11 months post-injection. Measures of QOL were significantly improved for eight to ten months post-injection. Scores on a GRA measure demonstrated improvement above baseline for eight months. Median time to failure was 11 months but women had longer intervals to failure (11.7 months) compared to men (7.2 months). Two patients had a PVR >200 mL that resolved without the need for clean intermittent self-catheterization (CISC).

Granese (2012) reported on 68 female patients (mean age 56 years) who underwent an injection of BTX-A 100U into the detrusor and were followed for 12 months.[214] At baseline, patients had moderately severe symptoms (9.5 urgency episodes/day; 15.1 voids/day; 2.5 nocturia episodes/day; 5.7 incontinence episodes/day). Symptoms improved markedly up to six months and then began to decay although at 12 months symptom levels had not yet returned to baseline. The same pattern was evident with some urodynamic parameters (e.g., bladder compliance, detrusor contraction). QOL measures also exhibited long-term improvement. A subset of 20 patients elected to have a second injection at 12 months and improvements in most measured parameters again occurred (follow-up to 3 months). PVR > 100 mL with lower urinary tract symptoms was judged as indication for CISC. At one month post-injection, 35% of patients after the first injection and 40% of patients after the second injection required CISC. At two months post-injection, 22% of patients after the first injection and 25% of patients after the second injection required CISC. At three months post-injection, 3% of patients after the first injection and 1% of patients after the second injection required CISC. UTI rates were 6% (after first injection) and 5% (after second injection) but resolved after month one.

Repeated injections: injection intervals, discontinuation rates, and discontinuation reasons. Mohee (2012) reported on 137 patients (mean age 57.3 years; all patients had DO with a minority having neurogenic DO) with at least 36 months follow-up.[215] At the beginning of the study, patients with idiopathic DO were administered 200U of BTX-A (in the detrusor); later the dose was reduced to 100U as published literature emerged indicating lower doses had equivalent efficacy. Mean re-treatment interval was 8 months. Of 104 patients with idiopathic DO, 66% (n=69) stopped treatment with BTX-A. The only difference between patients who continued and those who discontinued was the presence of incontinence at baseline (patients more likely to discontinue) and age (patients aged <50 years more likely to discontinue). Reasons for discontinuation were evaluated for the group as a whole (104 with idiopathic DO; 33 with neurogenic DO); these were: primary failure -- patients who had a single injection without benefit -16.8%; secondary failure -- patients who had benefit from the initial injection but not after two or more - 11.7%; tolerability -- patients who stopped BTX-A for reasons other than efficacy (e.g., having to perform CISC, urinary retention, recurrent UTIs) - 55.9% with an additional 16 patients who had primary and secondary failure also citing tolerability issues as a reason for discontinuation. Tolerability issues consisted of worsening symptoms (4.8%), need for CISC (49.2%), recurrent UTIs (36.5%), and unable to perform CISC (9.5%).

Veeratterapillay (2014) reported on 125 patients (median age 53 years, all with DO including a minority of patients with neurogenic DO) who had two or more BTX-A 200U injections (2 injections – 125 patients, 3 injections – 60 patients, 4 injections – 28 patients, 5 injections – 14 patients, 6 injections – 3 patients, 7 injections – 3 patients, 8 injections – 2 patients).[216] The overall median interval between injections was 14.4 months. Mean intervals between injections were: 17.6 months between injections 1 and 2; 15.7 months between injection 2 and 3; 15.4 months between injections 3 and 4; and, 11.6 months between the 4th and all subsequent injections. Of the 125 patients, 17% did not respond to repeated injections and opted for other treatments (e.g., long-term catheterization, SNS, surgery). Approximately 26% of patients developed PVR ≥ 150mL with 91% of these episodes occurring with the first two injections and all occurring within the first three injections. Approximately 18% of patients developed recurrent UTI.

Dowson (2012) reported on 100 patients, 63 of whom had two or more injections (53 had two, 20 had three, 13 had four, 10 had five, 5 had six, 3 had seven, 1 had eight, 1 had nine and 1 had ten injections).[200] Significant reductions in frequency, urgency, and UUI were observed following each injection. The most common reasons for discontinuing injections were poor efficacy (13%) and the need for CISC (11%). CISC was needed by 35% of patients after the first injection; 21% developed UTIs. AUR occurred in one patient; two patients required indwelling catheters. One patient developed urosepsis after his third injection. Additional adverse events were bladder pain persisting >1 week (2 patients), flu-like symptoms for 1 week (1 patient), transient arm paresthesia (1 patient), and leg weakness (1 patient).

Abeywickrama (2013) reported on 33 female patients (mean age 59.3 years) with idiopathic DO who had up to three injections of Dysport.[198] Patients received 500U which was increased to 750U if symptoms returned within six months; location of injections was not specified. After each injection, significant improvements occurred in frequency, nocturia, mean voided volume, and maximum voided volume. Scores on the ICIQ also improved after each injection. The mean interval between the first and second injections was 15.2 months and between the second and third injections was 19.2 months (statistically significantly longer). About 10% of patients required CISC (3 of 33); two patients developed UTIs after each injection.

