CUA guideline on adult overactive bladder

Jacques Corcos, MD, FRCSC[1]; Mikolaj Przydacz, MD[1]; Lysanne Campeau, MD, PhD, FRCSC[1]; Jonathan Witten, MD[2]; Duane Hickling, MD, MSCI, FRCSC[3]; Christiane Honeine, RN, BN[1]; Sidney B. Radomski, MD, FRCSC[4]; Lynn Stothers, MD, MHSc, FRCSC[5]; Adrian Wagg, MD, FRCP (Lond), FRCP (Edin), FHEA[6]

[1]Department of Urology, Jewish General Hospital, McGill University, Montreal, QC; [2]Northern Alberta Urology Centre, Edmonton, AB; [3]Division of Urology, Department of Surgery, The Ottawa Hospital, Ottawa, ON; [4]Division of Urology, Toronto Western Hospital, University of Toronto, University Health Network, Toronto, ON; [5]Department of Urological Sciences, University of British Columbia, Vancouver, BC; [6]Department of Medicine, University of Alberta, Edmonton, AB; Canada

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Introduction

The overactive bladder (OAB) picture has dramatically changed in the last 20 years. A quarter century ago, this symptom complex did not even exist. Bladder hyperactivity and urgency incontinence were separate entities poorly understood and treated only with the first-generation antimuscarinic medications, propantheline and oxybutynin. Only in early 2000 came the concept of this syndrome made of four intimately linked symptoms that we today call OAB. With this concept, new pharmacological agents were launched. These new agents may have not dramatically improved symptoms in comparison with older agents, but undeniably have a more tolerable side effect profile, leading to better compliance and adherence. Neuromodulation was introduced a few years later, giving hope to the worst OAB cases, but with a limited applicability due to its cost. A real revolution occurred around 2010 with the demonstration of onabotulinumtoxinA's efficacy in controlling the symptoms of OAB. Several years passed before it proved its place in the treatment algorithm for OAB. It is definitely time for the Canadian Urological Association (CUA) to produce guidelines to help Canadian urologists better integrate a sequence of investigation, diagnosis, and treatment, which has become more complex over the years.

To do so, the CUA gave a group of experts, Canadian physicians and nurses, the difficult task of putting together a comprehensive document to guide all interested professionals in the management of this interesting and common syndrome, which has so much impact on our patients' quality of life.

An executive summary of the CUA guideline on OAB is available as an Appendix at *www.cuaj.ca*.

Methodology

A comprehensive review of OAB studies was performed using PubMed, MEDLINE, and the Cochrane Library databases. In addition, the bibliographies of all relevant articles were searched to avoid exclusion of significant articles. Focus was on systematic reviews, meta-analyses, and evidence-based recommendations, when available. Data from the latest consensus of the International Continence Society (ICS), the American Urological Association (AUA), the European Association of Urology (EAU), the National Institute for Health and Care Excellence (NICE) were incorporated. All articles were reviewed using the evidence-based medicine levels, with the Oxford grading system for recommendations.[1] Where the literature was inconsistent or scarce, a consensus expert opinion was generated to provide appropriate guidelines.

Definitions and epidemiology

In presenting the epidemiology of OAB, it should be noted that no level 1, grade A data exist since most studies incorporate only surveys in large numbers.

Definitions

According to the ICS definition, OAB consists of urinary urgency with or without urgency urinary incontinence (UUI), often accompanied by frequency and nocturia, in the absence of urinary tract infection (UTI) or other obvious pathology.[2,3] The primary urodynamic abnormality underlying OAB is detrusor overactivity (DO). Lower urinary tract storage symptoms include OAB symptoms (urgency, urgency incontinence, frequency, and nocturia) and stress incontinence. Voiding symptoms include slow and/or interrupted stream, terminal dribble, hesitancy, and straining. The ICS defines urinary frequency as the patient complaint of urinating too often during the daytime.[2,3] The ICS definition of nocturia is one or more voids per night, preceded and followed by sleep. Urgency is the complaint of a sudden, compelling desire to pass urine that is difficult to defer. Urgency incontinence is the involuntary leakage of urine accompanied or immediately preceded by urgency. These standard definitions are, in places, controversial. Frequency has conventionally been considered as voiding ≥8 times per 24 hours.[4] Many clinical trials assessing the success of OAB medications have used this definition. Some of the epidemiological data presented below also have examined this definition. Along the same lines, many experts believe that one episode of nocturia per night may be considered normal.[5] As a result, nocturia of two or more times may be a more realistic determinant of significant symptoms and bother. The data presented below will incorporate both definitions.

Epidemiology

Although the overall prevalence of OAB is similar between men and women, there are sex-specific differences in the prevalence of various symptoms within the OAB complex.[6,7] Anatomical and physiological differences in the lower urinary tract of males and females may help to explain these variations.[7] Overall, OAB prevalence rates in large population-based studies range from 7–27% in men and 9–43% in women.[8-15] Interestingly, a proportion of OAB cases (37–39%) remit during a given year, but the majority of patients have persistent symptoms.[16,17]

The EPIC study is one of the largest population-based surveys that examined the prevalence of lower urinary tract symptoms (LUTS) and OAB. The study had over 19 000 participants and showed an overall OAB prevalence of 11.8% (10.8% in men and 12.8% in women) using ICS definitions.[12]

The National Overactive Bladder Evaluation (NOBLE) study estimated the prevalence of OAB, including the influence of sex on OAB and its symptoms, again using ICS definitions.[13] Furthermore, it focused on the impact of OAB on quality of life, sleep, and general mental health. Out of over 17 000 households that were contacted, 5204 participants completed the interview. The NOBLE study showed an overall OAB prevalence of approximately 16%, with no significant differences between the two sexes (16% in men, 16.9% in women). The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) survey was a population-based, cross-sectional survey conducted to evaluate the prevalence and bother of OAB, as well as to update the results of the NOBLE survey done in 2003.[10] In contrast to the EPIC and NOBLE studies, the EpiLUTS survey used symptoms that were defined as "sometimes." Using this definition, the study found the overall prevalence of OAB was 35.6%. When defined as "often," the overall prevalence decreased to 24.7%. Milsom et al also conducted a population-based study using specific definitions of symptoms of OAB, as well as stress incontinence and prostatic obstruction (these were not ICS definitions).[15] Similar to the NOBLE study, Milsom's group found an overall prevalence of OAB symptoms of 16.6%. The overall prevalence of OAB in a Canadian population was estimated to be 18.1% (14.8% in men, 21.2% in women) by Corcos and Schick.[9] More recently, Herschorn et al reported OAB symptoms in 13.9% of respondents (13.1% of men, 14.7% of women) in a Canadian population-based study.[14]

The prevalence of OAB symptoms increases with age in both sexes.[12,13,16] The EPIC study showed that among participants aged 40–59 years, 51% of men and 56% of women experienced storage symptoms.[12] Thirty eight percent of men and 49% of women under 39 years of age also experienced storage symptoms. In the NOBLE study, UUI increased with age in both sexes, increasing from 2% to 19% in women after the age of 44 years and 0.3% to 9% in men, with a marked increase after 64 years.[13] While there is a steady increase with age of OAB with UUI in women throughout their lifetime, the main increase in the prevalence of OAB with UUI in men only occurs after the age of 65 years. In contrast, the prevalence of OAB without UUI has a statistically significantly steeper age-related increase in men than in women. This increased in men from 8.5% in those less than 45 years of age to 21.8% in men after 55 years. In women, OAB without UUI increased gradually and reached a plateau after the age of 44 years. Similarly, the prevalence of OAB symptoms in men increased slowly until the age of 70, but then had a sharp increase after 75 years of age, with a slight fall in prevalence between the ages of 70–75 years.[15] In women, there was also a gradual increase seen until the age of 60, with a leveling off seen between 60 and 70 years of age and a gradual increase in prevalence thereafter. In the Canadian study by Herschorn et al, OAB symptoms were also more common with increasing age (23.8% for >60 years old vs. 12.2% for <60 years old.).[14]

The NOBLE study found that while the prevalence of OAB with and without UUI in women was similar (9.3% and 7.6%), in men the prevalence of OAB with UUI (2.6%) was much lower than the prevalence of OAB without UUI (13.4%).[13] Both the EpiLUTS and Milsom studies reported UUI to be more prevalent in women.[10,15] Nevertheless, these surveys largely excluded older persons living in institutions.

When examining individual symptoms, the prevalence may vary depending on the OAB definition used. In the EPIC study, using the ICS definition of nocturia as one or more voids per night, the general prevalence of nocturia was 48.6% in men and 54.5% in women.[5] In the same study, when nocturia was defined as two or more voids per night, the prevalence decreased to 20.9% in men and 24.0% in women.

Most patients have a combination of OAB symptoms. In the EPIC study, approximately 50% of OAB patients had a combination of two symptoms and approximately one-third of patients reported a combination of three OAB symptoms.[5] The EpiLUTS study also found that isolated symptoms were rare in OAB. At the other end of the spectrum, urgency, UUI, frequency, and nocturia together were found in 16% of men and 20% of women in the study.[10]

Several studies have shown an association between OAB and bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH) recognizing them as common comorbid conditions ***(Level of evidence 1b, Grade B)***.[18] Up to 50% of men with BOO are estimated to have OAB symptoms.[19,20] Some studies have noted that 50% of men with LUTS and urodynamically confirmed BOO have DO.[21] OAB symptoms may develop secondary to BOO.[22] Men younger than 50 years of age with OAB symptoms are less likely to have significant BOO.[20] De Nunzio et al examined 255 patients with symptomatic BOO who underwent urodynamic testing both at baseline and at a mean of two years of followup.[23] In general, DO was highly prevalent in patients with BOO. Overall, 52% and 40% of patients with BOO demonstrated DO at baseline and followup, respectively.[23] Lee et al studied 144 patients with LUTS in a prospective analysis;[19] 47% of patients had BOO and DO (DO was based on the absence or presence of involuntary detrusor contractions on cystometry).

Summary and recommendations: OAB is a symptom syndrome consisting of urinary urgency with or without urgency incontinence, often accompanied by frequency and nocturia, in the absence of UTI or other obvious pathology. OAB is common in both sexes, with increasing prevalence with age. The overall prevalence of OAB in a Canadian population is estimated at 14–18%. Most patients have a combination of OAB symptoms. In men with BPH, OAB and BOO often coexist (Evidence strength Grade B).

Impact on psychosocial life and patients' quality of life

Recent advances in the methods used to measure well-being and quality of life (QOL) have led to a greater understanding of the impact of bladder disease on the various facets of day-to-day life. Understanding how urinary incontinence (UI) influences changes in health status, including physical, emotional, social, and mental functioning is critical because of the chronic nature of the condition and the fact that these changes can be lifelong.[24]

It is important for both clinical and research purposes that OAB is accurately diagnosed and symptom severity classified.[25] Usually, a distinction is made between QOL and well-being in those patients with incontinence (OAB-wet) and those without (OAB-dry). A large array of specific tools are available to evaluate individual aspects of QOL, from the accomplishment of daily activities to sexual satisfaction.[26] QOL assessment should incorporate self-noted symptoms and patients' perceptions of their impact, and re-evaluation should occur following interventions.[27] In this way, the full impact of OAB and any resulting incontinence on daily life, social, and sexual activities is comprehensively quantified.

