<table>
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<th>Program Name:</th>
<th>Overactive Bladder: ‘Something to Live With’? Making Clinically Significant Change for Your Older Patients with OAB</th>
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Learning Objectives
At completion of the program, the participant will be able to:

- Recognize the importance of treating OAB symptoms to improve patients’ quality of life.
- Differentiate between classes and agents available for OAB management.
- Make recommendations for safe and effective management of OAB in elderly patients.

Introduction
Overactive bladder (OAB) is a bothersome condition with a significant impact on quality of life. As the prevalence of OAB increases in association with age, it is important to manage symptoms effectively to maintain patient function and quality of life.

Management in older patients presents special challenges. Recent reviews and guidance recommendations for this patient population will help guide the safe management of OAB in elderly, including frail elderly individuals.

This program will explore clinical practice considerations in two case-scenarios of older patients who are ‘living with’ their OAB symptoms.

Pre-Course Survey
To what extent do you agree with the following statements?

[Scale: 1 – 5; 1 = strongly disagree; 5 = strongly agree]

1. I feel that overactive bladder can have a significant impact on quality of life.
2. I consistently ask about overactive bladder symptoms in elderly patients.
3. I consistently recommend a management plan for overactive bladder when present.
4. I consider antimuscarinic therapy for overactive bladder to be too unsafe for use in the frail or vulnerable elderly.
5. I comfortably counsel patients about expectations of treatment for overactive bladder.

OAB in Primary Care
As the most accessible healthcare providers in primary care, pharmacists are in a unique position to be able to support older patients who are experiencing overactive bladder symptoms.

Without appropriate management, overactive bladder (OAB) can have a significant impact on older patients. The perception that OAB is ‘just part of getting older’ is a common barrier to effective care. This perception exists among both patients and healthcare providers, making it an especially significant obstacle when both patient and healthcare provider are in agreement in the assumption that the patient must manage with their symptoms as a natural consequence of aging.

Furthermore, the management of OAB is complex, with many available treatments and a patient cohort that is often older, with multiple comorbid conditions and polypharmacy. If first intervention attempts lead to side effects or interactions, poor patient adherence, or inadequate response, both patient and practitioner may be tempted to abandon treatment altogether.
Pharmacists who acquire skill and confidence in managing these complexities in collaboration with the healthcare team will be better able to overcome many of the common obstacles to effective care.

This program will explore clinical practice considerations in two case-scenarios of older patients who are ‘living with’ their OAB symptoms.

**OAB Definition**

Overactive bladder should be differentiated from urinary incontinence. Overactive bladder is defined by the International Continence Society (ICS) as “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.”

**Symptoms:**

- **Urgency:** Sudden, compelling desire to void that is difficult to defer
- **Daytime frequency:** The need to frequently urinate during the day
- **Nocturia:** Waking up at night to void

Urgency urinary incontinence may be present but is not necessary for a diagnosis of OAB.

→ Practice resource: Click here to access a urinary function screening tool from the Canadian Continence Foundation.

**Prevalence**

The Canadian Bladder Survey used a cross-Canada telephone survey to ascertain the prevalence of lower urinary tract symptoms (LUTS) and urinary incontinence (UI) in Canada (see Figure 1).

**The Canadian Bladder Survey found:**

- OAB symptoms were reported in 13.9% of respondents. Prevalence increased with age and rose to over 23% in those older than 60 years.
- The prevalence of OAB symptoms was similar in both sexes; (13.1% of men and 14.7% of women). In the 75+ years age group, OAB was more common in men.
- OAB with urgency urinary incontinence is more common in women (7.1% vs. 3.3%).

**Figure 1.** Prevalence of OAB in Canada

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Ask-the-Expert
What are some of the barriers to treatment of overactive bladder in the elderly population?

The Burden of OAB
Overactive bladder (OAB) is a prevalent and bothersome condition that has a significant impact on quality of life. Overactive bladder affects ~ 12 to 18% of Canadians, and is under-diagnosed and under-treated. Diagnosis and management are important to minimize OAB’s impact on daily functioning and quality of life.1-5

The burden of OAB is even heavier in the older patient population:

- OAB symptoms increase with age, and occur in over 23% in those older than 60 years.4,6-9 Overactive bladder will become an increasingly prevalent problem as the population ages.6,7,10
- OAB is associated with additional health risks in older patients, particularly falls and fractures, and is associated with increased mortality and may be a predictor of institutionalization (especially in the presence of urinary incontinence).6,7,11-14
- Older patients are less likely to discuss their OAB symptoms with their healthcare provider, and are more likely to be untreated or under-treated.11,15-18

Effects on Quality of Life
Quality of life is significantly affected by OAB, especially when incontinence is present. The impact of OAB on a patient’s quality of life is estimated to be the same or even greater than that of diabetes.19

This is due to:19,20

- Interference with social and occupational activities (the 2006 estimated total direct cost burden for OAB in Canada was over $300 million9)
- Psychological and social consequences (especially with incontinence). It is quite common for patients with OAB with incontinence to avoid sexual activity and other activities due to the fear of loss of bladder control
- Restricting activities to environments with washroom access – fear of leaving the house for extended periods
- Emotional consequences: patients with OAB experience embarrassment, frustration, anxiety, annoyance, depression, and fear of odour due to their symptoms19
- People with OAB have an average 20% more visits to their physician per year versus those without.21

OAB symptoms should not be tolerated as an inevitable part of aging. They are manageable, even in the frail elderly person and the importance of management is high in this population.6,7

Refer to the Canadian Urological Association for additional information.