More information regarding adverse events. Jackson (2012) reported on 94 patients who had 200U of BTX-A injected into the detrusor.[204] Patients with idiopathic DO had similar success rates (81%) as patients without idiopathic DO (89%) (success defined as patient reporting symptom improvement). Post-injection, 29% of patients required CISC. Kanagarajah (2012) reported on 32 patients without idiopathic DO, 19 of whom had OAB-dry and 13 of whom had OAB-wet.[205] Patients had 100U or 150U of BTX-A injected into the detrusor. QOL measures improved significantly by 3 months post-injection (UDI-6, VAS scale). Frequency improved significantly among OAB-dry patients; UUI improved significantly among OAB-wet patients, dropping by more than 50%. Three patients who received 150U and one patient who received 100U developed large PVRs and required CISC. Five patients developed UTIs.

Injection location. Manecksha (2012) reported on 22 patients randomized to trigone-including versus trigone-sparing injections of 500U Dysport into the bladder wall.[207] Patients were followed for up to 26 weeks. Both groups exhibited improvement on the OABSS at 12 and 26 weeks; the urgency subscale also showed improvement at 6, 12, and 26 weeks. The size of the improvement, however, was greater in the trigone-including injected group. No patients developed vesicoureteral reflux and magnitude of PVR increase and rates of CISC (2 patients in each group) were similar.

Dysport. Irwin (2013) reported on 73 patients administered 250U of Dysport into the detrusor and suburothelium.[202] Significant improvements were documented in frequency, nocturia, urgency, UI, and on QOL measures. CISC was required after 16.8% of procedures (some patients had more than one injection), was discontinued after three weeks in four cases, after three months in five cases, but the remaining seven patients "continue to self-catheterise 5-24 months following BTX treatment (median 11 months)."

BTX-A versus Dysport. Ravindra (2013) reported on 207 patients (detrusor injections including the trigone), 101 treated with BTX-A (200U) and 106 treated with Dysport (500 U initially later dropped to 300U).[213] Both forms of BTX significantly reduced daily frequency, nocturia, and incontinence episodes. Patient groups reported similar global improvement rates (81% of BTX-A group; 90% of Dysport group). Therapeutic effects had similar durations (mean 10.7 months in BTX-A group; mean 10.9 months in Dysport group). However, adverse event rates differed significantly between the two preparations. Among BTX-A patients, 23% required CISC compared to 42% of patients administered Dysport. Among patients who received 300U Dysport, the CISC rate was 46%; the rate in the 500U group was 37%.

Patient satisfaction. Brubaker (2012) reported on the same patients evaluated in Dmochowski (2010; the dose-finding trial in the current guideline).[199] Responses on the PSTQ and assorted global assessment measures indicated that greater proportions of patients in the BTX-A groups attained their primary OAB treatment goal (34.5% to 65.3%) compared to those in the placebo group (23.7%). El-Azab (2013) reported on 31 patients who had either BTX-A injections (100 or 200U into the detrusor) or augmentation ileocystoplasty (AC) for refractory idiopathic OAB. Treatment satisfaction was measured with the OAB-SAT-q at three and six months post-procedure. The AC patients had significantly higher OAB-SAT-q scores than did the BTX-A patients. BTX-A patients cited the need for repeat treatments to maintain symptom control as a primary reason for dissatisfaction. Makovey (2011) reported on 85 patients who had 150 or 200U BTX-A injected into the detrusor.[209] All patients had failed anticholinergic medications either for lack of efficacy (57 patients) or because of intolerable side effects (28 patients). Success was defined based on patient-reported symptomatic improvement and was more likely to occur in patients who could not tolerate medication side effects (86%) compared to patients who did not experience medication efficacy (68%).

Presence of antibodies. Hegele (2011) reported on the presence of antibodies post BTX-A injection in 31 patients.[203] Eleven patients were treated once, 16 were treated twice, and four were treated three times. Blood was collected before and three months post injection. In five patients (16%) BTX-A antibodies were detectable. One of these patients had a strongly positive titer and experienced complete failure of the treatment. The other four had slightly positive titers; one patient had a poor response to the second injection. Authors speculate that the presence of antibodies is involved in poor treatment responses.