Individuals who develop UI have their QOL affected in multiple ways; much depends on how the symptoms encountered and the complications they cause result in social and psychological restrictions like isolation, loss of confidence, depression, the avoidance of one's sexual partner, and reduced contact with family members.[28,29] Besides these biopsychological aspects of UI, some complications, like chronic irritation and infection, directly threaten health; UI interferes with work, as well as social activities, hence the economic impact of UI must also be considered.[30]

The assessment of QOL in health outcomes research is important. The National Audit of Continence Care from the U. K. investigated assessment of QOL in individuals with incontinence and concluded that it is underevaluated.[24]

Domains affected by overactive bladder with or without incontinence

Daily life

As numerous factors affect the overall quality of daily life of patients with UI, it is a difficult parameter to measure; the severity of incontinence, type of work, household duties, and requirement for taking care of personal hygiene during working hours are key issues.[31]

Recreational life

In industrialized societies, QOL is dictated to a large degree by the ability to include recreational activities, such as sports, hobbies, and travel. Women who experience UI often indicate that while their general health is satisfactory, their QOL is affected because they are no longer able to participate in their sport of choice or to engage fully in social activities they previously enjoyed.[32]

Psychological concerns

Numerous authors have reported a direct correlation between UI and depression.[33-35] Thirty percent of patients with OAB have depression; those who are depressed record more severe UI symptoms, greater disturbance to their daily living, and more adverse impact on their QOL compared to those without depression. Nygard et al reported that 80% of women with severe UI are likely to develop depression compared with 40% of those with mild incontinence.[36] Depression often manifests as a lack of self-motivation; behavioural therapies tend to have a limited effect in these patients.[37]

Isolation

OAB patients commonly report anxiety and constant worry about reaching a toilet in time to avoid UI.[38] For some, such anxiety induces feelings of hopelessness and depression that leads to social isolation. Nocturia-induced sleep disturbance also predisposes OAB patients to daytime fatigue and exhaustion that may exacerbate feelings of depression resulting from self-induced isolation.[38]

Sexuality

OAB has a broad adverse impact on female sexuality in sexually active women. Incontinent patients have a much higher prevalence of sexual dysfunction than those who are not incontinent.[39] Many studies report that dysfunction is the major, albeit multifaceted, issue that negatively impacts QOL.[40] Contributing factors include the occurrence of dermatitis caused by urine leakage and depression and a lower libido that may result from fear and embarrassment about experiencing UI during sexual intercourse.[39]

Work productivity

OAB generates substantial difficulties in the context of employment; work productivity questionnaires allow this to be evaluated.[41] Use of the Work Productivity and Activity Impairment questionnaire found that men and women with OAB were more likely to not be able to work and to have lower productivity when they did work when compared with those without OAB.[27] A comparable effect was found in the U.S. using a modified Work Limitations Questionnaire.[42]

Comparison suggests that the impairment on work in those with OAB is close to that reported in other chronic

conditions, including rheumatoid arthritis and asthma. These findings highlight the economic burden due to decreased productivity related to OAB; cost-benefit analyses in future research could estimate the impact of treatment results from an economic perspective.[41]

QOL questionnaires

In the context of the impact on OAB/UI on QOL, national and international guidelines identify questionnaires that can evaluate the type, severity, and impact of OAB/UI symptoms. These instruments are important measures in both a clinical and research context. They allow healthcare providers to quantify impact on QOL, aid understanding of patients experience and what their needs are, and evaluate the effects of medical and surgical treatment.[26] Shared with patients, the information derived from questionnaires also enables a better appreciation of how their symptoms affect their daily living.[43] Current questionnaires related to OAB with its impact on QOL, both with and without UI, cover different domains, and vary in terms of the number of question incorporated and how the score is applied (Table 1).

Special consideration for older persons

The absolute number of older people with LUTS and UI will increase as greater numbers of people survive into later life, something common to both the developed and the developing world. Currently, UI constitutes a problem that affects the lives of an estimated 400 million persons worldwide.[44-49] In Canada, data on the prevalence of LUTS/UI in persons over 65 years of age are sparse, but appear to follow the pattern observed in large, multinational studies.[12,14] UUI and OAB are the commonest underlying causes of incontinence in older persons.[3,12] OAB is also likely to be a marker of frailty in older persons; a case-control study of nursing home residents in the U.S. found that those with UI or OAB exhibited higher rates of cognitive impairment, mobility impairment, and higher numbers of comorbidities than those without.[50]

While UI and LUTS are often seen as benign, they are stigmatizing conditions, which are often underreported and undertreated, particularly in older individuals.[51-53] A recent review has identified that relative severity, attitudes to normal aging, self-care, and coping, along with limited knowledge of available treatments and relationships with care providers account for the majority of reasons of either not seeking help or delaying healthcare-seeking.[54] There is also a significant increase in the likelihood of institutionalization,[48] particularly when associated with a dementia diagnosis,[55] although this evidence is inconsistent.[56]

While there is a large body of evidence concerning the psychosocial impact of UI on community dwelling adults,[57-61] its impact on psychosocial well-being and QOL in older people has been seldom researched.[62] Specifically, the impact of OAB on older people with significant comorbidity has been the subject of little if any systematic research; a study of 252 men and women from Austria of mean age 75 concluded that individuals with pure urgency or mixed UI reported more moderate to severe impairment in QOL than those with pure stress UI (35% vs. 20%), like findings in the adult population. However, QOL impairment caused by UI was moderate: only 6.5% of men and 15% of women experienced a moderate to severe QOL impairment because of UI.[63]

Residents of institutional care are often excluded from research because of either significant physical or cognitive

Table 1. Covered domains in quality of life questionnaires related to overactive bladder

	Sexually active	Physically active	Socially active	Social isolation	Depression	Emotion	General health	Sleep	Physical limitation	UI
ICIQ	X					X				
I-QOL		X	X	X						
KHQ	X	X		X		X	X	X	X	X
FSFI	X									
PFIQ		X	X			X				
PISQ	X									
SF-36		X	X			X	X		X	
OBA-q			X					X		
UIQ-7		X	X		X	X				X
CES-D					X					
MOS sleep								X		
IIQ		X				X				X

CES-D: Centre for Epidemiologic Studies Depression Scale; ICIQ: International Consultation on Incontinence Modular Questionnaire; IIQ: Incontinence Impact Questionnaire; I-QOL: Incontinence Quality-of-Life Questionnaire; FSFI: Female Sexual Function Index; KHQ: King's Health Questionnaire; MOS sleep: Medical Outcomes Study sleep scale; OAB-q: Overactive Bladder Questionnaire; PFIQ: Pelvic Floor Impact Questionnaire; PISQ: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; SF-36: Short-Form (36) Health Survey; UIQ-7: Urinary Impact Questionnaire; UI: urinary incontinence.

impairment and thus there are even fewer data from this group. In one of the few studies from nursing homes, the impact of UI from 133 111 residents was examined in the Minimum Data Set Resident Assessment Instrument and a statistically significant association between UI and poorer QOL in residents with moderate cognitive and functional impairment was found. Moreover, new or worsening UI was second only to cognitive and functional decline in predicting poor QOL.[64] A single Canadian study using semistructured interviews conducted with six elderly women from two nursing homes noted a loss of dignity, inability to remain active, feelings of regression, dependence on others, and embarrassment, which affected their self-esteem. The women's embarrassment and belief that UI was untreatable led to secrecy about their UI, and they tended to socially isolate themselves.[65] Notwithstanding these qualitative studies, no validated assessment tool for QOL in the frail older person with UI exists, although one is under development under the auspices of the International Consultation on Incontinence.

Social isolation is often a consequence of incontinence, with a well-described association between UI and the restriction of social activities.[66] Whilst there is little published evidence of the specific influence of OAB, social isolation, and particularly loneliness, is of particular concern for the well-being of the elderly, having been implicated in intellectual decline and as a risk factor for the diagnosis of dementia.[67]

The association between depression and OAB has been reported by many investigators.[33,35,59,68] A single cross-sectional study of 153 Japanese people aged 70 years or older showed a significant association between OAB and depressive symptoms in univariate regression. Multivariate analysis showed that the risk of having OAB was significantly higher in subjects with depressive symptoms, with an odds ratio of 2.37 (95% confidence interval [CI] 1.60–3.52) ***(Level of evidence 3b, Grade C)***.[69] However, no study has specifically addressed those with multimorbidity or frailty, who might otherwise be considered "geriatric."

Summary and recommendations: Since OAB is not life-threatening, its impact on QOL plays a major role in the decision to treat patients. The significant negative impact that OAB has on daily activities, mental health, sexual function, and marital satisfaction has been highlighted by a number of studies. Furthermore, OAB symptoms are linked to depressive illness. Usually distinction is made between QOL and well-being in those patients with incontinence (OAB-wet) and those without (OAB-dry). Individuals who develop UI have worse QOL. There is limited evidence concerning the psychosocial impact of OAB in either frail or multimorbid older persons; however, currently available data suggest that it is a serious concern.

Diagnosis

Medical history and physical examination

There is a universal agreement that taking a history should be the first step in the assessment of OAB patients ***(Level of evidence 2b, Grade B)***.[70-76] The symptom history is both an important summary of patient's problems, as well as a useful guide for physical examination and further diagnostic procedures. Clinicians should document symptoms and signs that characterize OAB and exclude other disorders that could be the cause of the patient's symptoms. Furthermore, the interview should elicit information regarding the rapidity of onset, duration of symptoms, and baseline symptom levels. Questions about urinary symptoms associated with OAB should be subdivided into storage problems (frequency, urgency, nocturia, incontinence), voiding symptoms (hesitancy, straining, poor and intermittent flow), post-micturition symptoms (sensation of incomplete emptying, post-micturition dribble), and other symptoms (nocturnal enuresis, dysuria). Of note, clinicians should be aware that the symptoms of lower urinary tract pathology are subjective and perception of their severity is influenced by many physical and sociocultural factors.

The clinician should also assess the severity of bladder symptoms and their influence on patient's QOL and day-to-day activities. Severity can be assessed by asking about pad usage, including pad weight, size, number of used pads, and number of urinary incontinence episodes per day.

Amount and type of fluid intake can affect the bladder function. Excessive or inadequate fluid intake can produce or exacerbate some of the OAB symptoms. Therefore, fluid intake habits should be investigated. Patients should be asked how much fluid they drink each day, what type of fluids they prefer (with a special consideration for caffeine intake as an exacerbating factor for urgency and frequency), and how many times they void over a 24-hour period.[77] A voiding diary is an important tool helping the physician to differentiate between real small volume frequency (pollakiuria) and polyuria. Assessment of other potential bladder irritants (alcohol, carbonated drinks) is also important and provide an opportunity to educate the patients about modifiable habits.[78-81]

A wide variety of comorbidities may produce or worsen OAB symptoms. Possible related comorbidities include neurological diseases (i.e., stroke, Parkinson's disease, multiple sclerosis, spinal cord injury), endocrine disorders (i.e., complicated and uncontrolled diabetes, diabetes insipidus), urological conditions (i.e., BPH, urolithiasis, recurrent urogenital infections, bladder/prostate cancer), respiratory dysfunctions with chronic cough (i.e., chronic obstructive pulmonary disease), fecal motility disorders (constipation or

fecal incontinence), chronic pelvic pain, mobility deficits, prior pelvic surgeries, pelvic cancers, and pelvic radiation. Special consideration should be taken in regards to urogenital infections, as the associated irritative bladder symptoms can overlap with those of OAB. Careful assessment of painless hematuria and acute symptom onset should be conducted to rule out underlying pathology, such as malignancy or urolithiasis. In women, a thorough obstetric and gynecological history may help to understand the underlying cause and identify factors that may influence treatment decisions. Pelvic organ prolapse or previous surgery for both prolapse and incontinence may influence the success of future treatment.[82] A general obstetric history with labour duration, mode of delivery, birth weights of children, year of delivery, intrapartum complications (e.g., obstetric anal sphincter injury, peri-urethral lacerations, wound breakdown), as well as de novo post-partum urinary symptoms (e.g., urinary retention requiring prolonged catheterization or stress UI), which may be precipitated by caesarean section, epidural block, or prolonged labour, may be necessary for evaluation.[83-86] Clinicians should also be aware that psychiatric disorders such as depression, dementia and anxiety can contribute to abnormal voiding patterns.[87]

A carefully conducted medical history is important to ensure that there are no contraindications or risk factors for potential complications with the introduction of OAB pharmacotherapy. Conditions to consider include cardiac history, in particular a prolonged QT interval, uncontrolled hypertension, functional gastrointestinal pathology, myasthenia gravis, and uncontrolled narrow angle glaucoma, as well as renal and liver impairment.

The patient should also be asked for the details of current medications, both prescribed and over-the-counter, as these may precipitate or worsen OAB symptoms. Diuretics and sympathomimetics can cause urgency, frequency, and urgency incontinence.[88]

The prevalence and severity of OAB symptoms increase with age.[58] Thus, special attention should be paid to elderly patients. This population often has higher medication needs and a lower physiological reserve to deal with diagnostic investigations and adverse effects of treatment.[89] Elderly patients with possible risk factors, especially with cognitive dysfunction, reduced mobility, weakness, glaucoma, constipation, and individuals on polypharmacy should be identified during the diagnostic evaluation. An assessment of depressive symptoms, using validated screening tools (e.g., Geriatric Depression Scale, Centre for Epidemiologic Studies Depression Scale – revised) should be considered for older people presenting with OAB and mood disorder.

Clinical examination should be part of OAB assessment ***(Expert opinion)***. It should begin with a general evaluation of mental status, cognitive impairment, obesity, physical dexterity, and mobility. Abdominal examination should be routinely performed. Pelvic examination should assess tissue quality and sensation, urethra, pelvic floor supports/pelvic organ prolapse, and stress incontinence (cough test). Digital examination of the rectum and/or vagina should also be performed.[82,90-92] Neurological examination with a special attention to the sacral neuronal pathways from S1 to S4 with the assessment of perineal sensation, bulbocavernosus reflex, rectal sphincter tone, and ability to contract the anal sphincter should be performed in the presence of any neurological symptoms.

