Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Anticholinergic Medications

January to March 2024

For the quarterly medication reviews from January to March 2024, review the resident's medication list for anticholinergic medications or medications with anticholinergic effects to assess each resident's anticholinergic burden:

Prior to the QMR:

- Pharmacists are asked to flag anticholinergic medications or medications with anticholinergic effects on the QMR form with a focus on medications considered to have moderate to high anticholinergic activity (see attached reference list) or an anticholinergic burden score of 2 or 3 on an anticholinergic burden scales or online calculators as outlined on page 5 & 6.
    - Calculate the resident's total anticholinergic drug burden score using the scoring tools discussed on pages 5 and 6.
- Nurses are asked to assess and document on the QMR form if the resident is experiencing any anticholinergic side effects (see Figure 2 on page 3 for potential adverse effects of medications with anticholinergic properties).

During the QMR:

- Review the total anticholinergic burden score and determine if the resident has a high anticholinergic burden (e.g., a total score of at least 3).
- Assess if the resident is experiencing any anticholinergic effects.
    - Consider if the resident is taking medications for the management of anticholinergic effects (e.g., laxatives for constipation, eye lubricant for dry eyes, proton pump inhibitors (PPIs) for dyspepsia, mouth moisturizers for dry mouth).
- Assess the effectiveness of the anticholinergic medication(s) or medication(s) with anticholinergic effects.
- Consider deprescribing medications with high anticholinergic burden or switching to medications with a lower anticholinergic burden. Candidates for deprescribing anticholinergic medications include:
    - Residents who have continued use of medication without improvement.
    - Residents with a high total anticholinergic burden score of 3 or higher.
    - Residents prescribed a variety of anticholinergic medications for treatment of concomitant health conditions.
    - Residents with planned or current treatment with a cholinesterase inhibitor for dementia.
    - Residents experiencing adverse effects, refer to Figure 2.
- Identify residents who may be candidates for deprescribing medications for overactive bladder (OAB):
    - Residents using 2 or more medications for OAB. Consider if one or more medications can be reduced or discontinued.
    - Residents using medications for OAB who start showing signs of overflow incontinence due to urinary retention.[47]
    - Residents with cardiovascular conditions; antimuscarinics and mirabegron can affect the QT interval and heart rate.
    - Residents using mirabegron with blood pressure that becomes difficult to control.
    - Residents using incontinence products who may no longer require OAB treatment.

QMR Contents:

Attachments included with the QMR:

- *ANTICHOLINERGICS: Reference List of Drugs with Potential Anticholinergic Effects (2021)*
- *Medications for Overactive Bladder (January 2024)*

What are the Top Four Prescribed Drugs in Ontario LTC with Significant Anticholinergic Effect? 2016[15]

Most prescribed	Quetiapine (Seroquel®)
	Olanzapine (Zyprexa®)
	Loperamide (Imodium®)
Least prescribed	Ranitidine > 150mg/d (Zantac®)

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LTC Quarterly Medication Review Deprescribing Focus

Anticholinergic Medications

Background

- Medications with anticholinergic effects are commonly prescribed in the older adult population.[1]
- Some medications may be prescribed specifically for their anticholinergic actions[2] (e.g., to treat overactive bladder, diarrhea, tremor caused by Parkinson's disease)
- Some medications may have anticholinergic effects unrelated to their therapeutic effects. This often results in unwanted adverse effects.[2] (e.g., SSRIs/SNRIs antidepressants, tricyclic antidepressants, antihistamines)
- Various medications with anticholinergic properties have been identified as potentially inappropriate medications for use in older adults due to their adverse effects.[3]
  - The Beers' Criteria lists many of the medications with anticholinergic properties as ones to avoid in the elderly population. Despite this, these medications are still widely prescribed.[1]
  - Often, these medications are used long-term despite having minimal benefit, which can also lead to continued adverse effects, as depicted in Figure 2.[7]
- The anticholinergic effects of various medications can range from being minimal to severe.[4,5,6]

Anticholinergic Effects

- There are five types of muscarinic receptors (M_1-M_5) located throughout the body, with M_1-M_3 receptors exhibiting the most physiological responses.
- A summary of the muscarinic receptors types 1-3 and the action of acetylcholine at these receptor types is provided in Table 1.
- Figure 1 provides an example of the role of acetylcholine and the M3 receptor in detrusor muscle contraction in the bladder. [8]
- Medications with anticholinergic properties block muscarinic receptors preventing neurotransmission of acetylcholine. Anticholinergic medications have the opposite effect of acetylcholine that is outlined in Table 1.
- Blockage of muscarinic receptors may result in a therapeutic benefit (e.g., prevent the bladder from contracting and reduce symptoms of overactive bladder) but can also result in adverse effects at other parts of the body as seen in Figure 2.