Systematic review. Cui (2013) reports a systematic

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review and meta-analysis of 12 randomized BTX trials for idiopathic OAB.[220] Their meta-analysis indicates that in trials that measured incontinence (Flynn 2009, Sahai 2009, Tincello 2012), the mean difference in incontinence episodes between BTX-treated patients (any dose) and placebo patients is -3.85 (95% CI -4.79 to -2.90).[170,171,196] The mean difference in frequency in trials that reported that outcome (Flynn 2009, Sahai 2009) between BTX-treated patients and placebo-treated patients is -5.13 (95% CI -7.86 to -2.39).[170,171] The relative risk ratio for CISC in BTX-treated patients compared to placebo-treated patients (based on data from Brubaker 2008, Denys 2012, Flynn 2009, Fowler 2012, Sahai 2009, Tincello 2012) was 5.25 (95% CI 2.47 to 11.16).[168,170,171,194,196,218] The relative risk ratio for UTI (using data from Brubaker 2008; Denys 2012; Flynn 2009; Fowler 2012; Tincello 2012) in BTX-treated patients compared to placebo-treated patients was 2.36 (95% CI 1.58 to 3.53). [168,170,194,196,218]

The Panel interpreted these data to indicate that onabotulinumtoxinA injections can improve moderate to severe OAB symptoms in the context of adverse events that could require secondary intervention (e.g., an untreated UTI, undiagnosed urinary retention). The Panel notes that at the FDA-approved dose of 100U some adverse events appear to occur less frequently. For example, rates of urinary retention in study arms that administered 100U were <20% compared to up to 43% in study arms administering higher doses. Similarly, the percent of patients requiring CISC who were administered 100U was generally less than 10% compared to up to 43% in studies using higher doses. The Panel judged that the benefits of BTX-A at the 100U dose in the carefully counseled patient outweigh its risks/burdens and designated it a Standard. The Panel notes that 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 B given a body of evidence constituted by randomized trials. Limitations of the available evidence include short follow-up durations in the best-designed studies (ranging from 4 to 12 weeks for the RCTs), the variability in doses and injection sites across studies, and adverse event reporting that was variable.

Guideline Statement 19.

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

In the original literature review, eight studies reported in ten publications assessed the efficacy of PTNS to treat OAB symptoms.[103, 109, 221-228] 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 QOL. 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, 221-223] Additional studies did not report raw voiding data but reported improvements in symptoms and QOL with treatment[229, 230] that ceased when treatment ceased.[229] 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 2014 update literature search retrieved eleven new publications that reported outcomes from nine studies, including one RCT (Finazzi-Agro 2010),[231] one randomized design (Souto 2014),[232] and seven observational designs. Patient inclusion criteria remain varied with some studies requiring frequency and nocturia and others requiring UUI. Although most studies reported outcomes at 12 weeks, several

reported longer-term findings. Peters (2013a, 2013b) reported findings in a group of responders from the SUmiT trial who continued with PTNS therapy for up to 36 months.[233,234] Yoong (2013) reported one-year findings for a group of PTNS responders.[235] Several other papers reported partial findings beyond the formal study end date (see text below). Sample sizes remained relatively small (range 14 to 60 patients) with most studies having fewer than 25 patients in each treatment arm.

The best quality evidence comes from Finazzi-Agro (2010), a double-blind RCT (placebo arm received stimulation for 30 sec in the gastrocnemius and the device was then turned off; all patients were told they may not experience sensation during treatment).[231] PTNS patients had twelve 30-minute sessions three times a week; placebo patients had the same number and duration of sessions but with only 30 sec of active current in the alternate muscle location. Patients in the PTNS group, but not in the placebo group, experienced statistically significant improvements in incontinence, frequency, voided volumes, and I-QOL scores. In the PTNS group, 71% were characterized as responders (defined as experiencing at least a 50% reduction in UUI episodes) compared to 0% in the placebo group. In Souto (2014), patients were randomized to three groups: PTNS, oxybutynin ER 10 mg/daily, and PTNS + oxybutynin ER 10 mg/daily.[232] PTNS patients had treatments twice a week, for 30 min, for 12 weeks. At 12 weeks, all three groups showed similar improvements in frequency, incontinence, nocturia, ICIQ-SF scores, ICIQ-OAB scores, and symptom bother scores. The authors followed patients after treatment cessation for another 12 weeks. At week 24, the oxybutynin group had significantly worse scores compared to week 12 on the QOL measures – but not the two groups that had PTNS. Frequency, incontinence, and nocturia data at 24 weeks were only reported as proportions of patients exhibiting these symptoms; it appears that the oxybutynin only group had decaying responses compared to the PTNS groups. Three additional observational studies (Ugurlucan 2013; Zhao 2011; Onal 2012) generally reported improvements in voiding parameters and QOL outcomes after five to 12 weeks of treatment.[236-238]

Treatment effects duration. Several studies focused on documenting the duration of treatment effects once treatment ceased (e.g., Marchal 2011; Sherif & Abdelwahab 2013; Arrabal-Polo 2012).[239-241] Using protocols that ranged from 12 weekly sessions to a protocol that used tapering session frequency over five to six months, these studies generally reported that treatment benefits were retained for four to six months once treatment ceased.