Questionnaires and voiding diaries

Patient self-completed questionnaires are the most suitable method for assessing the patient's perspective of bothersome symptoms and impact on patients' QOL ***(Level of evidence 2b, Grade B)***.[93,94] Questionnaires should have been validated for use in either English or French. The rationale for use of validated questionnaires is to establish baseline measurements and to quantitate patients' responses to OAB treatment. The International Consultation on Incontinence has evaluated specific criteria for currently used questionnaires and developed a recommendation grading system.[95] Questionnaires with a Grade A recommendation (highly recommended) should be used in clinical practice. Among them are the Overactive Bladder Questionnaire (OAB-q), the Overactive Bladder Satisfaction Questionnaire (OAB-S), the Overactive Bladder Symptom Scores Questionnaire (OABSS), the Incontinence Impact Questionnaire (II-Q), and the Urogenital Distress Inventory (UDI). Each questionnaire can be used alone or in combination with other questionnaires to improve assessment or monitoring of treatment outcomes.[96] There is no evidence to indicate whether use of QOL or condition-specific questionnaires has an impact on outcomes from treatment.

Measurement of micturition frequency and fluid intake habits is an important step in the evaluation and management of lower urinary tract dysfunction, including OAB. Voiding diaries are a semi-objective method of quantifying fluid intake and urological symptoms, such as frequency and possible episodes of urinary incontinence ***(Level of evidence 2b, Grade B)***. Voiding diaries variants (micturition time charts, frequency/volume charts) can also be used. They should document the time, type, and volume of fluid intake, urine volume voided, urgency episodes, and incontinence episodes. Accurate record of these variables can allow for estimation of functional bladder capacity and calculation of 24-hour and nocturnal total urine volume.[97] Divergence between diary recordings and the patient rating of symptoms can be useful in patient counselling.[98-101] Diaries can also be used to monitor treatment response and are widely used in clinical trials. The reproducibility of data obtained from voiding diaries has been demonstrated.[102,103] However, there

is considerable variability of diary data within a 24-hour period.[4,104] A voiding diary observation with 3–7 days duration is therefore recommended.[102] A number of observational studies have demonstrated a close correlation between data obtained from voiding diaries and standard symptom evaluation.[70,105-109] In voiding diaries, OAB patients are usually characterized by small and frequent voids with possible incidences of UI. Bladder diaries are especially useful in behavioural therapies and bladder training programs. Moreover, they can be used for patient monitoring, both by clinicians and patients themselves.

Urinalysis and urine culture

Urinalysis may indicate UTI, proteinuria, glycosuria, or hematuria and require further assessment. Negative results for nitrite and leucocyte esterase in reagent strip ('dipstick') analysis or absence of pyuria/bacteriuria on microscopic examination reliably exclude UTI in people without additional risk factors for infections of uncommon etiology and should be included in the evaluation of all patients with suspected OAB ***(Level of evidence 3b, Grade C)***.[110] OAB symptoms may occur during symptomatic UTI[111] and existing symptoms may worsen during UTI.[112] If evidence of infection is detected, a urine culture should be performed and the infection treated appropriately. After recovering from infection, OAB patient evaluation should be again performed. Low count bacteriuria (10^3–10^5 CFU/ml) might be associated with a wide range of LUTS and thus should be treated in patients with OAB symptoms.[113] Of note, asymptomatic bacteriuria (>10^5 CFU/ml), highly prevalent in older persons, diabetic and catheterized patients, or in those with neurogenic lower urinary tract dysfunction, should not be routinely treated except in pregnant women ***(Level of evidence 1a, Grade B)*** and before urological procedures within the urinary tract ***(Level of evidence 3b, Grade B)***.[114-116] Urine cytology is not recommended in the routine evaluation of patients with uncomplicated OAB ***(Level of evidence 5, Grade D)***.

Post-voiding residual volume

Post-voiding residual (PVR) volume indicates poor voiding efficiency. It may worsen symptoms and increase the risk of UTI, upper urinary tract dilatation, and renal insufficiency.[117] Elevated PVR has a multifactorial etiology, but is usually caused by BOO or detrusor underactivity. Measurement of PVR is not mandatory for uncomplicated OAB patients with no risk factors or history of urinary retention ***(Level of evidence 3b, Grade B)***.[118,119] However, PVR should be evaluated in patients with obstructive symptoms, neurological diagnoses, and history of either prostatic or incontinence surgery. In these patients, PVR should be measured prior to starting antimuscarinic treatment. In patients already treated with antimuscarinics, especially those with existing risk factors for urinary retention, PVR may be elevated.[120] Ultrasound measurement of PVR is preferable to catheterization.[121-125] PVR >250–300 ml warrants special attention if antimuscarinic treatment is intended and consideration should be made as to the existence of other possible pathologies.[126]

Bladder/renal ultrasound, cystoscopy, other imaging techniques

Bladder/renal ultrasound, cystoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) are not recommended in the initial assessment of uncomplicated OAB patients ***(Level of evidence 4, Grade C)***. For patients who have failed multiple OAB treatments, the use of additional diagnostic testing should be based on patient history and symptoms. Special consideration should be taken for neurological causes of bladder overactivity and should include renal ultrasound for upper urinary tract surveillance. Cystoscopy may be used to exclude other causes for the symptoms associated with OAB (bladder tumour, carcinoma in-situ, ulcers, bladder stones, foreign bodies, cystitis) and is recommended in patients with recurrent UTI, persistent pyuria, hematuria, bladder pain, a history of stress incontinence or pelvic surgery, those with suspected fistula, urethral diverticulum, or urinary tract malformation. Cystoscopy should also be considered in patients with possible obstructive pathology. Neurological evaluation with spine imaging (CT, MRI) may also be considered for patients with associated neurological symptoms.

As OAB pathophysiology has been associated with DO, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). Recently published data suggest that routine clinical assessment of BWT for monitoring the effects of OAB/DO treatment is not clinically useful ***(Level of evidence 1b, Grade A)***.[127,128] Furthermore, standardization of the technique is lacking.[129] No consensus regarding the relationship between OAB and increased BWT/DWT exists.[130] DWT/BWT is not currently recommended for diagnosis or monitoring of patients.

Urodynamics

OAB cannot be precisely and directly measured by the cystometric urodynamic study (UDS). Thus, it is not recommended in the initial patient assessment ***(Level of evidence 1b, Grade A)***.[131,132] However, UDS is indicated when the diagnosis remains uncertain after history and physical examination, when the symptoms do not correlate with physical findings, or after failed previous treatment.[133-135] UDS should be taken into consideration in initial diagnosis of patients with neurogenic voiding dysfunction, a history of radical pelvic surgery and pelvic radiation, and those at risk of upper urinary tract deterioration.[136] Obtained data

can help in the management of patients with OAB symptoms, even in the absence of DO.[137] Patients suffering from refractory urgency incontinence may have concomitant urodynamic stress UI or BOO. Correction of these associated conditions may greatly improve symptoms related to urinary urgency; however, these tests may not precisely predict outcomes of treatment.[138] Successful responses to non-surgical and surgical interventions for OAB do not correlate with a pre-intervention finding of DO on UDS.[131,132,139] There is only low-grade evidence for the added value of imaging to UDS.[140] Thus, the role of videourodynamics in OAB has not been determined and this technique is not currently recommended ***(Level of evidence 5, Grade D)***.

Summary and recommendations: Patients with OAB require comprehensive assessment. There is universal agreement that taking a history should be the first step in the assessment of OAB patients (Evidence strength Grade B). Clinical examination should be part of assessment of people with OAB (Expert opinion). Patient self-completed questionnaires are the most suitable method for assessing the patient's perspective of bothering symptoms and further implications on patients' QOL(Evidence strength Grade B). Questionnaires should be validated for use in English or French. Measurement of micturition frequency and fluid intake habits should be performed with voiding diaries (Evidence strength Grade B). A voiding diary observation with 3–7 days duration is recommended. As OAB symptoms may occur during symptomatic UTI, urinalysis should be included in the initial evaluation of all patients suspected of OAB (Evidence strength Grade C). PVR volume measurement (Evidence strength Grade B), bladder/renal ultrasound (Evidence strength Grade C), cystoscopy (Evidence strength Grade C), CT/MRI (Evidence strength Grade C), and UDS (Evidence strength Grade A) are not recommended in the initial assessment of the uncomplicated OAB patient. Additional tests are indicated when the diagnosis remains uncertain after history and physical examination, when the symptoms do not correlate with physical findings, or after failed previous treatment (Expert opinion).

Treatment

First-line treatment (behavioural therapies and lifestyle changes, patient education)

Since OAB is not a life-threatening condition, all patients who desire treatment should start with some form of behavioural therapy and/or lifestyle changes, as they are non-invasive and reversible; however, these forms of therapy require a significant time commitment and effort on the patient's part, with regular followup to achieve success.[141] Furthermore, behavioural therapies and lifestyle changes can easily be combined with other OAB treatments and should form part of any treatment plan. The main difficulty in assessing the success of behavioural therapies and lifestyle changes is due to the tremendous variability in how each is performed, with little consistency from study to study. As a result, there are few Level 1, Grade A studies to compare. In the end, because these treatments have little to no morbidity associated with them, recommendations to use them are generally warranted.

Behavioural therapy

This form of therapy includes two main treatments, bladder training (BT) and pelvic floor muscle therapy (PFMT). BT includes the use of bladder diaries, bladder control strategies, timed voiding, prompted or scheduled voiding, or delayed voiding. These are all used to alter patient voiding patterns. PFMT may also include urgency suppression, control strategies, and biofeedback.[142] In general, there is good literature to support the use of BT and PFMT in patients with OAB ***(Level of evidence 1b, Grade B)***.[143-145] One important factor, as mentioned above, is although there have been a number of randomized controlled trials (RCTs) using PFMT, there is no consistency between them, which makes it difficult to compare studies. Often in regards to PFMT, the mode of delivery, intensity, duration of treatment, and exact techniques used are different between studies. Significant improvement in urinary frequency using BT has been shown in both men and women ***(Level of evidence 1b, Grade B)***.[143,146-148] Wyman et al compared PFMT to BT and to PFMT + BT. They found at three month followup that all three groups had similar improvement in incontinence reductions and QOL scores ***(Level of evidence 1b, Grade B)***.[149] When behavioural treatments were compared to medications, they either were equivalent to or superior to medications in regards to reducing incontinence episodes, improvement in frequency, nocturia, and QOL ***(Level of evidence 1b, Grade B)***.[144-148,150-153] The use of BT in the elderly, who require a caregiver, can be challenging. Flanagan et al reviewed all the RCTs looking at prompted voiding in patients that had incontinence.[154] They showed that prompted voiding had a positive effect on continence outcomes ***(Level of evidence 1b, Grade A)***.

Lifestyle changes

Lifestyle changes include fluid and caffeine intake, diet management, and weight loss. Subak et al demonstrated that weight loss in obese women reduced overall incontinence episodes per week by 47% and urgency incontinence episodes by 42% compared to 28% and 26% in controls, respectively ***(Level of evidence 1b, Grade B)***.[155] Hashim and Abrams showed that a 25% reduction in fluid intake reduced frequency and urgency significantly **(Level of evidence 1c, Grade B)**.[156] In a RCT Bryant et al showed that there was a

35% reduction in voids/day and 61% reduction in occasions of urgency symptoms (but not incontinence) after one month of caffeine reduction, which was statistically significant **(Level of evidence 1b, Grade B)**.[157] Gleason et al examined data from the National Health and Nutritional Examination Surveys (NHANES) specifically looking at caffeine and UI in U.S. women.[158] They found that caffeine intake ≥204 mg/day was associated with any UI, but not with moderate/severe UI ***(Level of evidence 1c, Grade B)***.

Management/treatment of other medical conditions (i.e., diabetes, congestive heart failure, obstructive sleep apnea syndrome, etc.) may improve OAB and incontinence; however, the best study published demonstrated that improved diabetic control did not improve UI ***(Level of evidence 3a, Grade B)***.[159] The EAU guidelines on incontinence published in 2014 felt this paper was the best available, with Level 3 evidence.[160] Chiu et al assessed urological symptoms in patients with chronic heart failure (CHF).[161] They found that patients with CHF had more storage urinary symptoms suggestive of OAB than did age-matched controls. Furthermore, they found that greater NYHA class heart function was significantly associated with OAB and LUTS ***(Level of evidence 3a, Grade B)***. The relationship between obstructive sleep apnea (OSA) and OAB is still unclear and studies present rather conflicting results ***(Level of evidence 2b, Grade B)***.[162] Nevertheless, a prospective study of 53 patients with moderate to severe OSA conducted by Miyazato et al showed improvement of nocturia with continuous positive airway pressure treatment.[163] The concurrent results were presented by Miyauchi et al[164] There are a number of studies that have shown an association between constipation, UI, and OAB ***(Level of evidence 3a, Grade B)***;[159,165-168] however, the evidence supporting improvement in UI and other OAB symptoms when constipation is treated is scarce. Charach et al, in a small prospective cohort study, did show that treatment of constipation improved urgency and frequency ***(Level of evidence 4, Grade C)***.[169] Despite this, the EAU guidelines on incontinence recommend that for adults with UI, co-existing constipation should be treated.[160] This would seem a logical recommendation since treatment of constipation is relatively non-invasive and would benefit patients overall health.