Ask-the-Expert
Why is it important to identify and manage overactive bladder in the elderly?

Differential Diagnosis
Common conditions that can share symptoms (frequency, urgency, nocturia) with OAB, and that are usually considered in the differential diagnosis include:22
• Acute urinary tract infection* (UTI)
• Prostatic enlargement in men, with symptoms due to bladder obstruction
• Bladder stones
• Tumour
• Stress urinary incontinence

* not asymptomatic bacteriuria, which is common in the older patient

Practice Tip
Potential causes of reversible urinary incontinence: Remember ‘DIPPERS’

- Delirium
- Infection
- Pharmaceuticals
- Psychological problems
- Excess urine output
- Reduced mobility
- Stool impaction

Discussion Forum
Do you feel that antimuscarinic agents are safe for use in the elderly? Why or why not?

Case Study 1
Paul is 77-year-old man, who until about a year ago remained quite active. Paul’s history includes myocardial infarction (7 years ago), and a radical prostatectomy 9 months ago.

Paul has not been coming into the pharmacy recently, although he used to be in regularly. His wife has been picking up his prescriptions for him. Today he visits the pharmacy in person and you take the opportunity to speak with him.

Case Challenge 1
Sensitive subjects can be difficult to discuss. Which approach do you think would tend to work best when discussing bladder symptoms with elderly patients?

a) Wait for the patient to raise the issue, so that you know they are comfortable discussing it
b) Raise the subject, with sensitivity. Otherwise you might never get a chance to discuss it.

Paul Revisited
As you inquire about his health, and how he is recovering from his surgery. You specifically ask if he has any troubles with his bladder. He mentions that these days he has to make sure that wherever he goes there will be a bathroom. As you reassure Paul that this is a common concern and that there are ways to treat it, he begins to open up about how the problem has been affecting him.

You learn that Paul has become increasingly restricted in his activity because of his urinary frequency and urgency. He also has occasional urinary incontinence. He is dismayed that he can no longer visit his
daughters and grandchildren because long excursions from home cause him tremendous anxiety about whether he will be able to reach a bathroom when needed.

Even short trips away from home for such tasks as going into town to shop for necessities are becoming problematic, and he increasingly relies on his wife to do these things.

He also feels “useless” because he cannot do the chores he used to do, such as mowing his lawn or gathering and stacking wood for winter. He is beginning to feel isolated and depressed.

Paul’s weight is 70 kg and his blood pressure is 126/84.

Paul’s medication:

- levothyroxine 50 mcg once daily
- rosuvastatin 10 mg once daily
- low-dose ASA 81 mg once daily
- amlodipine 5 mg once daily
- pantoprazole magnesium 40 mg once daily
- gabapentin (for neuropathic pain) 300 mg once daily
- metoprolol SR 50 mg BID
- ramipril 5 mg BID
- furosemide 40 mg BID

ASA: acetylsalicylic acid

Case Challenge 2
Pharmacists are important in assessment of medically complex patients who are experiencing overactive bladder symptoms. Which of the following of Paul’s medications may be contributing to his overactive bladder symptoms?

a) levothyroxine  
b) rosuvastatin  
c) low-dose ASA  
d) amlodipine  
e) pantoprazole magnesium  
f) gabapentin  
g) metoprolol SR  
h) ramipril  
i) furosemide

Factors to Consider
Certain factors or conditions can create signs or symptoms that may mimic or contribute to OAB symptoms (see Table 1).25
Table 1. Factors that Affect Symptoms\(^{25}\)

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<thead>
<tr>
<th>Conditions, Medications, Dietary Habits that Could Contribute to OAB Symptoms</th>
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<tr>
<td><strong>Neurological Conditions</strong></td>
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<tr>
<td>• Multiple sclerosis, spinal cord injury, stroke, Alzheimer disease, dementia, Parkinson’s disease</td>
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<tr>
<td><strong>Systemic conditions</strong></td>
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<td>• Congestive heart failure, diabetes mellitus, constipation</td>
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<td><strong>Medications (see further information in next section)</strong></td>
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<tr>
<td>• Diuretics, anticholinergics, opioids, calcium channel blockers, cholinesterase inhibitors, alpha-agonists, antihistamines</td>
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<tr>
<td><strong>Dietary and lifestyle concerns</strong></td>
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<tr>
<td>• Excessive intake of caffeine and/or alcohol</td>
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<tr>
<td>• Impaired mobility can interfere with ability to reach toileting facilities</td>
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<td>• Excessive fluid intake</td>
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**Medication Effects**