Table 1: Sites and Actions of Muscarinic Receptors Types 1-3 [8,9]

Receptor	Site	Action of acetylcholine at the receptor
M1	Brain	Increases memory, attention, and emotional responses
	Autonomic Ganglia	Alters autonomic nerve messaging
	Gastric Glands	Histamine release and acid secretion
M2	Heart	Decreases heart rate
	Smooth Muscle	Increase smooth muscle contraction
M3	Pupils	Constriction (miosis)
	Salivary Gland	Stimulates salivation
	Airway	Constricts airway
	Stomach	Stimulates activity
	Intestines	Stimulates activity
	Bladder	Contracts bladder

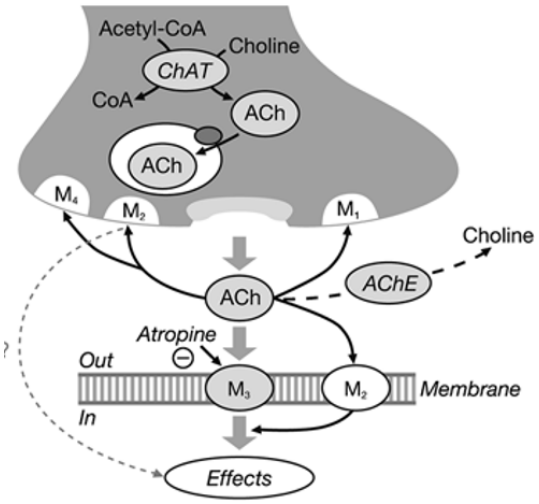

Figure 1: The role of acetylcholine and the M3 receptor in detrusor muscle contraction in the bladder. [8]

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Anticholinergic Medications

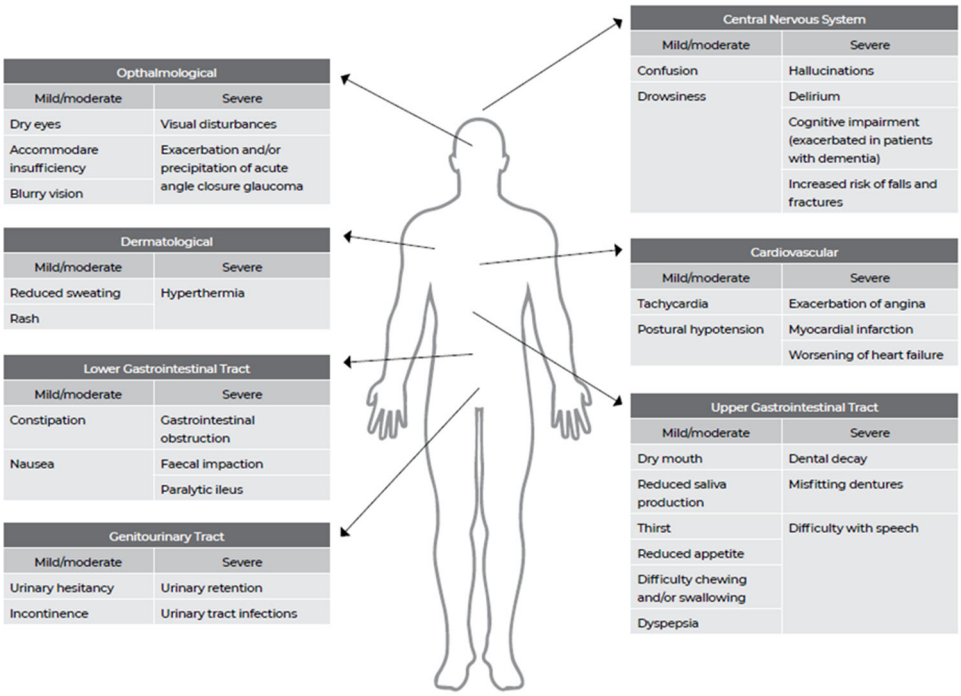

Figure 2: Adverse Effects of Medications with Anticholinergic Properties.[7]