Longer-term outcomes in patients who undergo

maintenance treatments. Peters (2013a, 2013b) reported long-term outcomes for PTNS responders identified during the SUmiT trial who were willing to continue with therapy.[233,234] Patients in the SUmiT trial (Peters 2010) had 12 weekly PTNS treatments.[242] Responders received PTNS therapy in sessions that tapered during a transition phase: two treatments at 14-day intervals, two treatments at 21-day intervals; one treatment at a 28-day interval. After tapering, patients had a customized treatment plan in which PTNS sessions were prescribed based on patient report of increasing OAB symptoms. Throughout the 36 month follow-up period, patients reported significant improvements in frequency, nocturia, urgency episodes, and UUI. Scores on the OAB-q and HRQOL as well as symptom severity scores also remained significantly improved. Among study completers, patients received a median of 1.0 treatments per month (IQR 0.9 to 1.2) with 41% receiving <1 treatment/month, 55% receiving 1.0 to <2.0 treatments/month, and 4% receiving 2.0 to <3.0 treatments/month.

Yoong (2013)[235] also reported long-term follow-up data on a group of PTNS responders originally discussed in Yoong (2010).[243] Of the original 30 patients who reported positive responses defined as OAB symptoms no longer dominant, 50% reduction in frequency, and 25% reduction in IIQ-7 scores, 23 continued to receive maintenance treatments (30 min sessions). The sessions were scheduled by the patients when they felt they needed a treatment. At two years, frequency, UUI, nocturia, pad use, and IIQ-7 scores were statistically indistinguishable from those recorded after initial responses to treatment, indicating treatment effects had been maintained. Patients received a median 8.42 treatments per year and median time between treatments was 64.3 days.

Systematic reviews and meta-analyses. Since the completion of the original guideline, five systematic reviews assessing PTNS have been published.[244-248] In general, these reviews conclude that there is convincing evidence for the efficacy of PTNS in comparison to placebo or sham conditions, that from 37% to 100% of patients are reported to meet criteria for success (but success criteria varied across studies), and that adverse events are minimal. Burton (2012) also provided a meta-analysis.[245] When the randomized trials with placebo or sham control groups are considered, the relative risk ratio (RR) for successful treatment is 7.02 (95% CI 1.69 to 29.17); that is, PTNS patients were seven times more likely to report success compared to placebo patients. In an analysis that included prospective non-randomized trials, the pooled subjective success rate in PTNS patients was 61.4% (95% CI 57.5% to 71.8%; differing definitions of success) and the pooled objective success rate (based

on voiding parameters but also with different definitions of success) was 60.6% (95% CI 49.2 to 74.7%). In trials that compared PTNS to anti-muscarinics, there were no differences in efficacy. The authors conclude that PTNS significantly improves OAB symptoms, that the effects are similar in magnitude to anti-muscarinics, but that PTNS has a better adverse event profile. The primary weakness identified by this group of papers is the lack of long-term follow-up in a randomized design.

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 both during the initial treatment phase and to obtain maintenance treatments in order to achieve and maintain treatment effects. Reported adverse events were minor; the most frequently reported events were painful sensation during stimulation that did not interfere with treatment and minor bleeding at the insertion site. In the Panel's view, benefits outweigh risks/burdens for the use of PTNS in the thoughtfully-selected and counseled patient who is highly-motivated to make the required office visits.

As a group, the PTNS studies constitute Grade C evidence because of the predominant observational designs, varying patient inclusion criteria, small sample sizes, and short follow-up durations for most studies.

Guideline Statement 20.

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)*

In the original literature review 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.[249-261] 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.[252, 257, 260] 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.[250] An additional study reported on urodynamics outcomes for patients evaluated by Schmidt (1999) and noted that patients with UI, with and without DO, had similar improvements in urodynamic parameters.[256, 262] 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).[254] 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.[255] Approximately 63% of patients were able to maintain symptom improvement by using the on-demand procedure during the two-week test.

The 2014 updated literature review retrieved an additional 16 relevant treatment studies, including one prospective randomized multi-center trial,[263] one crossover study,[264] and 14 observational studies. Seigel (2014) reported findings at six months of follow-up for the InSite trial, an ongoing FDA-mandated post device approval study that included a subsample of patients randomized to SNS or to standard medical therapy (SMT; anti-muscarinic medications).[263] The study used a less invasive procedure than in older studies and also used the newer tined lead. A total of 147 patients were randomized (SNS – 70; SMT – 77) and 130 patients completed six months of treatment (SNS – 59; SMT – 71).