Diuretics, especially rapid-acting agents, cause a rapid increase in bladder volume, which may precipitate urgency and detrusor overactivity. Anticholinergic agents, opioids, and calcium-channel blockers decrease bladder contractility and may cause urinary retention with a decreased functional bladder capacity. Cholinesterase inhibitors could contribute to detrusor overactivity by increasing acetylcholine levels, and should be suspected in patients in whom symptoms develop after initiation of treatment.\(^{25,26}\)

**Non-pharmacological Treatment**

The Canadian Urological Association recommends conservative measures as the first approach to management of OAB. Goals include: increasing bladder capacity, reducing urinary frequency, and suppressing urgency. Strategies include:\(^{3,19,20,25,27}\)

- Limiting fluid consumption to ~ 2-2.5 L/day
- Limiting consumption of caffeine and alcohol
- Limiting fluid intake 2 hours before going to bed
- Bladder training
- Pelvic floor muscle training

**Pelvic floor muscle training (PFMT)**

The sling of muscles and connective tissue that extend across the base of the pelvis supports the pelvic organs and bladder. Pelvic floor muscle training employs exercise protocols designed to strengthen the pelvic floor muscles, which may improve function.\(^{28}\)

PMFT is available to patients in the form of:

- PFMT/\textit{Kegel exercises (women)}/\textit{Kegel exercises (men)}\(^{28}\) (See also Canadian Continence Foundation)
- Pilates classes\(^{29}\)
These approaches have been shown to be similarly effective in improving pelvic floor muscle function.

**Bladder Training**
Bladder training can increase the interval between micturitions, and help patients control the urge to urinate. Bladder retraining involves having the patient urinate on a regular schedule, and gradually increasing the interval between micturitions. The purpose is to retrain the brain-bladder connection and to increase the bladder’s capacity for storage.

**Paul Revisited**
Based on your recommendation, Paul’s physician has made some adjustments to his medication regimens. He has also made some lifestyle changes including reducing his caffeine intake.

However, despite these drug changes and behavioural interventions over the past month, Paul has continued to have persistent symptoms and occasional urgency incontinence.

You are concerned about the rapid decline in Pauls’ daily functioning since the onset of his OAB symptoms.

Research has shown that urinary incontinence in patients over age 65 years is associated with a more than two-fold risk of impaired functioning in activities of daily living, possibly heralding the onset of frailty.\(^{30,31}\)

Factors in urinary incontinence in the frail or medically complex patient are not restricted to the genitourinary tract. For example, changes in the connectivity between brain regions may precipitate the onset of urinary incontinence.\(^{30,32–35}\)

You recommend to Paul that he begin pharmaceutical treatment. You ask him what kinds of changes would make a difference for him, if the treatment works.

**Pharmacological Treatment**
Three classes of treatment are indicated in the management of OAB:

- Clinical guidelines recommend first-line pharmacotherapy with **antimuscarinic** agents, which have been in use for 30 years.\(^{3,36}\)
- A newer treatment option is a selective beta 3 adrenoceptor agonist, **mirabegron**, which was approved in Canada in 2012.\(^{37}\)
- **Botulinum toxin type A** was approved in 2013 in Canada for intradetrusor injections for the second-line treatment of OAB in adult patients who have an inadequate response to or are intolerant of antimuscarinic medication.\(^{38}\)

**Ask-the-Expert**
What misperceptions exist with respect to treatment approaches?

**Antimuscarinic Treatment**
Antimuscarinics are the mainstay of treatment for OAB. They have been shown to reduce the frequency of micturition, the sensation of urgency, and episodes of urgency urinary incontinence, with high levels of evidence.\(^{3,39,40}\)
First-line treatment is with the antimuscarinics

These agents help relieve OAB symptoms, especially when combined with non-pharmacological approaches (i.e., pelvic floor muscle training and normalizing fluid intake)

Patients should be educated about the onset of effect, which may take several weeks

A major meta-analysis of trials of antimuscarinic agents for OAB found antimuscarinics efficacious compared to placebo. Differences in the relative efficacy of the agents was not apparent, except that some results showed statistical significance in favour of the higher dosage of fesoterodine and solifenacin over placebo and lower dose antimuscarinics.41

For complete prescribing information, see product monographs.