Summary and recommendations: Behavioural therapies and lifestyle changes should be the first-line therapy in all patients because of the non-invasive nature of the treatment. BT and PFMT may be effective methods of treatment in certain cases (Evidence strength Grade B). Lifestyle changes involving modifications of fluids/caffeine intake, weight control, dietary modifications, management of bowel regularity, and optimization of other comorbidities (i.e., diabetes, CHF, OSA) can be effective (Evidence strength Grade B/C).

Patient education

Patient education is an important principle in OAB. Education empowers patients to engage and participate in their treatment. Active participation on the part of a willing patient is necessary when interventions are related to behavioural and lifestyle changes. The patient's understanding can affect their motivation and adherence, which can influence the effect and outcome of treatment. To facilitate the conversations, patient education should be modified to fit the patient's needs and level of understanding. Normal lower urinary tract function should be explained in terms that the patient understands. Thus treatment planning should be based on the patient's desired outcome; higher satisfaction is achieved when the patient understands that voiding is a manageable behaviour ***(Level of evidence 5, grade D)***.[142]

If advanced age and/or cognitive impairment are present, a caregiver or family member willing to assist in the interventions must be involved in the education.[142,170]

The foundation of behavioural treatment is patient education and counselling, which can be provided by different clinicians, such as the physician, the nurse and, in some cases, the physiotherapist specialized in pelvic floor physiotherapy. Treatment goals should be aimed at symptom control, aiming to improve QOL.[171-174] To optimize treatment, the clinicians should incorporate education to promote bladder health into routine visits. A report on the challenges of managing OAB found that one of the recurring challenges was the lack of patient education due to time and resource constraints on the healthcare provider.[175] Patient education is a key factor in the success of behavioural treatments, but it also requires patients to make significant changes in their habits and daily activities. To allow for compliance and adherence to the treatment, patients must include these changes in their daily life to increase success rate.[176] An appropriate duration of 8–12 weeks of therapies is necessary for full evaluation of effects.[142] A minimum of six weeks of therapy is recommended, as per the NICE guidelines ***(Level of evidence 5, Grade D)***.[177]

Weight control

Obesity is an associated a risk factor for UI in many studies. A patient with a body mass index greater than 30kg/m² is at increased risk for the onset of OAB symptoms.[170,176,178,179] Thus, some patients may require specialized nutrition counselling provided by a dietitian. Weight loss has been shown to improve OAB symptoms, even when it is only moderate loss in overweight women[155,176,180-182] ***(Level of evidence 1B, Grade B)***.

Management of fluid intake

Individualized fluid intake management restrictions should be promoted, but they must be based on the patient's 24-hour intake and subsequent 24-hour urinary output. Thirst must be avoided and an appropriate level of fluid must be maintained.[170,176] The physician should take into consideration the patient's comorbidities, such as renal or cardiac disease. Restricting fluid intake 2–4 hours before bedtime, or after 6 pm decreases nocturia and night time incontinence[171,176,183] ***(Level of evidence 2B, Grade B)***.

Dietary modifications

The reduction or elimination of caffeinated and alcoholic beverages, as well as aspartame from the diet may improve symptoms.[171] These items can act like a diuretic or worsen OAB symptoms;[176] however, in view of inconsistent results,[157,184] the best approach would be an individualized one, where patients reduce these items from their diet and a continuous evaluation is completed in parallel to assess symptom management ***(Level of evidence 2B, Grade C)***.

Management of bowel regularity

Constipation is regularly found in men and women with OAB.[176,185,186] Patients should be provided with strategies to avoid constipation, such as increasing fibre in their diet[176] ***(Level of evidence 3B, grade B)***.

Physical exercise

Regular physical activity is shown to strengthen the pelvic floor muscles, which can decrease OAB symptoms.[170] Increasing physical activity can reduce OAB symptoms, but strenuous exercise can also worsen symptoms.[187-190] The association between physical activity and lower level of incontinence was observed in women who did moderate exercise;[191,192] however, it should be noted that moderate physical activity could also assist the patient in a weight loss program, which is a recommended lifestyle modification ***(Level of evidence 3B, Grade C)***.

Smoking cessation

Nicotine has been shown to irritate the bladder detrusor, causing increased activity and OAB symptoms.[171] There is also an association between increased intra-abdominal pressure from recurrent coughing in smokers causing urinary leakage.[171,193] Smoking cessation is a recommendation even though a Cochrane review described the effect of nicotine on OAB as uncertain.[194] Smoking cessation remains a general public health intervention.[195] ***(Level of evidence 3B, Grade D)***.

Timed voiding

To encourage an appropriate voiding frequency, caregivers use the timed voiding technique. Instead of waiting for the patient to voice an urge to void, the patient is prompted to toilet at regular intervals or based on a schedule. In two systematic reviews, this technique has shown beneficial results in comparison to standard care.[154,170,196] A Cochrane review has demonstrated inconsistencies in the results in cognitively impaired adults.[197] Timed voiding can still be recommended, considering it has no negative impact on the patient ***(Level of evidence 2A, Grade C)***.

Urgency control and suppression techniques

This technique involves teaching the patient to control urgency by performing general relaxation, such as slow, deep breathing. This can decrease the intensity and urgency, therefore delaying the voiding process.[176] They can also use self-determination and self-motivational statements for encouragement.[176,198] They can also perform 6–10 quick pelvic floor muscle (PFM) contractions, which prevent the sphincter from relaxing when the urge is present. These contractions need to be well timed to provide increased benefit.[176,199] ***(Level of evidence 3B, grade B)***.

BT

BT involves the use of different strategies to restore normal bladder function. The main strategy is implementing a voiding schedule and lengthening the intervals between voids until a normal pattern is established. Techniques for urgency control and suppression must be used in conjunction. The voiding intervals are determined on an individual basis, depending on baseline pattern. They are increased by 15–30 minutes each week, depending on patient compliance and tolerance, until a voiding interval of 3–4 hours is achieved.[176,198] Different studies demonstrate that BT is more effective in symptom control than not providing physical behavioural therapy[145,170,177,194,200] ***(Level of evidence 1B, Grade B)***.

PFMT

PFMT strengthens and improves the function of the pelvic floor. It has also shown improvement in urethral stability, which in return decreases OAB symptoms.[170,201] This technique is only effective if the patient tightens the PFM correctly; it should result in a closing and lifting sensation without tensing the leg, buttock, or abdominal muscles. To

facilitate teaching, the patient can be asked to imagine the passing of gas without tensing any of the previously mentioned muscles. This helps the patient isolate the proper PFM. The PFMT regimen consists of repeating the contraction for 10 seconds, 15 times in a row with equal breaks of 10 seconds a total of time times a day, totalling 45 PFM contractions in a day.[176,202] The PFMT should be incorporated into the activities of daily life to promote compliance and adherence. It should be done in different positions, such as sitting, standing, and lying down.[176,203] Continuous training is needed to maintain the gained strength of PFMs.[176] A meta-analysis demonstrated that PFMT improves QOL and decreases symptoms. A Cochrane review of 21 RCTs concluded that increased intensity of PFMT demonstrated better outcomes and that there was no difference between individualized therapy or group therapy settings[170,204] ***(Level of evidence 1B, Grade B)***.

Summary and recommendations: Patient education empowers patients and engages them in their treatment plan. First-line treatments for OAB strongly rely on patient compliance and adherence. Patients with OAB and UI have an improved QOL when they have a comprehensive knowledge of their medical problem and seek to develop an avoidance-oriented stress-coping lifestyle that promotes social contact, thus, emphasizing the importance of patient education (Expert opinion). Lifestyle changes and physical therapies should be incorporated in the activities of daily life to facilitate compliance and adherence to the program.

Second-line treatment (pharmacological management)

Pharmacological management of OAB aims to control and alleviate bothersome symptoms of urgency, frequency, and urinary incontinence. The current available literature includes individual studies and systematic reviews for antimuscarinic agents and beta-3 adrenoceptor agonist (primarily mirabegron).

The goals of pharmacological treatment are therefore mainly to improve QOL of patients suffering from OAB by decreasing their symptoms. The preferable option should be safe, efficacious, tolerable, and allow long-term adherence for patients. Therefore, each treatment options will be assessed for these characteristics. Most studies report on efficacy, based on changes in number of micturitions, incontinence, urgency, or UUI episodes. Safety and tolerability outcomes are also reported by identifying the number of patients with certain side effects, with limited data on adherence.

Antimuscarinics

The antimuscarinic agents (AM) available for the treatment of OAB in Canada are oxybutynin (immediate release [IR], extended release [ER], transdermal), tolterodine (IR, ER), darifenacin, trospium (IR), solifenacin, propiverine, and fesoterodine. They have an antagonistic action on muscarinic receptors throughout the body, but improve OAB symptoms by blocking the M2 and M3 receptors in the bladder and urothelium, and therefore affect both involuntary detrusor contraction and increased sensory afferent signalling.

Efficacy

The latest Cochrane review reported a meta-analysis of RCTs comparing one AM vs. another or different doses, using QOL as a primary outcome measure. Tolterodine-IR had similar efficacy vs. oxybutynin-IR, but with less withdrawal due to adverse events and less dry mouth. Similarly, tolterodine-ER had less risk of dry mouth compared to oxybutynin-ER. It was found that ER preparations of oxybutynin or tolterodine provided similar improvement, while having less risk of dry mouth compared to IR. Transdermal oxybutynin and tolterodine-ER had similar rates of dry mouth, but the transdermal patch was associated with a higher withdrawal rate due to skin reactions. Therefore, tolterodine-ER would be a first choice compared to other formulations of tolterodine and oxybutynin ***(Level of evidence 1a, Grade A)***. The highest of the two doses for both solifenacin and fesoterodine (10 mg and 8 mg, respectively) had better clinical efficacy, but with higher rates of dry mouth than the lowest doses at 12 weeks (5 mg and 4 mg, respectively) ***(Level of evidence 1a, grade A)***. Solifenacin had better clinical efficacy and less dry mouth rates compared to tolterodine-IR ***(Level of evidence 1a, Grade A)***. Fesoterodine had favourable clinical outcomes compared to tolterodine-ER, but higher rates of withdrawal due to adverse events and risk of dry mouth ***(Level of evidence 1a, Grade A)***. All included trials were of 12 weeks duration with the exception of one-year studies on trospium and oxybutynin.[205]

A meta-analysis on the effects of AM on health-related QOL measures in patients with OAB reported that active treatment with four different AM formulations (oxybutynin-TDS, tolterodine-IR, tolterodine-ER, trospium) had a significant difference for mean change of score compared to placebo ***(Level of evidence 1a, Grade A)***. There were no significant differences between the different interventions when comparing active-controlled trials ***(Level of evidence 1a, Grade A)***.[206]

An update of a systematic review of the tolerability, safety, and efficacy of seven drugs (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium) in OAB by Chapple et al found that active treatment had higher efficacy in reducing the number of incontinence episodes, urgency episodes, micturition frequency, and return to continence compared to placebo ***(Level of evidence 1a, Grade A)***.[207] Combining different AMs has limited clinical improvement with much higher adverse events ***(Level of evidence 2b, Grade C)***.[208] A network meta-analysis with

complete assessment across different drugs by Buser et al performed an efficacy and adverse events analysis, along with a trade-off analysis between these two components. The longest duration of treatment for all trials included was 12 weeks. It was found that trospium 40 mg, oxybutynin topical gel 100 mg/g, and fesoterodine 4 mg had the most favourable efficacy/adverse events relationship, while higher doses of oral oxybutynin and propiverine had the least favourable ***(Level of evidence 1a, Grade A)***.[209]

Safety, tolerability, and persistence

The most common adverse events reported in a meta-analysis was dry mouth (29.6% and 7.9% of active treatment and placebo arm patients) followed by pruritus ***(Level of evidence 1a, Grade A)***.[207] The most commonly adverse events reported groups are gastrointestinal, followed by neurological, ocular, and renal/genitourinary ***(Level of evidence 1a, Grade A)***.[209] A network meta-analysis comparing adverse events of AMs identified 82 reports, with most of them being parallel and placebo-controlled. They found that the overall adverse event profile was comparable for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium. However oral oxybutynin, in doses of or exceeding 10 mg/day was associated with the worst adverse event profile ***(Level of evidence 1a, Grade A)***.[210]

Although drug persistence is generally low in chronic diseases, AM have an overall poor adherence profile, with 17–35% of patients still taking their prescribed drug at one year.[211-213] A better tolerability profile may increase rates for long-term treatment of OAB.

AMs are contraindicated in patients with uncontrolled narrow-angle glaucoma due to their antagonistic actions on M3 and M5 receptors in the eye. The anticholinergic action can induce or precipitate acute angle-closure glaucoma.[214] AMs contribute to the overall anticholinergic burden. Anticholinergic burden has been linked to cognitive dysfunction ***(Level of evidence 1b, Grade B)***,[215] but also with increased mortality and cardiovascular risk ***(Level of evidence 1b, Grade B)***.[216] These effects should be considered in the potential use of a medication for a prolonged duration of time. There are limited long-term data on the use of AM and their effect in different patient populations, particularly the elderly.