Siegel (2014) differs from the studies discussed above in that patients had less severe symptom levels at baseline (SNS: mean 11.2 voids/day; mean 2.4 incontinence episodes/day, mean 1.1 pads/day; SMT: mean 11.9 voids/day, mean 2.7 incontinence episodes/day; mean 1.5 pads/day).[263] In addition, the primary outcome was OAB therapeutic success defined as ≥50% improvement in average incontinence episodes/day or voids/day or a return to normal voiding frequency of <8 voids/day rather than change in voids or incontinence episodes. At 6 months, the OAB success rate was 61% in the SNS group compared to 42% in

the SMT group (p=0.02). In addition, <8 voids/day was achieved by 61% of SNS patients compared to 37% of SMT patients (p=0.04). The SNS group also improved more on the OAB-QOL than did the SMT group (p<0.001), SNS female patients reported a greater improvement in sexual function than did SMT female patients (p<0.05), and the SNS group exhibited greater improvements in Beck Depression Inventory scores than did the SMT group (p=0.01). However, limited information is reported regarding the intervention content of the SMT arm; the report notes only that 96.1% of SMT participants used OAB medications between randomization and the six month follow-up, that 70% used medication on at least 80% of the days during the follow-up period, and that some participants (proportion not specified) used more than one medication. Lack of information regarding medication use and that fact that patients had mild symptoms compared to most other SNS studies limits the interpretability of SMT outcomes compared to SNS outcomes.

The crossover study evaluated whether different stimulator settings altered outcomes.[264] Patients in this study had had an SNS implant with a tined lead for at least three months prior to study beginning and were refractory to conventional treatments including medications at the time of SNS implant. Settings were 5.2 Hz, 14 Hz, or 25 Hz and were maintained for one week. Numbers of incontinence episodes and pad changes were significantly affected by rate such that the 14 Hz and 25 Hz settings reduced these outcomes compared to the 5.2 Hz setting.

The observational studies evaluated a wide range of patient subgroups, clinical questions, and outcomes. More than half of the studies followed patients for one year or longer.

Testing phase outcomes. Davis (2013) reported success rates during the testing phase in patients who presented for SNS because of lack of medication efficacy or intolerable medication side effects.[265] Success rates at the testing phase were similar (70% and 71% respectively). Yazdany (2011) also reported on testing phase success in a group of patients with severe incontinence (mean 10.4 episodes/day); the authors note that patients with >10 incontinence episodes per day were more likely to have a successful stage I trial compared to those with less than 5 episodes/day.[266] Levin (2012) reported on the impact of obesity on stage I success rates.[247] Of 149 patients, 80 (53.7%) were obese (BMI mean 37.3) and 69 (46.3%) were non-obese (BMI mean 25.6). The overall stage I success rate was 81% and the success rates for non-obese patients (83%) was statistically indistinguishable from the success rates for obese patients (78%). Gleason (2013) reported on stage I SNS effects on

periurethral sensation and urethral sphincter activity.[267] Baseline urethral sensation did not differ between patients who were classified as stage I responders versus non-responders, however, responders had larger amplitude, longer duration, and more turns and phases at baseline, indicating more successful urethral re-innervation, than did non-responders.

Treatment phase outcomes. Lee (2013) compared motor and sensory responses to SNS and noted that patients with compound muscle action potential (cMAP) were more likely to report the sensation of stimulation than patients without cMAP.[268] Nineteen of 31 patients did not have cMAP. Of these, 16 were successfully reprogrammed to achieve cMAP, resulting in improvements in nocturia, incontinence, and UI that did not reach statistical significance. Cardarelli (2012) reported significant decreases in UUI episodes, frequency, nocturia, and pad use as well as significant increases in voided volumes at 48 weeks post-implant.[269] Moon (2013) evaluated patients with severe levels of UUI, frequency, and nocturia and reported at 12 months post-implant significant decreases in urgency episodes, UUI, frequency, nocturia, and in the severity of urgency episodes.[270] Various urodynamics parameters also improved as did scores on the OAB-q. Improvements were similar for patients with OAB-wet compared to OAB-dry. Yih (2013) reported on changes in sexual functioning in women after SNS implant.[271] At 12 months post-implant, FSFI scores improved significantly from mean 13.5 at baseline to mean 15.9 and ICSI-PI composite score improvements were similar among women with baseline FSFI scores of < 26 compared to ≥ 26.

Older patients. Angioli (2013) reported in patients >age 65 years (mean patient age 76 years) that at 12 months post-implant, 27.8% of patients reported improvement and 55.5% of patients reported complete success with cessation of UUI episodes.[272] Overall, UUI episodes decreased from mean 6.3/day to mean 0.5/day. Incontinence episodes, frequency, nocturia, and number of pads used daily also significantly decreased. All subscales of the OAB-q exhibited significant improvement. Peters Killinger (2013) compared patients aged 40 to 64 years with patients older than age 64.[273] Most of the patients in these two groups had OAB (a subset had IC or urinary retention). For both groups, incontinence episodes, frequency, urgency, nocturia, OAB-q scores, and ICSI-PI scores improved significantly at 26 weeks.