Agents

Antimuscarinic treatment options include:42–50

- Darifenacin extended release tablets 7.5mg, 15mg
- Fesoterodine fumarate extended-release tablets 4mg, 8mg
- Oxybutynin chloride 5mg regular (immediate release) or extended release tablets 5 mg, 10 mg; gel 10%; transdermal continuous delivery, twice weekly dosing, 36 mg (3.9 mg / day system)
- Solifenacin succinate tablet, 5 mg, 10 mg
- Tolterodine L-tartrate regular or extended release capsules 2 mg, 4 mg
- Trospium chloride coated tablet 20 mg

Side Effects

Antimuscarinics differ in their frequency of administration, receptor selectivity and specificity, binding affinity, and other characteristics. The primary sites of activity are the M2 and M3 receptors of the bladder, which mediate contraction. Selectivity for muscarinic receptors is the main reason for variation in side effects across the antimuscarinic agents. Action on muscarinic receptors in the body beyond the detrusor muscle leads to side effects:3,42–50

The side effect profile of each antimuscarinic differs with possible adverse effects that can, depending on the agent, include dry mouth, constipation, headache, blurred vision, pruritus, tachycardia, somnolence, and impaired cognition.

For complete prescribing information, see product monographs.

Cautions and Contraindications

In antimuscarinic agents used in the management of OAB, cautions or contraindications include:3,42–50

- These agents should be used with caution in patients with renal insufficiency (CrCl<30 mL/min).
- Antimuscarinics are not contraindicated but should be used with caution in patients with bladder outlet obstruction. Urinary retention was reported in postmarketing experience with patients taking antimuscarinic medications, and in patients with bladder outlet obstruction. Monitoring is advised when administering antimuscarinics in patients with clinically significant bladder obstruction, due to risk of urinary retention.
- Antimuscarinics are contraindicated in patients with uncontrolled narrow angle glaucoma, urinary retention, gastric retention (gastric stasis), or unstable cardiovascular status.

For complete prescribing information, see product monographs.
Interactions

Antimuscarinic interactions include:3,42–50

**Drugs that may increase antimuscarinic effects:** amantadine, antihistamines, disopyramide, monoamine oxidase inhibitors, and tricyclic antidepressants.

**CYP3A4 inhibitors:** Solifenacin and fesoterodine levels may increase in the presence of potent CYP3A4 inhibitors because these agents are metabolized by CYP3A4. Dose adjustment is recommended (refer to the individual product monograph per agent) in patients taking moderate or strong CYP3A4 inhibitors such as fluconazole, ketoconazole, itraconazole, miconazole and clarithromycin.

**CYP3A4 inducers:** Induction of CYP3A4 may lead to reduced plasma levels of the active metabolite of solifenacin and fesoterodine. Concomitant use of CYP3A4 inducers such as rifampicin or carbamazepine is not recommended.

**Antiarrhythmics:** Darifenacin and tolterodine may increase risk of arrhythmias when given with antiarrhythmics.

*For complete prescribing information, see product monographs.*

**Mirabegron**

Mirabegron is an oral, once-daily, selective beta-3 adrenoceptor agonist that has shown similar efficacy to antimuscarinics.3,37 Mirabegron seems to act on the storage phase of bladder function to facilitate smooth muscle relaxation, for increased bladder capacity and lengthened interval between voiding.3,28,37,51

Mirabegron extended-release tablets are available in 25 mg and 50 mg.

*For complete prescribing information, see product monograph.*

**Side Effects**

Mirabegron is generally well tolerated; the most commonly reported adverse reactions (>3% of patients taking mirabegron 50mg/day) were hypertension, urinary tract infection, headache, and nasopharyngitis. The incidence of dry mouth and other side effects was similar in rate to placebo.37

*For complete prescribing information, see product monograph.*

**Cautions and Contraindications**

Mirabegron is **contraindicated** in:37

- Patients with severe uncontrolled hypertension* defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg
- Patients who are pregnant

Patients should be educated about the onset of effect, which may take several weeks.

Mirabegron should be used with caution in patients with bladder outlet obstruction. Urinary retention was reported in postmarketing experience with patients taking mirabegron or antimuscarinic medications, and patients with bladder outlet obstruction. Caution is advised when administering
mirabegron in patients with clinically significant bladder obstruction or in patients taking antimuscarinic drugs, due to risk of urinary retention.\textsuperscript{37}

**Cautions:**

**QTc Prolongation:** Mirabegron was associated with dose-dependent QTc prolongation that was more pronounced in females. At the maximal recommended therapeutic dose of 50 mg, the largest mean difference from placebo in the QTc interval was <5 ms in healthy male and female subjects at steady-state. Consider these observations in clinical decisions to prescribe mirabegron to patients with a known history of QT prolongation, risk factors for torsade de pointes (e.g. hypokalemia) or patients who are taking medications known to prolong the QT interval.\textsuperscript{37}

**Blood Pressure:** Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with mirabegron, especially in hypertensive patients. Also, mirabegron was not studied in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg) and, therefore is not recommended in these patients.\textsuperscript{37}

*For complete prescribing information, see product monograph.*

**Interactions**

Mirabegron is a moderate *inhibitor of CYP2D6.*\textsuperscript{37}

- The dose of mirabegron should not exceed 25 mg when co-administered with narrow therapeutic index CYP2D6 substrates, such as flecainide, propafenone, metoprolol, and desipramine.