Beta-3 adrenoceptor agonist

The only commercially available agent, mirabegron, is approved in Canada for the treatment of OAB. It activates beta-3 adrenoceptors, allowing bladder relaxation, improving bladder filling and storage of urine. A starting dose of 25 mg, and increasing to 50 mg is recommended. The lowest dose is also recommended for renal and hepatic impairment.

Efficacy

A meta-analysis of four phase 3 RCTs found that mirabegron was more effective than placebo in treating OAB by decreasing the mean number of incontinence episodes, mean number of micturition, mean volume voided per micturition, and mean number of urgency episodes per 24 hours ***(Level of evidence 1a, Grade A)***.[217] The trials, SCORPIO,[218] ARIES,[219] CAPRICORN,[220] and 178-CL-048[221] were all of 12 weeks duration. The overall treatment-emergent adverse events (TEAEs) of hypertension, cardiac arrhythmias, and urinary retention, and discontinuation rates were similar between mirabegron and placebo. A pooled efficacy analysis of these trials also found that mirabegron 50 and 100 mg decreased the number of incontinence episodes and micturitions per 24 hours compared to placebo ***(Level of evidence 1a, Grade A)***.[222] The NICE 2013 report also indicates that mirabegron 50 mg has a significant improvement in urinary frequency and incontinence episodes compared to placebo ***(Level of evidence 1a, Grade A)***.[223] A post-hoc responder analysis of pooled data from three phase 3 RCT showed that patient reported outcomes (PROs) were significantly improved compared to placebo ***(Level of evidence 1a, Grade A)***.[224]

In an incontinent population at baseline, a post-hoc analysis of pooled data from three randomized phase 3 trials found that mirabegron 50 mg statistically significantly reduced the mean number of incontinence episodes, micturitions, and urgency episodes per 24 hours, and improved mean volume voided per micturition. The treatment effect was positively correlated with increasing severity of incontinence at baseline ***(Level of evidence 1a, Grade A)***.[75] A post-hoc analysis of SCORPIO showed similar efficacy in subgroups of patients who were AM-naïve and those with prior use of AM ***(Level of evidence 1b, Grade B)***.[225]

There were two phase 3 trials that included a tolterodine 4 mg active treatment arm. The SCORPIO study compared tolterodine to placebo, but did not make any direct comparison between mirabegron and tolterodine.[218] Yamaguchi et al randomized OAB patients to placebo, mirabegron 50 mg, and tolterodine 4 mg, but did not test for non-inferiority of efficacy and safety.[226]

The 12-month safety and efficacy was evaluated in a randomized, double-blind, active controlled phase 3 study. Patients received either mirabegron 50 or 100 mg or tolterodine 4 mg. Although there was no placebo arm, efficacy was maintained in each treatment group throughout 12 months, as determined by the change from baseline in number of micturitions per 24 hours, mean number of incontinence episodes per 24 hours, and improvements in mean volume voided per micturition ***(Level of evidence 1b, Grade B)***.[227]

Combination treatment

The SYMPHONY trial was a 12-week placebo- and monotherapy-controlled phase 2 trial looking at combination treatment of mirabegron and solifenacin for OAB. Combining mirabegron 25/50 mg with solifenacin 5/10 mg significantly improved PROs and micturition frequency compared with placebo or solifenacin 5 mg ***(Level of evidence 1b, Grade B)***.[228] The BESIDE study was a phase 3b 12-week trial where OAB patients, still incontinent after four weeks of solifenacin 5 mg, were randomized to a combination of mirabegron with solifenacin 5 or 10 mg. Mirabegron could be increased from 25 to 50 mg after four weeks. Combination treatment improved daily micturitions compared to solifenacin 5 and 10 mg, and daily incontinence compared to solifenacin 5 mg. A higher percentage of patients were dry with combination treatment (46%) vs. solifenacin 5 or 10 mg (37.9% and 40.2%), and the safety profile was similar across the different groups ***(Level of evidence 1b, Grade B)***.[229]

Safety, tolerability, and persistence

A prospective pooled analysis of three 12-week randomized phase 3 trials and of a one-year randomized phase 3 trial looked at the rates of adverse events, serious AE (SAE), and TEAEs. The most common TEAEs for mirabegron were hypertension, nasopharyngitis, and UTI in the pooled 12-week studies. Headache and back pain also occurred in the one-year study. Tolerability profile was not clinically significantly different between age groups (cutoffs of 65 and 75 years old), sex, or race to warrant special precautions. The adverse event profile was similar across mirabegron, tolterodine, and placebo, except for dry mouth, which was fivefold more frequent in the tolterodine group. The incidence of SAEs was low and they were not directly related to the study drug ***(Level of evidence 1a, Grade A)***.[230]

Persistence data from retrospective claims in Canada showed that overall persistence rates at 12 months were greatest with mirabegron (31.7%), and lowest with oxybutynin IR (13.8%). Persistence for the treatment experienced group at 12 months was 39% for mirabegron vs. 14–35% for antimuscarinics. For the naïve group, the persistence for mirabegron was 30% vs. 14-21% for antimuscarinics. Adherence was higher in treatment-experienced patients compared to treatment-naïve patients, regardless of treatment ***(Level of evidence 2b, Grade C)***.[231] In a small, prospective, randomized study, the 12-month persistence rates were similar between mirabegron and solifenacin, but the reasons for discontinuation were different: side effects for solifenacin, and lack of efficacy for mirabegron ***(Level of evidence 2b, Grade C)***.[232]

Mixed treatment comparison

In a Bayesian mixed treatment comparison analysis by Maman et al, mirabegron 50 mg had a similar efficacy in decreasing the number of micturition frequency, UUI episodes, and overall incontinence episodes, compared to all AM except for solifenacin. Only solifenacin 10 mg had a higher efficacy than mirabegron 50 mg in the improvement of micturition frequency and UUI episodes ***(Level of evidence 1a, Grade A)***. Mirabegron 50 mg had a similar rate of dry mouth and constipation compared to placebo. For dry mouth, all other AMs had higher rates than mirabegron 50 mg; for constipation, darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg, solifenacin 10 mg, and trospium 60 mg had higher rates than mirabegron 50 mg ***(Level of evidence 1a, Grade A)***.[233]

Although there is no direct comparison, mirabegron appears to have similar clinical effectiveness compared to most AMs, but has a different sideffect profile. There is limited data on cost-effectiveness, persistence, or effect of long-term treatment with the medication.

Summary and recommendations: Second-line treatment of OAB should include the use of oral AMs, transdermal oxybutynin or oral beta-3 adrenoceptor agonist (Evidence strength Grade A). The lowest recommended dose should first be prescribed, followed by dose increases in order to obtain the best clinical improvement while monitoring for adverse events (Evidence strength Grade B). If the initial selected drug is not tolerated or does not provide adequate symptom relief, patients should be offered an alternative medication, preferably with a different mechanism of action (Expert opinion). The adverse event profile and possible contraindications should be considered when prescribing the drug of choice as second-line treatment (Expert opinion). Immediate release formulations of AMs should be avoided if other formulations are available (Evidence strength Grade A). Patients who remain incontinent after the initial treatment with an AM could be offered combination treatment with solifenacin and mirabegron (Evidence strength Grade C). Recommended doses of drugs are presented in Table 2.

Special considerations in frail older people

Age-related changes in pharmacology

Specific age-related changes in pharmacokinetics, alteration in drug absorption, distribution, metabolism, and clearance, and their potential effect on UI drugs, are shown in Table 3. The numerous factors potentially affecting drug clearance in older, frail patients, as well as previous and/or crossover compounds, may confound observed drug effects.

Table 2. Summary of pharmacological management of overactive bladder

Category	Drug	Brand name	Grade	Recommended doses	Considerations in medically complex elderly	Dose adjustment	Adverse events	Contraindications
Antimuscarinics	Oxybutynin	Ditropan Ditropan XL	A	IR: 5 mg BID, TID, or QID ER: 5 or 10 mg OD	Data show efficacy of 2.5mg bid.[235,272] Doses of 20 mg daily consistently associated with cognitive impairment, unreported by patients[252]	Elderly	Dry mouth, constipation, CNS AE	Pregnancy or breast-feeding; drug hypersensitivity; Uncontrolled narrow-angle glaucoma; urinary retention, paralytic ileus, GI or GU obstruction
	Oxybutynin transdermal	Oxytrol® Gelnique	A	36 mg (3.9 mg/day) patch twice weekly 10% gel: 1 sachet (100 mg/g) OD	No cognitive impairment reported in cognitively intact elderly[273]		Application site reaction, dry mouth, CNS AE	
	Tolterodine	Detrol Detrol LA	A	IR: 2 mg BID (or 1 g BID) ER: 4 mg OD (or 2 mg OD)	No cognitive impairment in cognitively intact elderly[274]	Concomitant CYP3A4 inhibitors, Renal, hepatic	Dry mouth, constipation, CNS AE, QT prolongation	
	Darifenacin	Enablex®	A	7.5 or 15 mg OD	No cognitive impairment in cognitively intact elderly [275]	Concomitant CYP3A4 inhibitors, hepatic Geriatric, Renal, hepatic	Dry mouth, constipation, dyspepsia, nausea	
	Trospium	Trosec®	A	IR: 20 mg BID	No cognitive impairment reported in cognitively intact elderly[276]	Concomitant CYP3A4 inhibitors, Renal, hepatic	Dry mouth, co nstipation, urinary retention, dry eyes, blurred vision, tachycardia, increased heart rate, and palpitation	
	Solifenacin	Vesicare®	A	5 or 10 mg OD	No cognitive impairment reported in elderly with mild cognitive impairment at 5 mg dose[277]	Concomitant CYP3A4 inhibitors, renal, hepatic	Dry mouth, constipation, blurred vision	
	Fesoterodine	Toviaz™	A	4 or 8 mg OD	No cognitive impairment in cognitively intact elderly[278]	Renal, hepatic	Dry mouth, constipation, dry eyes and dyspepsia	
	Propiverine	Mictoryl®	A	Modified release: 30 or 45 mg OD	No difference in cardiac events in elderly patients[279]	Renal, hepatic	Dry mouth, headache, accommodation disorder, visual impairment, constipation, abdominal pain, dyspepsia, and fatigue	
Beta-3 adrenoceptor agonist	Mirabegron	Myrbetriq®	A	25 or 50 mg OD		Renal, hepatic	Nausea, headache, hypertension, UTI, nasopharyngitis	Severe uncontrolled hypertension, pregnancy

BID: twice a day; CNS AE: central nervous system adverse effects; ER: extended release; GI: gastrointestinal; GU: genitourinary; IR: immediate release; OD: once a day; QID: four times a day; TID: three times a day; UTI: urinary tract infection.

Table 3. Specific age-related changes in pharmacokinetics, alteration in drug absorption, distribution, metabolism, and clearance, and their potential effect on urinary incontinence (UI) drugs

Parameter	Age-associated changes	UI drugs potentially affected
Absorption	Minimal quantitative change despite ↓ gastric motility, yet little known regarding effect on slow-release agents	Extended-release preparations
	↓ Skin thickness	Transdermal preparations
Distribution	Decrease in lean body mass leads to ↓ Vd/ ↓ T½ for hydrophilic drugs and Vd/T½ for lipophilic agents	Lipophilic agents, tricyclic antidepressants
	Decreased protein binding in frail patients with low albumin, leading to higher concentration of free drug	Tolterodine
Hepatic metabolism	↓ Phase I reactions (oxidation/reduction)	Tricyclic antidepressants
	No change in phase II reactions (glycosylation)	
	↓ Hepatic blood flow and ↓ hepatic mass, leading to reduced clearance for agents with first-pass metabolism	Oxybutynin, tolterodine, solifenacin, darifenacin
	Stereoselective selectivity in metabolism (hypothetical)	Enantiomers
	Cytochrome P450	Oxybutynin, tolterodine, solifenacin, darifenacin, mirabegron, 5-hydroxymethyl tolterodine (clearance only)
Clearance	Decrease in renal clearance	Tolterodine fesoterodine (5-hydroxymethyl tolterodine)

T½: half-life; Vd: volume of distribution.