Patients with concomitant bowel dysfunction. Faucheron (2012) evaluated patients with both urinary and fecal incontinence.[274] At more than 5 years post-implant, UUI episodes (and fecal incontinence episodes) were significantly reduced. Approximately 74% of patients were satisfied with their improvements in both forms of

incontinence and all QOL measures also exhibited significant improvement (e.g., the Fecal Incontinence QOL measure and the Ditrovie score). Gill (2012) reported on patients with UUI of which 83% had concomitant bowel dysfunction (either constipation or fecal incontinence).[275] At 4 months post-implant, Likert scale ratings (patient perception of disease) were significantly improved from baseline and indicated that symptom severity and disease state had become "normal." UDI-6 and CRADI-8 scores also reflected significant symptom improvement. When patients were examined separately based on type of bowel dysfunction, the improvement in scores appeared to occur for the constipation group rather than the incontinence group.

Patients who discontinued BTX-A. Smits (2013) reported on a group of patients who had discontinued BTX-A therapy because of lack of efficacy (85%) or the desire for a treatment that was more permanent (15%).[276] The primary outcome was improvement in leakage, defined as greater than 50% improvement in leakage episodes and severity of leakage measured on a 1 to 4 scale. Secondary outcomes were improvement in frequency and urgency defined as greater than 50% improvement (measurement not specified but presumably also on a 1 to 4 scale). Mean interval between last BTX-A treatment and SNS test phase was 23 months. At one year post-implant, 11 of 14 patients (79%) reported satisfaction with treatment.

In contrast to PTNS studies, 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 (1.1 to 8.6% of patients), infection/irritation (2.2 to 14.30% of patients), electric shock (5.5 to 10.2% 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.[259] 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).[254]

Additional useful information is provided by Lai and Grewal (2013) who investigated the bacterial colonization rate of the connector and lead during staged testing.[277] During the stage II procedure, aerobic and anaerobic cultures were obtained by swabbing the connector pocket, the connector, and the permanent lead itself. Of 38 patients, 9 (24%) had a positive culture at the connector or lead site. Of the 9 patients with a positive culture, 3 (33.3%) subsequently developed device infection that required explant compared to 3% of patients who did not have colonization but who subsequently developed an infection. Longer percutaneous testing was associated with a greater colonization rate. Of 10 patients who underwent >14 days of staged testing, 50% developed connector and/or lead colonization. In contrast, only 4 (14%) of the 28 patients who had ≤ 14 days of testing developed colonizations.

Cameron (2013) reported on reprogramming and battery explant rates from 1997 to 2007 in a 5% sample of Medicare beneficiaries at mean follow-up 60.5 months.[278] Among OAB-wet patients and OAB-dry patients, during the first year there were mean 2.14 and 2.26 reprogramming events respectively. Reprogramming events declined over time; at the 5-year point, rates were 0.24 and 0.95 respectively. Explant rates for OAB-wet were 10.9% (32/294) and for OAB-dry 8.7% (10/115). In comparison, IC patients had an explant rate of 57.9%.

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 QOL 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.
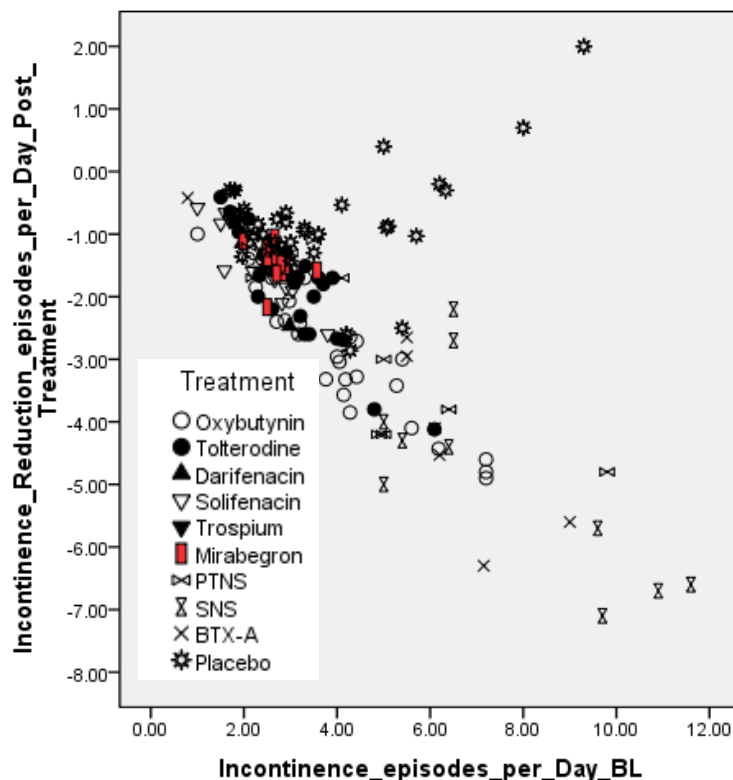
Guideline Statement 21.