Mirabegron is a weak *inhibitor of permeability-glycoprotein (P-gp).*\textsuperscript{37}

- For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.
- The potential for inhibition of P-gp by mirabegron should be considered when mirabegron is combined with sensitive P-gp substrates e.g. dabigatran, fesoterodine, trospium, or darifenacin.

The effect of mirabegron on multiple doses of warfarin has not been fully investigated.\textsuperscript{37}

*For complete prescribing information, see product monograph.*

**Botulinum Injections (Surgical)**

Botulinum injections are now indicated in Canada for the treatment of OAB when there has been inadequate response to antimuscarinic therapy.\textsuperscript{38}

**About Botulinum Injections**\textsuperscript{38}

- Clostridium botulinum type A, a neurotoxin, is injected into the detrusor muscle via a flexible or rigid cystoscope.
- The needle is inserted into the detrusor, and 20 injections are delivered (see Figure 4).
Clinical improvement may occur within 2 weeks. Patients may be considered for reinjection when the clinical effect of the previous injection has diminished, but no sooner than 3 months from the prior bladder injection.

Figure 4. Botulinum Injections

For complete prescribing information, see product monograph.

Adverse Reactions
The most common adverse reactions with botulinum injections and the rate at which they occurred in the first 12 weeks after intradetrusor injection in double-blind, placebo-controlled clinical trials were:

- urinary tract infections (26%)
- dysuria (11%)
- bacteriuria (8%)
- urinary retention (6%)
- increased residual urine volume* (3%)
- pollakiuria (daytime frequency) (2%)

Procedure-related events: dysuria (6%) and hematuria (2%)

* Elevated postvoid residual (PVR) volumes not requiring catheterization

If the patient has had botulinum injections for OAB, they might mention that they received catheterization. Some patients experience urinary retention after treatment and may require catheterization. Catheterization was initiated in 6.5% following treatment versus 0.4% in the placebo group. Patients who are not catheterizing prior to treatment may subsequently require catheterization for urinary retention. In patients who are not catheterizing, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks. Patients should be instructed to contact their physician if they experience difficulties in voiding.

For complete prescribing information, see product monograph.

Warnings
Serious Warnings and Precautions:
Adverse events after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, respiratory compromise, pneumonia, and/or other significant debility. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

This treatment should only be administered by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.

*For complete prescribing information, see product monograph.*

**Other Interventions**

Other interventions to address overactive bladder symptoms include:

- Electrical detrusor muscle stimulation (This is with sacral neuromodulation or percutaneous posterior tibial nerve stimulation that act to modulate detrusor contractions. The mechanisms of action not fully understood).
- Surgery (bladder augmentation or substitution)

These interventions may vary in cost-reimbursement and availability across Canada.

**Barriers to OAB Management**

Older patients with OAB are more likely to be untreated or under-treated.¹¹,¹⁴–¹⁶,¹⁸

Barriers to treatment include:¹¹,¹⁵–¹⁸

- patient and practitioner perceptions that OAB is just part of aging
- patient reluctance to discuss OAB symptoms with their healthcare provider
- concern that older patients are too frail or too ‘complex’ for treatment if multiple conditions are present
- perception of low treatment efficacy, or previous treatment failure
- concern that rates of cognitive side effects are too high a risk in this group (older patients)
- concerns about common side effects of treatment (e.g., constipation)
- other safety concerns, such as acute urinary retention (AUR)

Unmanaged side effects can also present a barrier to management, leading to the high attrition rates seen with OAB treatment.¹⁷

Concerns about the problematic nature of pharmacological management of OAB are not unwarranted. A recent systematic review examined the appropriateness of many drugs commonly used for urinary symptoms in older patients and identified only a few as having potential benefit.⁵⁴,⁵⁵
LUTS-FORTA
A systematic literature review and international consensus validation process (LUTS-FORTA 2014) systematically evaluated the appropriateness of 16 drugs commonly used for the treatment of lower urinary tract symptoms in older persons, on the basis of efficacy, safety and tolerability. The interdisciplinary group of experts concluded that:

- the drugs differed widely in their appropriateness for the older population
- there was limited evidence for the use of the majority of the reviewed drugs in older people, especially α-blockers and antimuscarinics, and that most of these should be avoided or used with caution
- the only agents identified as potentially beneficial were the 5α-reductase inhibitors dutasteride and finasteride and the antimuscarinic fesoterodine. (The 5α-reductase inhibitors are indicated for benign prostatic hyperplasia (BPH) but not for treatment of OAB in Canada, however antimuscarinic agents are indicated in OAB.)

Cognitive Side Effects
Despite the higher prevalence of OAB among older adults, concerns about the possibility of cognitive impairment as a side effect of antimuscarinic treatment likely contribute to the under-treatment of OAB in this patient group.

Cognitive impairment is a concern when using antimuscarinic agents because the M1 and M2 muscarinic receptors are expressed densely in the prefrontal cortex and hippocampus, which have roles for attention, executive function, and memory. Older individuals have added risks that include: increased permeability of the blood-brain barrier, changes in hepatic and renal function, and the presence of comorbidities and concomitant drugs that may have additive antimuscarinic effects or compete for metabolic resources.