Availability of low-dose agents

One effect of the underrepresentation (if not exclusion) of frail older persons in UI drug studies is a lack of knowledge regarding minimal effective drug doses for this population. The age-related changes in pharmacology suggest that some UI drugs may be effective at lower than standard doses in frail older persons with concomitant decreased adverse effects.[234] There are some data supporting the effective use of low-dose oxybutynin in older persons **(Level of evidence 2b, Grade C)**.[235,236] A single study has assessed low standard doses of trospium chloride and solifenacin in combination in older persons (not frail) of average age 69 years in comparison to higher doses, showing higher efficacy of combination lower-dose therapy ***(Level of evidence 2b, Grade B)***.[237]

Polypharmacy

Approximately 60% of people over age 65 take at least one prescribed medication and about one-third take more than five prescribed drugs. In addition, many older persons take over-the-counter, naturopathic, or herbal agents and dietary supplements, with the rate of use varying across countries and cultures. In 2010–2011, approximately 15.1% of older adults were at risk for a potential major drug-drug interaction compared with an estimated 8.4% in 2005–2006 ($p<0.001$).[238] The likelihood of adverse drug reactions (ADEs) and drug interactions rises exponentially as the number of medications increases. Changes to existing drug regimens should be considered in the management of UI in all frail older people ***(Level of evidence 3, Grade B)***.

ADE

ADEs are extremely common in older persons,[239] with rates up to 35% among community-dwelling persons aged >65 in the US. Factors associated with higher ADEs in older persons are higher drug doses, age-related pharmacological changes, polypharmacy, comorbid conditions and the interactions between them, and female sex.[240,241] Older people are at higher risk of ADEs from AMs because of age, and comorbidity-related changes in muscarinic receptor number and distribution, blood-brain barrier transport, and drug metabolism.[242] Whereas AM ADEs in younger persons are bothersome, in the frail elderly they can result in serious morbidity, such as sedation, heat intolerance, delirium, and falls. Xerostomia is common in older people.[243] In general, older people, women, and those taking multiple medications are more likely to report the symptom. A subcut analysis of a Canadian randomized controlled trial of solifenacin 5 mg/day vs. oxybutynin 5 mg three times daily, examined the tolerability of both drugs in subjects under and over the age of 65 years. The study found that dry mouth was no more common amongst those over the age of 65, but was more common and more severe with oxybutynin ***(Level of evidence 1b, Grade B)***.[244] In those over 75 years of age treated with 8 mg vs. 4 mg of fesoterodine from a pooled analysis of data from registration trials, dry mouth was more common in the older sample; this finding was duplicated in a prospective trial of fesoterodine in older patients ***(Level of evidence 1b, Grade B)***.[245,246] Another AM ADE to which the frail elderly may be predisposed is decreased visual accommodation, yet this has been specifically evaluated only in young, healthy volunteers[247] and a single prospective cohort including patients up to the age of 60 years.[248] Drug trials typically report only "blurred vision," without further characterization.

Anticholinergic medication and cognitive impairment

There have been a number of reports linking anticholinergic medication to cognitive impairment, an increase in incident dementia diagnosis, and a possible increase in mortality.[215,249,250] Older persons commonly use medications with anticholinergic properties. As much as there is a reported increase in overall medication prescribing for older persons, temporal trends also reveal an increase in anticholinergic medication prescribing for older persons.[251] Due to the nature of the cohorts of persons studied, data on medications used for OAB and UUI are limited to identifying immediate-release oxybutynin as a consistent significant factor in exposure. In the study of Gray, over 10 years, those with the highest cumulative burden of oxybutynin exposure had a significant association with cognitive impairment ***(Level of evidence 2b, Grade B)***.[215] Cognitive effects may be underdetected because they are clinically subtle, neither asked about nor reported by the patient, or mistaken for age-related diseases and ageing.[252,253] It is clear that duration of exposure and extent of exposure to medications with anticholinergic properties are significant factors in the observed associations with cognition. Persons with pre-existing cognitive impairment (especially from conditions known to affect central cholinergic pathways) may be at greater risk for cognitive impairment, although there are also some data to suggest that those with established dementia may not experience cognitive decline following therapy with anticholinergic agents.[254]

Drug interactions

Because frail older people take higher numbers of drugs and usually have several comorbid conditions, drug interactions are more common.[255] Drug-drug interactions for oxybutynin, solifenacin, darifenacin, and tolterodine include potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, cyclosporin, and vinblastine). Fesoterodine, a pro-drug that is converted to tolterodine by non-specific esterases, is also dependent upon CY3A4 for its excretion. There is one case report of interaction between tolterodine and warfarin in two older patients, which has not been seen in healthy volunteers ***(Level of evidence 4, Grade C)***.[256] Naturopathic/herbal preparations should also be considered for potential interactions, especially in areas where these agents are frequently used. Evidence regarding the co-prescription of bladder AM agents and cholinesterase inhibitors (CEIs) used for dementia are of poor- to moderate-quality. There is evidence CEIs can cause or worsen UI ***(Level of evidence 3b, Grade C)***,[257,258] but this finding has not been replicated in a large Dutch dataset analysis ***(Level of evidence 2b, Grade C)***.[259] Concomitant use of AMs and CEIs in nursing home residents was associated with a decline in ADL function in the most functionally able residents, but there was no worsening of cognition in one study.[260] In a study of trospium chloride in older people with dementia treated with galantamine, no effect on cognition or activities of daily living was detected ***(Level of evidence 2b, Grade C)***.[261] A small study reported some positive effect of the treatment of UI with propiverine in subjects with probable AD taking CEIs ***(Level of evidence 2b, Grade C)***.[262] Although intuitively illogical, given the opposing pharmacological actions, there seems to be no reason not to use bladder AMs for older people with dementia, ensuring that the CEI is warranted and effective, that the incontinence is sufficiently bothersome to warrant treatment, and that the patient (where possible) and the caregiver are fully informed.

Potentially inappropriate drugs for older persons

A revised Beers criteria was introduced in 2015.[263] These guidelines focus on drugs with lower risk-benefit ratios and higher potential for drug-drug and drug-disease interactions, and are used for nursing home regulation and quality performance measurement. More recently, a system for prescribing appropriate medications for older persons, the Fit fOr The Aged (FORTA) criteria have been published with respect to drugs for LUTS.[264]

Special issues unique to frail older men

Frail older men are under-represented in UI treatment trials, whether behavioural, pharmacological, or surgical. Results from treatment trials in frail women cannot be directly extrapolated to men for several reasons:

- Differences in comorbidity: Frail older women have higher rates of functional impairment and chronic disease and geriatric syndromes, which may mean that frail men may be more likely to respond to behavioural intervention.[265]
- Benign prostate disease: The prevalence of histological BPH, BPE, and BOO increases with age, and is associated with LUTS, UI, and DO. In a UDS of older persons, 29% of men had BOO and 59% had DO as the predominant cause of UI vs. 4% BOO and 61% DO in women.[266]
- Differences in device usage: A nationally representative survey of adults in the U.S. showed that older men were nearly three times less likely than older women to use pads to contain leakage (15% vs. 45%).[267] In a survey of patients recruited from family practice clinics in the Netherlands, the gender difference for pad usage by older adults with UI was even higher, with four out of five women using pads vs. one of nine men.[268] Men are also more likely to be users of indwelling catheters, both in the long-term care setting[269] and in the community.[270]

– Differences in medical treatments: The interactions of UI and other conditions with regards to orthostatic hypotension and risk of falls merits attention. In a German registry of 3414 patients with Parkinson's disease, for those with UI (716; 21%), orthostatic hypotension was reported for 14% of the men, yet only 9% of the women.[271]

Special considerations of pharmacological management in medically complex elderly are included in Table 2.[235,252,272-279]

Summary and recommendations: Age-related changes in pharmacokinetics affect AM drugs for UI and these factors should be incorporated into treatment planning (Evidence strength Grade B). Drugs may be effective at lower doses in frailer compared with healthier older persons (Evidence strength Grade C). Polypharmacy increases the chance of adverse reactions to drug therapy, which are more common in the frail elderly (Evidence strength Grade A). Furthermore, drug-drug and drug-disease interactions are common in frail older persons (Evidence strength Grade A/B). AMs for treatment of OAB remain as potentially inappropriate medications for frail older people (Evidence strength Grade B/C). CEI treatment is associated with either precipitation or worsening of OAB symptoms (Evidence Strength Grade C).

Third-line treatment: OnabotulinumtoxinA

Strong, Level 1 (Grade A) evidence supports intradetrusor onabotulinumtoxinA 100 U as an effective, safe, and long-term treatment option for OAB with UUI refractory to second-line OAB pharmacotherapies.

Efficacy and safety

There are two 24-week, phase 3, randomized, double-blind, placebo-controlled multicentre trials, which demonstrate that onabotulinumtoxinA 100 U is both effective and safe when compared to placebo in patients with refractory idiopathic OAB.

Nitti et al randomized 557 patients with idiopathic OAB inadequately treated with or intolerant to anticholinergic therapy to receive onabotulinumtoxinA 100 U or placebo ***(Level of evidence 1b, Grade A)***. Treatment was administered as 20 evenly distributed intradetrusor injections of 0.5 ml per injection site using flexible or rigid cystoscopy and sparing the trigone.[280] Followup visits occurred at two, five, and 12 weeks, and every six weeks thereafter until study exit at 24 weeks. Patients completed a three-day bladder diary before each study visit to collect information on OAB symptoms and volume per void. Perception of treatment benefit was assessed using the treatment benefit scale (TBS) and health-related QOL was assessed at Week 12 using validated patient questionnaires, including the Incontinence Quality of Life (I-QOL) instrument and King's Health Questionnaire (KHQ). Co-primary efficacy variables were defined as: 1) the change from baseline in daily average frequency of UI episodes; and 2) the proportion of patients with a positive treatment response on treatment benefit scale (TBS) at Week 12. Secondary efficacy variables were the change from baseline in daily average frequency of micturition and urgency episodes, the I-QOL total summary score, and two KHQ multi-item domain scores. Other efficacy variables were change in nocturia, volume per void, and proportion of patients achieving 50% or greater or 100% reduction in UI episodes. Adverse events, PVR, and clean intermittent catheterization (CIC) were evaluated at two, six, and 12 weeks or at any other time if needed. Urinary retention was defined as PVR >200 ml or greater that required CIC. UTI was defined as a positive urine culture $>10^5$ CFU/ml together with leukocyturia greater than 5/HPF regardless of symptoms. At 12 weeks, there were 3–4-fold decreases from baseline in mean daily frequency of UI for onabotulinumtoxinA 100 U vs. placebo (-2.65 vs. -0.87; $p<0.001$); 57.5% of patients treated with onabotuliumtoxinA 100 U achieved a 50% or greater reduction in UI episodes and 22.9% were continent compared to 28.9% and 6.5%, respectively, for those treated with placebo. A majority of 60.8% of onabotulinumtoxinA patients reported a positive treatment response on TBS compared to 29.2% of those who received placebo ($p<0.001$). All secondary efficacy outcomes were significantly different between groups favouring onabotulinumtoxinA, including mean decreases in number of micturitions (-2.15 vs. -0.91; $p<0.001$), urgency (-2.92 vs. -1.21; $p<0.001$), and nocturia (-0.45 vs. -0.24; $p<0.05$) per 24 hours. The most frequently reported adverse event was uncomplicated UTI occurring in 15.5% of onabotulinumtoxinA- and 5.9% of placebo-treated patients. Dysuria (12.2%), bacteriuria (5%), and urinary retention (5.4%) occurred at a higher rate in those patients treated with onabotulinumtoxinA. The proportion of patients who initiated CIC was 6.1% in the onabotulinumtoxinA group vs. 0% in the placebo group. The duration of CIC was six weeks or fewer for more than half of those who required it.

Chapple et al performed a similarly large, phase 3, multicentre, randomized, double-blind, placebo-controlled study **(Level of evidence 1b, Grade A)**.[281] Eligible patients included those with idiopathic OAB inadequately managed by anticholinergic therapy with urinary incontinence; >3 UUI episodes and an average of >8 micturitions per day in a three-day bladder diary; and a PVR urine volume <100 ml. A total of 548 patients were randomized to receive either onabotulinumtoxinA or placebo. The co-primary efficacy end points were change from baseline in number of UI episodes and proportion of patients with a positive treatment response on TBS at 12 weeks. OAB symptoms were assessed via three-day voiding diary and health-related QOL was assessed using I-QOL and KHQ. Safety measurements included adverse events and

PVR urine. OnabotulinumtoxinA significantly decreased the co-primary endpoint of UI compared to placebo (-2.95 vs. -1.03; p<0.001). The patient's perception of positive change in their condition demonstrated a large and significant difference between onabotulinumtoxinA and placebo groups (62.8% vs. 26.8%; p<0.001). Significant reductions in all other OAB symptoms and improvement in health-related QOL measures were found following treatment with onabotulinumtoxinA 100 U. Uncomplicated UTI was the most frequently reported adverse event and occurred in 20.4% and 5.2% of the onabotulinumtoxinA and placebo groups, respectively. The proportion of patients requiring CIC was 6.9% in the onabotulinumtoxinA group vs. 0.7% in the placebo group.

Observational studies provide insight into the efficacy and adverse events in specific populations with refractory idiopathic OAB treated with onabotulinumtoxinA.