Practitioners and patients should persist with new treatments for an adequate trial in order to determine whether the therapy is efficacious and

tolerable. Combination therapeutic approaches should be assembled methodically, with the addition of new therapies occurring only when the relative efficacy of the preceding therapy is known. Therapies that do not demonstrate efficacy after an adequate trial should be ceased. *Expert Opinion*

The Panel members note that they regularly encounter patients who present for second-line (pharmacologic management) or third-line treatments (BTX-A, PTNS, or SNS) who have never undergone a comprehensive evaluation (i.e., completion of a voiding diary to ensure the OAB diagnosis is correct) or who have never had a trial of behavioral therapy or who have had an inadequate trial of behavioral therapy. Similarly, it is not uncommon for patients to present for non-medical treatments who have not had an adequate trial of medications. On the other hand, the Panel also encounters patients who are being treated with multiple simultaneous therapies without clear evidence of the efficacy of the individual therapies or their combination. The Panel encourages practitioners and patients to persist with new treatments (4 to 8 weeks for medications and 8 to 12 weeks for behavioral therapies) for a sufficient duration to achieve clarity regarding efficacy and adverse events for a particular therapy before abandoning the therapy prematurely or before adding a second therapy. If a comprehensive
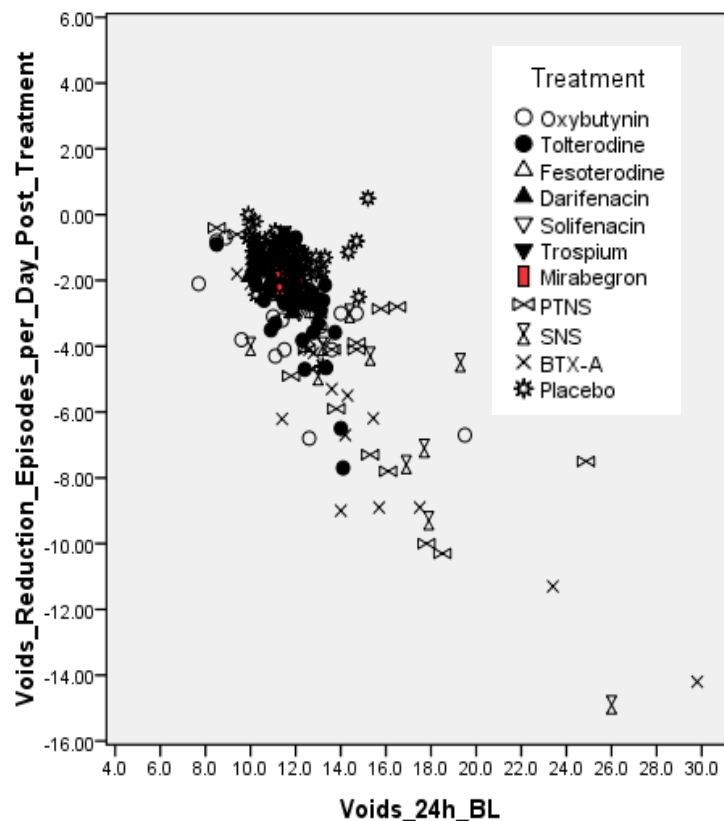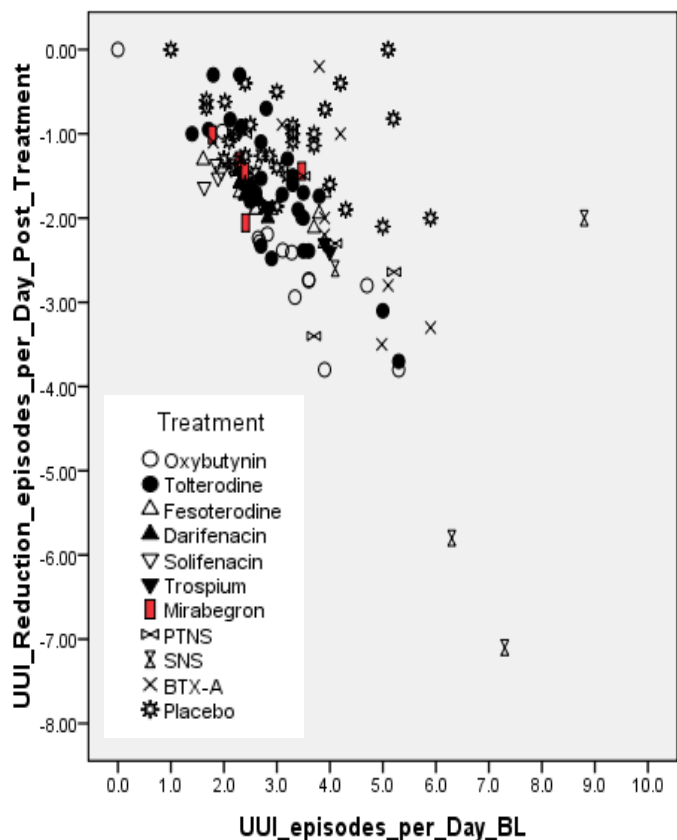
Fourth-Line Treatments: Augmentation Cystoplasty and Urinary Diversion

Guideline Statement 22.