However, antimuscarinics vary in their effects. Differences in properties are important to consider, especially:

- interactions with the M1 receptors in the central nervous system
- binding profiles
- lipophilicity
- ability to cross the blood-brain barrier

Brain penetration has been found to be low for antimuscarinics that are hydrophilic quaternary amines and P-gp substrates (fesoterodine, darifenacin, trospium), and higher for those that are lipophilic tertiary amines that are not P-gp substrates (oxybutynin, solifenacin, and tolterodine).

Recent evidence has shown that antimuscarinic agents do not have a negative effect on cognitive function in older adults, even in the presence of Alzheimer disease. Rather, they were found to positively impact daily life activities, depression, and quality-of-life.

The Mini Mental State Examination (MMSE) can be a helpful tool to monitor mental state in individuals for whom this is a concern.
Risk of Acute Urinary retention (AUR)
A major barrier to treatment of OAB in men is the concern that acute urinary retention may develop as an effect of antimuscarinic treatment when voiding symptoms are present (i.e., obstructive symptoms such as incomplete voiding, hesitancy, poor stream, or terminal dribbling).

However, published placebo-controlled, open-label and active-comparator studies show that the risk of acute urinary retention with antimuscarinics is less than 3%. 63

Additionally, clinical trial evidence has shown that adding antimuscarinic treatment to alpha blocker therapy in men with bothersome OAB symptoms can significantly improve frequency and urgency episodes. 63,64

Post void residual volume should be monitored in patients complaining of voiding symptoms. The combination of alpha-blockers and antimuscarinics have been found to be an appropriate option (see below). 3

“The combination of an alpha-blocker and an antimuscarinic agent is an appropriate and valid option for male patients with voiding symptoms and persistent storage symptoms, providing their post-voiding residual is ≤ 200 mL.”


Risk of Dry Mouth
A 2012 Cochrane review of antimuscarinic treatments in patient in OAB (note that this study did not focus specifically on elderly patients) concluded that: 65

• Between oral immediate release oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth. A lower starting dose of 1 mg twice daily tolterodine (instead of the usual 2 mg twice daily) might be equally effective, with less risk of dry mouth.
• Extended release preparations (of oxybutynin or tolterodine) might be preferred to immediate release preparations for reduced risk of dry mouth.
• Between solifenacin and immediate release tolterodine, solifenacin might be preferred for greater efficacy and reduced risk of dry mouth. A higher starting dose of 10 mg once daily solifenacin (instead of the usual 5 mg once daily starting dose) might provide better efficacy but with increased risk of dry mouth.
• Between fesoterodine and extended release tolterodine, fesoterodine might be preferred for better efficacy, bit with higher risk of dry mouth.

Discussion Forum
How do you guide patients’ expectations of treatment?

Case Study 2
Mary is a frail 80-year-old female patient, with type 2 diabetes. She resides in an assisted living facility in a major urban centre.
Mary has had some appetite decline over the past year, and has lost approximately 7% body weight. She experienced a couple of episodes of confusion which might have been associated with hypoglycaemia. Her insulin was recently discontinued because her blood sugar levels have been lower since her weight-loss.

Mary is complaining of sleeplessness. On further inquiry, she reveals her nocturia is the main cause of her disrupted sleep.

Mary’s current oral OAB treatment is oxybutynin IR 5mg bid, which she has been taking for eight years.

Mary’s medications:
- oxybutynin IR 5mg bid
- metformin 500mg four times daily
- atorvastatin 10 mg once daily
- enalapril / hydrochlorothiazide 5/12.5 mg BID
- low dose ASA 81 mg once daily

Case Challenge 1
Do Mary’s episodes of confusion mean that her antimuscarinic therapy should be discontinued?

a) Yes, behavioural interventions alone should be used
b) Yes, her therapy should be switched to mirabegron
c) No. Antimuscarinic therapy and can be continued (with consideration of switching agents)

Ask-the-Expert
What are the risks or safety concerns for treating OAB in the elderly population?

Who is the Frail Patient?
The frail patient is defined as “a clinical phenotype combining impaired physical activity, mobility, balance, muscle strength, motor processing, cognition, nutrition, and endurance; associated high medication use and being homebound or in a care institution and a high risk of intercurrent disease, increased disability, hospitalization and death.”

Ask-the-Expert
What type of monitoring should be involved when treating elderly patients for OAB?

Evidence in the Complex Older Patient
DuBeau 2014
A 2014 study by DuBeau et al is the first antimuscarinic study in a community based, significantly older, medically complex older patient population with urgency urinary incontinence. In this study, flexible dose fesoterodine (4 mg once daily for 4 weeks, with option to then increase to 8 mg once daily) significantly improved urgency urinary incontinence episodes versus placebo, and was generally well tolerated.