Liao and Kuo evaluated the efficacy and safety of intradetrusor onabotulinumtoxinA (100 U) in 166 patients, including 61 frail elderly, 63 elderly, and 42 younger patients with idiopathic, refractory DO ***(Level of evidence 2b, Grade B)***.[282] Frailty was defined as age >65 years and three or more of any of unintentional weight loss of 4.54 kg in the last year, self-reported exhaustion, weakness (grip strength), slow walking speed, and/or low physical activity. All patients were closely monitored at 1–2 weeks, one and three months, and every three months thereafter until the response to onabotulinumtoxinA disappeared. Videourodynamics, seven-day bladder diary, and the International Prostate Symptom Score (IPSS) QOL index were obtained at baseline and at three months. The primary efficacy outcome was change in the Patient Perception of Bladder Condition (PPBC) with a decrease in PPBC of two considered successful. Procedure-related adverse events were recorded and included acute urinary retention (post-void greater than 350 ml, necessitating catheterization), gross hematuria, generalized weakness, large PVR (>150 ml), straining to void, and UTI. The primary outcome was similar between groups at three months (frail elderly 83.4%; elderly 91.2%; younger 88.9%) and at six months (frail elderly 49.4%; elderly 52.1%, younger 49.4%); however at 12 months, success rates were significantly lower for the frail elderly compared to elderly and younger groups (frail elderly 6.28%; elderly 22.3%; younger 23.1%). The rates of acute urinary retention, straining to void, and hematuria were similar across groups; however, the frail elderly were more likely to have a large PCR (frail elderly 60.7%; elderly 39.7%, younger 35.7%) and to report generalized weakness (frail elderly 6.6%, elderly 0%, younger 0%).

Wang et al retrospectively compared 48 patients with type II diabetes mellitus and refractory DO who received intravesical onabotulinumtoxinA 100 U to 48 age-matched, non-diabetic, controls ***(Level of evidence 2b, Grade B)***.[283] Success rates, defined as at least a two-point decrease in PPBC score, were similar between groups during the six-month followup period. Improvements in all OAB symptoms, as measured by seven-day bladder diary and urodynamic parameters, were comparable between the two groups. Diabetic patients had significantly greater incidence of large PVRs (60.4% vs. 33.3%; p<0.007) and generalized weakness (10.4% vs. 0%; p<0.028) compared to non-diabetic patients. Acute urinary retention (10.4% vs. 6.3%; p=0.357, straining to void (54.2% vs. 41.7%; p=0.154), hematuria (8.3% vs. 10.4%; p=0.500), and UTI (12.5% vs. 12.5%; p=0.621) were similar.

Long-term followup

Patients who completed either of the two aforementioned phase 3 trials were eligible to enter a three-year extension and continue treatment with onabotulinumtoxinA 100 U as needed for management of OAB symptoms.[284] Prespecified re-treatment criteria included 12 weeks or more since previous treatment, two or more UUI episodes on a three-day bladder diary, and PVR <200 ml. A total of 839 patients entered the open-label extension study, with 430 (51.3%) completing the 3.5-year study period. The median duration of effect of onabotulinumtoxinA was 7.6 months. The median duration of effect was six months or less in 34.2%, 6–12 months in 37.2%, and greater than 12 months in 28.5%. The rate of discontinuation due to lack of efficacy or adverse events was 5.7% and 5.1%, respectively. Only 0.5% discontinued due to treatment-related adverse events, including UTI, urinary retention, dysuria, and bladder pain. Therefore, the majority of patients discontinued treatment for other reasons (personal reasons, loss to followup, and study burden). Reductions in number of UI episodes per day remained constant throughout treatment and consistently high proportions of patients reported improvement or great improvement on the TBS across all treatments ***(Level of evidence 2b, Grade B)***. Reductions in other OAB symptoms and improvements in health-related QOL were sustained with long-term onabotulinumtoxinA treatment. Importantly, long-term treatment with onabotulinumtoxinA was well-tolerated, with no evidence of increasing occurrence of adverse events with repeat onabotulinumtoxinA treatments. De novo CIC incidence decreased from 4% after the first treatment to less the 2% for all subsequent treatment cycles. There was no incidence of onabotulinumtoxinA neutralizing antibody formation in those receiving the approved 100 U doses.

Summary and recommendations: OnabotulinumtoxinA (100 U) may be offered as long-term therapy to carefully selected patients with symptoms of frequency, urgency, and urgency incontinence who have had an inadequate response to or are intolerant of OAB pharmacotherapy (Evidence strength Grade A). Patients considering onabotulinumtoxinA must be carefully counselled regarding the need for close followup, the possible need for catheteriza-

tion (indwelling or CIC), and likelihood of repeat injections to maintain symptom improvement.

Third-line treatment: PTNS, SNM

Along with onabotulinumtoxinA injections, third-line treatment for OAB includes peripheral tibial nerve stimulation (PTNS) and sacral neuromodulation (SNM). Unlike the pharmacological management, onabotulinumtoxinA and SNM are considered invasive, with side effect profiles that may not be immediately reversible or may be permanently irreversible. Both PTNS and SNM are supported by Grade B evidence due to the observational nature of the majority of available studies, small sample sizes, disparate inclusion criteria, and short followup periods. The lack of long-term followup continues to be the main weakness in studies.[285-288]

PTNS

From the available literature, 18 studies and six systematic reviews were reviewed in consideration of PTNS. Compared to AMs, the treatment effect of PTNS is similar, but with a more tolerable side effect profile. The majority of studies demonstrated improvements in incontinence, frequency, nocturia, and QOL, and minimal side effects (bleeding at insertion site and inconsequential sensation of pain during stimulation) ***(Level of evidence 2a, Grade B)***. The general PTNS protocol included stimulation for 30 minutes, once a week, for three months, with followup periods from four weeks to 36 months. Baseline incontinence was typically >3 episodes/day (2.2–9.8) and was reduced by 1–3 episodes/day. Frequency of 11.8–16.5 episodes/day was reduced by 2–5 episodes/day. Nocturia episodes were reduced by 1–2 episodes/night.[289-298] Furthermore, when PTNS was compared to a sham-PTNS, improvements were only seen in the active treatment group ***(Level of evidence 1b, Grade B)***.[293]

On its own and combined with tolterodine 2–4mg daily, the use of PTNS appears to improve baseline symptoms when compared to tolterodine alone ***(Level of evidence 2b, Grade B)***.[289,290] Studies with 44–52 weeks of followup showed that improvements were sustained when therapy was continued ***(Level of evidence 2b, Grade B)***.[289,291-293]

In one double-blind, randomized, controlled trial, Finazzi et al showed that patients in the PTNS group (71% experienced >50% reduction in UUI episodes) achieved statistically significantly improved incontinence, frequency, voided volumes, and I-QOL scores ***(Level of evidence 2b, Grade B)***.[299] In another randomized trial, three groups, PTNS, oxybutynin ER 10 mg/day, and PTNS + oxybutynin ER 10 mg/day, showed similar improvements over 12 weeks ***(Level of evidence 2b, Grade B)***.[300] At 24 weeks, the oxybutynin only group demonstrated worsening of response rate when compared to the PTNS groups.

In line with the duration of treatment effects seen above, some studies showed sustained benefit from PTNS up to 4–6 months following end of treatment, despite varying treatment regimens ***(Level of evidence 2b, Grade B)***.[301-303] In studies involving maintenance treatment regimens for patients who initially responded to PTNS, statistically significant improvements were sustained through 24–36 months following varying protocols.[293,304] Analyzing six prospective non-randomized trials, subjective and objective success rates in PTNS patients were 61.4% and 60.6%, respectively, though the definitions of success varied.[305] In a meta-analysis of RCTs in which the control comprised either placebo or sham groups, PTNS patients were more likely to consider treatment a success with a relative risk of 7.02 (95% CI 1.69–29.17) ***(Level of evidence 1a, Grade B)***.[286]

Of note, PTNS does require a system capable of providing frequent clinic appointments, typically lasting 30 minutes to one hour in length, and patients must be compliant and able to continue frequent followup. Therefore, attention must be paid to the patient's level of motivation and travel resources.

Summary and recommendations: Physicians and patients should consider PTNS safe and effective as third-line treatment in a carefully selected population (Evidence strength Grade B).

SNM

SNM has been widely available since the late 1990s. It has been supported by predominantly observational data and few rigorous studies, including four RCTs, in a review of 23 studies in the recent literature. The treatment effects duration for SNM responders is similar to the pattern of PTNS in that maintenance of symptom improvement occurs only with continued use of the intervention. Separating SNM from PTNS and onabotulinumtoxinA injections is the different adverse event profile, including the need for surgical re-intervention in up to 39.5% of patients, with up a third of patients in the majority of studies requiring revision. SNM was also complicated by pain at the stimulator site (3.3–19.8%), pain at the lead site (4.5–19.1%), lead migration (2.2–8.6%), electric shock (5.5–7.9%), and infection/irritation (2.2–14.3%).[306] Positive bacterial colonization of the connector or lead site, measured at the time of the Stage II implant, occurred in 24% of patients (9/32).[307] One third of colonized patients went on to develop infection of the device requiring explantation. Only one patient who was not colonized developed infection. When the Stage I period was >14 days, 50% of patients showed colonization; when Stage I was ≤14 days, 14% developed colonization.[307] Furthermore, SNM is complicated by the preclusion of pelvic or abdomen MRI studies while the device is in place.

In review, typical study patients were characterized by the following: baseline incontinence 5.0–11.6 episodes per day,

or >4 pads per day, and frequency typically >13 episodes per day.[308-318] The success rate of Stage I implants, the testing phase, in patients who previously failed standard medical therapy or stopped due to medication side effects was found to be about 70% ***(Level of evidence 3b, Grade B)***.[319] Patients with worse incontinence (>10 episodes/day) fared better than patients with less severe incontinence (<5 episodes/day) **(Level of evidence 3b, Grade C)**.[320] In patients who had previously tried onabotulinumtoxinA injection, 79% (11/14 patients) were satisfied with treatment.[321] Obesity does not affect the chance of success.[322]

In Stage II implants, the treatment phase, respectable followup periods of up to five years were reported. When treatment success was defined as ≥50% decrease in the number of daily incontinence episodes or pads used, the initial 87% success rate one month post-procedure decreased to 62% five years post-procedure ***(Level of evidence 3b, Grade C)***.[309] Several studies in a cohort of patients comprised of urgency-frequency patients compared to urgency-incontinence patients reflect this trend, demonstrating 56% success in the urgency-frequency group and 68% success in the urgency-incontinence group at five years ***(Level of evidence 2b, Grade C)***.[311,316] Long-term patient satisfaction was surveyed to be 90% at a median post-implant interval 6.4 years.[313] Older patients, with mean age of 76 years, reported improvement (27.8%) and complete success with cessation of UUI episodes (55.5%).[323] Banakhar et al evaluated the effects on female sexual function and its impact on QOL in 23 sexually active women using the Female Sexual Function Index (FSFI) and Short-Form Health Survey (SF-36). At four months, statistically significant improvements were found in desire and orgasm categories, as well as in QOL in: physical function, energy, emotional well-being, social functioning, and general health ***(Level of evidence 3b, Grade C)***.[324] Twelve-month outcomes in sexual function using the FSFI were also significantly improved.[325]

Two notable RCTs include the In-site Trial and the Rosetta Trial.[326,327] The In-site Trial was a prospective, multicentre, FDA-mandated approval study evaluating the safety of the tined lead at six months and included a subset of patients with mild OAB symptoms randomized to SNM or standard medical therapy (SMT).[326] Of the initial 147 patients, 130 completed six months of therapy, 59 in the SNM group and 71 in the SMT group. At the six-month mark, 61% of the SNM group and 42% of the SMT group (p=0.02) achieved ≥50% improvement in average incontinence episodes/day or voids/day or a return to normal voiding frequency of <8 voids/day. Additionally, the SNM group responded significantly better in OAB QOL, improvement of sexual function, and improvement in depression ***(Level of evidence 1b, Grade B)***. The major limitations of this study include the mild nature of symptoms (SNM: mean 11.9 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, and mean 1.1 pads/day), and the relatively undefined OAB medication regimen. The Rosetta Trial was a randomized, open-label, active-control trial comparing the effectiveness of 200 U of onabotulinumtoxinA vs. sacral neuromodulation therapy for refractory UUI at six months.[327] Of the initial 386 patients, 190 in the onabotulinumtoxinA group and 174 in the SNM group both completed the six-month followup and were fit for primary analysis. The primary outcome was change from baseline in mean number of daily episodes of UUI averaged over six months, as recorded over three consecutive days in monthly bladder diaries. In the intention-to-treat population, patients treated with onabotulinumtoxinA had a greater six-month mean decrease of 3.9 episodes of UUI per day than did the SNM group of 3.3 (mean difference 0.63; 95% CI 0.13–1.14; p=0.01). This difference is small and may not be clinically relevant. In secondary outcome analysis, patients in the onabotulinumtoxinA group experienced greater improvement in symptom bother and treatment satisfaction, but there was no significant difference in QOL, treatment preference, convenience, or adverse effects ***(Level of evidence 1b, Grade B)***. The major limitations of this study are the exclusion of varying onabotulinumtoxinA injection techniques and the exclusion of men.