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

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 QOL. There are substantial risks to these procedures, however, including the likely need for long-term intermittent self-catheterization and the risk of malignancy.[279] In the Panel's judgment, therefore, a surgical approach to OAB treatment is appropriate only in the extremely rare patient.

Additional Treatments

Guideline Statement 23.

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*

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.

Follow-Up

Guideline Statement 24.

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

Expert Opinion

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 QOL. 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 or mirabegron 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 QOL, then strategies to manage specific adverse events, such as ameliorating constipation with appropriate bowel management, should be implemented before abandoning anti-muscarinic treatment.

For peripheral tibial nerve stimulation and sacral neuromodulation, 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
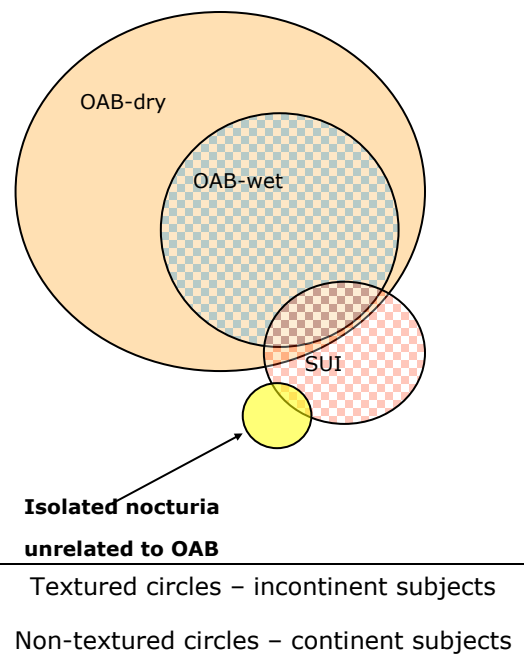
evaluated.

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 that 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.

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-understood. While not specifically targeting epidemiology of OAB, there are large community-based studies that assess

Isolated nocturia unrelated to OAB

Textured circles – incontinent subjects

Non-textured circles – continent subjects

prevalence of lower urinary tract symptoms and urinary incontinence.[280, 281] 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.[282, 283] 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.[284]

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[285] remains poorly assessed. As defined by IUGA/ICS,[4,27] "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;[286-288] 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.

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Further research is needed focused on therapy utilizing different combinations of anti-muscarinics and β3-adrenoceptor agonists as well as other drug classes looking at both efficacy and adverse effects. Further, the use of vaginal estrogen should be studied as a monotherapy for OAB as well as in combination with other therapies, including behavioral and pharmaceutical.

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,[289] corticotrophin releasing factor,[290] prostaglandins[291] and inflammatory factors such as C - reactive protein.[292] 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).[293] 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 CNS (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.[294, 295]

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 electrophysiologic testing as a research tool has been described both in asymptomatic and OAB individuals.[296-298] A recent review has also highlighted the potential interaction of the bladder urothelium, suburothelium and interstitial cells with the sensory afferent pathways.[299] 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.[300] 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.[301] A more complete understanding of sensory mechanisms could lead to novel OAB therapies.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AUA	American Urological Association
BOD	Board of Directors
CISC	Clean intermittent self-catheterization
cMAP	Compound muscle action potential
CNS	Central nervous system
DO	Detrusor overactivity
EPC	Evidence-based practice center
ER	Extended release
ICS	International Continence Society
II-Q	Incontinence Impact Questionnaire
IR	Immediate release
IUGA	International Urogynecological Association
MMSE	Mini-Mental State Examination
NICE	National Institute for Health and Care Excellence
OAB	Overactive bladder
OAB-q	Overactive Bladder Questionnaire
PFMT	Pelvic floor muscle training
PGC	Practice Guidelines Committee
PRO	Patient reported outcome
PTNS	Peripheral tibial nerve stimulation
PVR	Post-void residual
QOL	Quality of life
RCT	Randomized controlled trial
SNS	Sacral neuromodulation
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
TDS	Transdermal
TEAE	Treatment emergent adverse event
UDI	Urogenital Distress Inventory
UTI	Urinary tract infection
UUI	Urgency urinary incontinence

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AUA/SUFU Guideline

Overactive Bladder

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Conflict of Interest Disclosures

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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Disclaimer
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.

Funding of the committee was provided by the AUA and the Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Committee members received no remuneration for their work. Each member of the committee provides an ongoing conflict of interest disclosure to the AUA.

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.