Additionally, the fesoterodine group had significant reductions in micturitions (p <0.001) and daytime and nocturnal urgency episodes (p <0.001 and p= 0.02, respectively) versus placebo (see Figure 6).
Figure 6: Change in frequency and urgency after 4 and 12 weeks for patients treated with fesoterodine vs placebo.\(^{66}\)

SOFIA Trial
Also, in the SOFIA Trial\(^*\), in 654 older OAB patients with multiple comorbidities and polypharmacy, treatment with the antimuscarinic fesoterodine demonstrated efficacy in reducing urgency episodes and urgency urinary incontinence episodes after 12 weeks of treatment, compared with placebo.

Findings from the SOFIA Trial\(^*\)\(^{67}\)
- Fesoterodine was found to be generally well tolerated in older OAB patients with multiple comorbidities and polypharmacy.
- The most frequently reported adverse events were dry mouth (6.0% placebo and 23.5% fesoterodine) and constipation (4.3% placebo and 11.1% fesoterodine), which were mild to moderate in intensity in most patients.
- No overall differences in safety and efficacy were observed between patients <65 years and those \(\geq\) 65 years; however, the incidence of antimuscarinic adverse events was higher in patients \(>75\) years as compared to younger patients.
- There were no changes in Mini-Mental State Examination score and very few adverse cognitive events were reported in either the fesoterodine or placebo groups.

Dosing Considerations in the Elderly
Some key considerations when selecting an antimuscarinic and dose for older patients include.\(^{6,66,67,67,68}\)
- When flexible dosing is available, the higher dose option might be required to achieve optimal efficacy in the older patient.
- A guiding principle is to start low and go slow. Initiate at the lowest available dose form (see Table 2) and then increase dose gradual to achieve efficacy as tolerated.
- If side effects occur, flexible dosing options allow for dose reductions (see Table 3).
- Immediate-release formulations should be avoided for older patients, to minimize side effects.
- Tell the patient that the side effects will appear before the beneficial effect on OAB symptoms. It takes about 4 to 6 weeks to see the optimal response.
• The magnitude of reduction in urinary urgency after four weeks is a good guide as to whom may need a dose increase

Table 2: Available Dosing Forms

<table>
<thead>
<tr>
<th>Name</th>
<th>Available Dosing</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin ER</td>
<td>7.5 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td></td>
<td>15 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Fesoterodine ER</td>
<td>4 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td></td>
<td>8 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>2.5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>1 mg/mL (syrup)</td>
<td>20 mg (5 mg QID)</td>
</tr>
<tr>
<td>Oxybutynin ER</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>30 mg (5 mg X6)</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin transdermal patch</td>
<td>1 patch (36 mg)</td>
<td>1 patch every 3 to 4 days</td>
</tr>
<tr>
<td>Oxybutynin transdermal gel</td>
<td>1 sachet (10 % oxybutynin)</td>
<td>1 sachet</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td></td>
<td>4 mg</td>
<td>4 mg (2 mg BID)</td>
</tr>
<tr>
<td>Tolterodine ER</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Trosospum</td>
<td>20 mg</td>
<td>40 mg (20 mg BID)</td>
</tr>
</tbody>
</table>

Table 3: Dose Adjustments for Antimuscarinics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (hours)</th>
<th>Renal Dose Adjustment</th>
<th>Liver Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin (ER)</td>
<td>13-19</td>
<td>None</td>
<td>CP class B: 7.5 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CP class C: avoid</td>
</tr>
<tr>
<td>Fesoterodine (ER)</td>
<td>7</td>
<td>CrCl&lt;30: 4 mg daily</td>
<td>CP class C: avoid</td>
</tr>
<tr>
<td>Oxybutynin IR/ER</td>
<td>2–3/13.2</td>
<td>Caution advised</td>
<td>Caution advised</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>45–68</td>
<td>CrCl&lt;30: 5 mg daily</td>
<td>CP class B: 5 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CP class C: avoid</td>
</tr>
<tr>
<td>Drug</td>
<td>OAB Class</td>
<td>CrCl&lt;30:</td>
<td>CP Class</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
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<td>-------------------</td>
</tr>
<tr>
<td>Tolterodine (IR)</td>
<td>2.2</td>
<td>1 mg BID IR</td>
<td>CrCl&lt;30: caution advised CP class A or B: avoid</td>
</tr>
<tr>
<td>Trospium</td>
<td>20/35</td>
<td>20 mg once daily (IR)</td>
<td>CrCl&lt;30: caution advised CP class B: avoid</td>
</tr>
</tbody>
</table>

CP = Child-Pugh


Discussion Forum
What adherence-counselling approaches do you use with older patients who are on antimuscarinic therapy for OAB?