Summary and recommendations: Physicians and patients should consider SNM as more invasive and higher-risk than other third-line treatment, but a suitable option for patients with OAB symptoms refractory to preferred treatment options (Evidence strength Grade B).

Additional treatment (indwelling catheters, augmentation cystoplasty, urinary diversion)

Beyond the behavioural, lifestyle, and medical/interventional management provided in second- and third-line treatment of OAB, the adult, non-neurogenic population has few options supported by current literature. In the patient with contraindications to other treatment options, including intolerance to medications, allergy, severe debilitation or immobility, and cognitive deficit or expected cognitive decline, indwelling or intermittent catheterization may be tried. However, this carries a high risk of catheter-associated UTIs, long-term issues of urethral erosion (indwelling urethral catheters), and development of bladder calculi, and comes at the requirement of patient compliance and/or caregiver support. The use of catheterization in any form will require ongoing symptom evaluation and close, conscious followup, often by primary care physicians, for adverse effects/calculi. Though rare, malignancy has been described as a complication of enterocystoplasty, mostly in case reports. The majority of malignant tumours were adenocarcinomas, but urothelial carcinoma, carcinoid, and sarcomata have been seen.[328]

In very rare cases, surgery is an option, including augmentation cystoplasty or urinary diversion ***(Level of evidence***

5, Grade D). Most case series documenting the use of these surgical options do so in the treatment of neurogenic and paediatric patient populations, and are not suitable from which to draw conclusions for the adult, non-neurogenic patient. Furthermore, the patient's perceived benefit from treatment earlier in the treatment algorithm is primarily assessed in terms of QOL. Surgical intervention should probably be reserved for patients in whom other treatments either fail or result in an unacceptable QOL. The severity of potential adverse effects of surgical intervention must be weighed against the likely benefit in QOL.

Summary and recommendations: Indwelling catheterization, augmentation cystoplasty, or other urinary diversions are rare long-term management strategies for OAB and should only be considered after all other medical and surgical options have been exhausted and only after careful consideration of the likely benefits and risks. (Evidence strength Grade D)

Followup

The intent of followup is to ascertain compliance and efficacy, and to assess for adverse events. Ideally, measurements using validated OAB-specific instruments should be obtained and repeated at each subsequent visit. Therefore, the International Consortium for Health Outcomes Measurement proposed the Standard Set for OAB.[329] Followup schedules should be individualized according to the prescribed treatment and level of concern for patient safety.

Clinicians should be aware of the differences between OAB treatments with respect to expected efficacy and probability and type of adverse event. For example, the potential of AM agents to improve OAB symptoms may not be fully realized for a period of 12 weeks, whereas side effects, such as dry mouth, constipation, and central nervous system effects, may present earlier with varying degrees of severity. Thus, patients and their caregivers (in the case of elderly or frail elderly) should be informed of these nuances to promote compliance and patient safety and should be subsequently queried at all followup visits. Information gathered at each visit will help the clinician and patient decide on next management steps, particularly if the patient either does not respond or experiences untoward side effects. Initially, patients who have received intradetrusor onabotulinumtoxinA must be followed closely, with assessment of PVR for the possibility of acute urinary retention and need for catheterization. If onabotulinumtoxinA is deemed effective and safe, a repeat injection can be offered at six months and adjusted according to individual response. Neuromodulation, including PTNS and SNM, should be assessed pre- and post-treatment and after any setting adjustment with appropriate instruments, such as a bladder diary. Adverse events unique to neuromodulation should be routinely assessed including wound complications, persistent nerve pain, and collateral stimulation. Patients with urinary diversion, including indwelling catheterization, or lower urinary tract reconstructive surgery should be followed regularly for symptom control and potential complications.

Summary and recommendations: Patient followup should be routinely offered and individualized based on current treatment(s) and concern for patient safety. At each followup visit, the clinician should assess for compliance, efficacy, and potential side effects. If management is deemed ineffective or intolerable, then alternative treatment options should be presented, including drug dose-modification, change within drug class, change or addition of drug class, or consideration of third- or, rarely, additional OAB therapies (Expert Opinion).

Required research and future trends

Future research in OAB should further investigate all discussed areas, in particular pathophysiology, epidemiology, and clinical practice, including diagnosis and treatment options.

Pathophysiology research and further implications

New discoveries in the pathophysiology of OAB are warranted. Nowadays, alterations have been observed in the cholinergic, purinergic, adrenergic, serotonergic, glycinergic, GABAergic, and nitrergic pathways, as well as in production levels of different specific and non-specific transmitters like nerve growth factor, rho-kinase, and prostaglandins.[330] Emerging roles of ion and transient receptor potential channels have been observed lately.[331] Recent advances in cell-depended mechanism of bladder contraction have demonstrated the presence of the interstitial cells of Cajal in bladder suburothelium and detrusor muscle compartments.[332] It should be noted that new research findings do not only lead to an understanding of the pathophysiology of OAB, but can also contribute to new diagnostic methods and proper drug development. Each of these functional units expresses a distinct pattern of sensor and effector mechanisms that are potential diagnostic and therapeutic targets.

In the research for a reliable and non-invasive test for OAB patients, much interest has focused on biomarkers, with their potential for bedside testing. Markers of high- or low-grade infection or inflammation detectable both in urine and blood have now been noted to be raised in OAB, including serum C-reactive protein and different cytokines, with the greatest concern on nerve growth factor and prostaglandin E2.[333]

Drugs preventing acetylcholine-mediated involuntary detrusor contractions are the mainstay of OAB treatment and have the largest scientific background. Nevertheless, there are now several alternative therapeutic options available. Modernization of presently used drugs and designing new

compounds are intended to specifically target the urothelium and afferent nerves involved in pathophysiology of OAB. Moreover, future studies should also be aimed at determining the need for long-term chronic administration and its potential impact of an individual patient's health.

New AM molecules, novel modes of drug delivery, and even new combinations of existing treatments are presently studied; however newly developed AM agents, imidafenacin and tarafenacin, did not show any difference in terms of efficacy or side effect profile in comparison to currently used drugs.[334] To minimize systemic absorption and related side effects, vaginal and intravesical routes of oxybutynin delivery have been developed.[335,336] Intravesical instillation therapy using biodegradable devices have also been studied, as these could represent a good alternative to existing treatment for OAB.

The recent success of mirabegron as a new targeted drug for beta-3-adrenoceptors has moved to further studies on this signalling pathway. While use of mirabegron avoids many of the unwanted AM effects, it has a similar rate of adverse events and there remains concern about cardiac events, despite a recent meta-analysis.[337] The beta-3 agonist solabegron showed a statistically significant improvement in the number of incontinence episodes, with side effects rates and vital signs recordings similar to placebo. In view of these positive findings, solabegron is in the final phases of research.[338] Other beta-3-adrenoceptor agonists (aryloxypropanolamine h, Trk-380, AJ-9677, CL 316,243) are currently under investigation.[334]

New insight into pathophysiology of OAB resulted in possible new treatment objectives. Presently, the most promising targets seem to be the purinergic and cannabinoid systems, with different members of the transient receptor potential channel family.[331]

The underlying pathophysiology associated with idiopathic OAB is widely acknowledged to be multifactorial. Thus, phenotyping/profiling of patients with different underlying defects originating in the urothelial/mucosal layer of the bladder, the detrusor muscle cell layer, and the central nervous system could potentially improve the clinical problem of failed treatment.[339] A major challenge in profiling patients with subtypes of idiopathic OAB is the lack of a validated list of screening strategies or phenotypic markers to identify trial participants with different underlying pathophysiologies. Such phenotyping markers would need to indicate specific pathophysiological situations in which a disturbance in the urothelial/suburothelial/mucosal layer of the bladder, the detrusor muscle cell layer of the bladder, or the central nervous system could lead to the genesis of OAB symptoms. To overcome these issues, all future clinical trials should include patient profiling classifications based on suspected underlying pathophysiology.

Epidemiological research and further implications

No appropriate management could be implemented without reliable epidemiological data. Information on development and natural history of OAB is scant. Associated comorbidities and OAB related risk factors have not been sufficiently studied. Even though OAB has a significant effect on a patients' QOL, it is not clear whether this issue has an impact on outcomes of treatment. Well-conducted epidemiological studies could help in development of potential preventive interventions.

Reports on prevalence and incidence of OAB consistently identify it as a highly prevalent condition in both men and women;[9] however, many people with OAB do not seek medical attention and opt to suffer in silence, possibly without realising that treatments are available.[340] These serious issues may lead to major limits in patients' social and professional lives implicating further emotional distress, depression, and social isolation. Thus, the emerging role of social media in medicine should also be exploited in urology, particularly in OAB patients.[341]

Clinical research and further implications

To this day, disparities exist among OAB treatment-response assessment in clinical trials and different multidimensional PROs were used as primary or secondary endpoints in clinical research.[342] Given the heterogeneity of symptoms and multifaceted impact of OAB, measurement of outcomes in clinical trials is complicated. Researchers are confronted with the problem of balancing between objective findings in assessment and subjective outcomes reported by patients.[343] Moreover, this significant heterogeneity even exists between the response and non-response definitions in terms of symptom-based and patient-reported outcomes.[344] No consensus exists when it comes to measuring treatment outcomes with bladder diaries and PRO questionnaires. The usefulness of voiding diaries in OAB clinical trials is limited, mainly due to lack of validation/variations of content, format, and duration of data capture. OAB studies report a high level of placebo effect and the placebo response is poorly understood.[345] The symptom-based definition of OAB is useful to enter patients into treatment process; however, it fails to address what is most important to patients and doesn't allow investigation of underlying patholphysiology. Thus, it is clear that a new, simpler approach, with incorporated symptoms and health-related QOL evaluation should be employed to provide a more comprehensive and standardized approach to OAB assessment.

Population aging has emerged as a major worldwide demographic trend, both in developed countries and the developing world. It is known that OAB symptoms become increasingly prevalent with aging.[12] Furthermore, older persons are less likely to receive evidence-based care[346] and are more reluctant

to seek assistance[347] than younger people, thus OAB often remains undiagnosed and untreated. Clinical presentation and management of OAB are complicated in the vulnerable elderly by the presence of baseline frailty and multiple coexisting chronic conditions. Urological symptoms, incontinence in particular, are significantly connected with increased risk of falls, fractures,[348] and hospitalization.[349] Currently available drug treatments for OAB are usually poorly tolerated and often discontinued.[350] Needless to say, there is a dearth of evidence from clinical studies relating to the frail elderly, as clinical trials rarely include this population. Future clinical trials and research studies should focus on this group of patients to improve their prognosis and health-related QOL. Treatment outcomes must be tailored and individualized and should be coordinated with other medical care providers.

Conclusion

To summarize, our knowledge of the OAB syndrome has increased immensely over recent years. New OAB discoveries might help us make an earlier diagnosis, prevent progression, predict treatment response, and obtain better outcomes. As researchers begin to systematically explore both the genome and the metabolome of the urinary tract, with a special attention to transitional studies and clinical research, we will probably expect great improvement of our practice and in OAB patients' relief in the future.

Competing interests: Dr. Corcos is an advisor for Allergan, Astellas, Pfizer; a speaker for Allergan and Duchesnay; has received payments/grants/honoraria from Astellas; and has participated in clinical trials supported by Allergan and Ipsen. Dr. Przydacz has participated in clinical trials supported by Bristol-Myers Squibb. Dr. Campeau is an advisor for Astellas and Pfizer; a speaker for Astellas, Duchesnay, and Pfizer; has received payments/grants/honoraria from Astella and Pfizer; and has participated in clinical trials supported by Pfizer. Dr. Gray is an advisor for Astellas; a speaker for Astellas, Merus, and Pfizer; has received grants/honoraria from Astellas, Merus, and Pfizer; and has participated in clinical trials supported by Biones. Dr. Hickling is an advisor for Astellas and Pfizer; a speaker for Allergan and Pfizer; has received grants/honoraria from Boston Scientific; and has participated in clinical trials supported by Astellas. Dr. Radomski is an advisor for Allergan, Astellas, Duchesnay, Lilly, Merus, and Pfizer; a speaker for Astellas, Olympus, and Pfizer; and has participated in clinical trials supported by Allergan, Astellas, and Pfizer. Dr. Wagg is an advisor for Astellas and Pfizer; has received payment/grants/honoraria from Astellas, Duchesnay, Pfizer, and SCA AB; and has participated in clinical trials supported by Astellas and Pfizer. Dr. Stothers and Ms. Honeine report no competing personal or financial interests.

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Correspondence: Dr. Jacques Corcos, Department of Urology, Jewish General Hospital, Montreal, QC, Canada; jcorcos@uro.jgh.mcgill.ca