Adherence
Tips for encouraging adherence:

- Ask patients about tolerability concerns and whether they find they can stick to their treatment without side effects
- Support patients with any side effects they might be experiencing (aids for dry mouth or constipation, for example)
- Educate patients about the duration of treatment before benefits are seen (usually several weeks), and the importance of adherence for outcomes. Initial side effects may be overcome, and the treatment effect may take a few weeks.
- Ensure that patients understand their dosing and administration
- Check for potential drug interactions

Key Points

- It is important to work with patients to identify the degree of reduction on symptom bother that they consider an acceptable goal of treatment.
- The recommended first approach to management is with behavioural interventions. It is important to take a thorough patient history, and also to ask patients about factors that may influence their symptoms (e.g., alcohol consumption and caffeine use).
- First-line pharmacotherapy is antimuscarinic treatment. A novel treatment for overactive bladder is the selective beta-3 adrenoceptor agonist mirabegron.
- If antimuscarinic treatment fails, botulinum toxin injections are now a second line option for treatment in Canada.
- The LUTS-FORTA systematic review identified only 3 agents as potentially beneficial in older patients with OAB: the 5α-reductase inhibitors dutasteride and finasteride and the antimuscarinic fesoterodine. The 5α-reductase inhibitors are not currently indicated for treatment of OAB in Canada, however antimuscarinic agents are.
- Older ‘complex’ patients on polypharmacy who have OAB have been found to benefit from the addition of OAB treatment with antimuscarinics. The group of antimuscarinic treatments that are most likely to have cognitive side effects are those that are not P-gp substrates because these penetrate the blood-brain barrier.
• To achieve optimal symptom control, older patients might require the higher dose of antimuscarinic when flexible dose options are available.
• Flexible antimuscarinic dose options allow for treatment to be adjusted, starting at a low dose and increasing, as tolerated, to achieve efficacy.

Post-Test
1. The International Continence Society (ICS) characterizes overactive bladder as:
   a) Urinary urgency, usually associated with daytime frequency and nocturia
   b) Urinary urgency usually associated with frequency and incontinence
   c) Urinary urgency, usually associated with frequency and pain
   d) Urinary frequency, usually associated with urgency and stress incontinence

2. The Canadian Urological Association recommends that the first approach to management of OAB should be:
   a) Behavioural modifications
   b) Botulinum toxin A injections
   c) Beta-3 AR therapy
   d) Antimuscarinics

3. Botulinum toxin type A is approved in Canada for intradetrusor injections, for what use?
   a) As first-line pharmacological treatment of overactive bladder when behavioural interventions alone have been inadequate
   b) As second-line pharmacological treatment of overactive bladder for patients who have failed on first-line pharmacotherapy
   c) Only for overactive bladder due to a neurological condition
   d) Only for overactive bladder with recurrent UTI

4. Mirabegron has its primary site of activity at:
   a) Muscarinic receptors M1 and M2
   b) Muscarinic receptors M2 and M3
   c) Beta-3 adrenoreceptors
   d) Beta-1 adrenoreceptors

5. According to the available evidence, what is the risk of acute urinary retention with antimuscarinic therapy?
   a) Less than 3%
   b) From 9 to 21%
   c) From 25 to 48%
   d) More than 56%

6. Based on the evidence in the older population, which of the following statements about dose and formulation applies, when flexible dosing with ‘lower’ and ‘higher’ dose options is available:
   a) Lower doses of antimuscarinics are usually required to achieve optimal efficacy in the elderly; also, immediate-release formulations are preferable.
b) Higher doses of antimuscarinics are usually required to achieve optimal efficacy in the elderly; also, immediate-release formulations are preferable.

c) Lower doses of antimuscarinics are usually required to achieve optimal efficacy in the elderly; also, extended-release formulations are preferable.

d) Higher doses of antimuscarinics are usually required to achieve optimal efficacy in the elderly; also, extended-release formulations are preferable.

7. Antimuscarinics that do not cross the blood-brain barrier are less likely to cause cognitive effects. Additionally, brain penetration is low for antimuscarinics that are P-gp substrates. (P-gp = permeability-glycoprotein)

These include:
   a) trospium, oxybutynin, and darifenacin
   b) oxybutynin, solifenacin, and tolterodine
   c) darifenacin, solifenacin, and tolterodine
   d) fesoterodine, darifenacin, and trospium

8. In a 2014 systematic review (LUTS-FORTA 2014) of drugs commonly used in the management of lower urinary tract symptoms in older adults, the only agents identified as potentially beneficial were:
   a) dutasteride, finasteride, and fesoterodine
   b) oxybutynin, solifenacin, and mirabegron
   c) trospium, oxybutynin, and darifenacin
   d) fesoterodine, mirabegron, and trospium

9. Which characteristic of antimuscarinic medications used in the treatment of OAB causes side effects?
   a) degree of beta adrenoreceptor non-selectivity
   b) degree of muscarinic receptor non-selectivity
   c) antimuscarinics that are hydrophilic quaternary amines
   d) antimuscarinics that are P-gp substrates

10. Which of the following agents is associated with QT prolongation?
    a) fesoterodine
    b) oxybutynin
    c) mirabegron
    d) darifenacin

References