Medications with Anticholinergic Effects and Prescribing Cascades

- Blocking acetylcholine neurotransmission at muscarinic receptors can result in anticholinergic adverse effects that could be misidentified as new health conditions and subsequently treated with a new medication (prescribing cascade).
  - Cognitive decline as a result of anticholinergic medications may be perceived as a new onset or worsening of dementia resulting in a new start or increased dose of a cholinesterase inhibitor.[17,18,19]
  - Delayed gastric emptying as a result of anticholinergic medications could be mistaken for gastrointestinal reflux (GERD) and treatment with a PPI gets started.
    - A large Nova Scotia cohort study of seniors with dementia suggested that anticholinergics increased PPI dispensing consistent with a prescribing cascade. Cox regression demonstrated an increased risk of starting a PPI within 180 days when initiating any medication from the anticholinergic burden scale (HR 1.38, 95%CI [1.29–1.58]) [44].
  - Constipation as a result of anticholinergic medications may lead to increased laxative use.
    - In a retrospective cross-sectional multicenter study of 2602 patients recruited from 27 Italian nursing home residents, antidepressant use (tricyclics and mirtazapine) increased laxative use by three times compared to non-users (tricyclic use: OR 2.98, 95% CI 1.31-6.77; mirtazapine use: OR 1.37, 95%CI 1.09-1.71).[43]

Concomitant use of medications with anticholinergic effects and cholinesterase inhibitors (ChEIs)

- ChEIs and anticholinergic medications have opposing actions and concomitant use may reduce the benefits of both types of medication.
- Anticholinergic medications are sometimes initiated to manage symptoms of urinary incontinence caused by ChEIs[17,18,19]
- In a retrospective analysis of 37,087 nursing home residents with severe dementia, 15% of the sample studied experienced co-prescribing of anticholinergics and ChEIs[42]
  - It was also observed that discontinuation of ChEIs was associated with a reduced likelihood (HR 0.58 [95% CI, 0.47-0.71]) of discontinuing any medications with anticholinergic properties that had been started, except for bladder antimuscarinics (HR 1.32 [95% CI, 0.83-2.09])
- It may be more beneficial to reduce the dose of the cholinesterase inhibitor rather than adding an anticholinergic medication to treat the side effects (e.g., for incontinence)[17].
- Reassess any residents currently prescribed both an ChEI and anticholinergic medication to determine if one or both can be deprescribed.

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Anticholinergic Medications

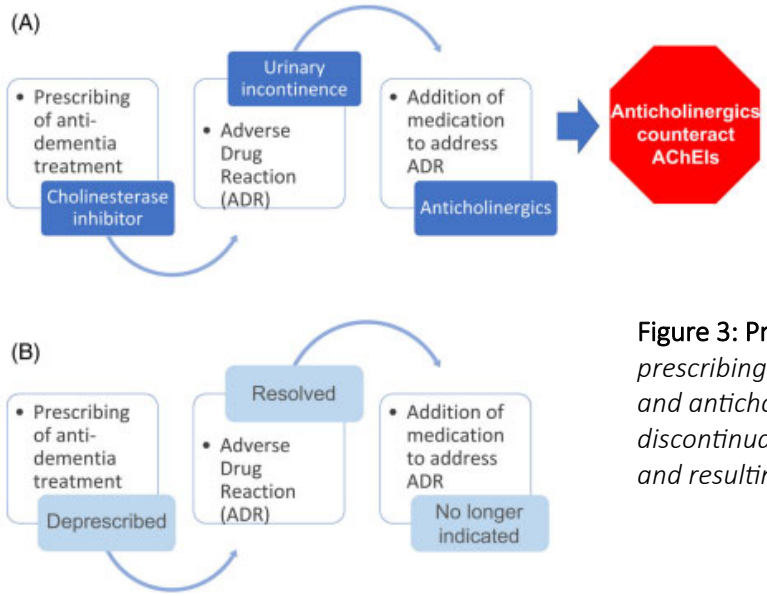

Figure 3: Prescribing and deprescribing cascade. *(A): The prescribing cascade featuring cholinesterase inhibitors (ChEIs) and anticholinergics. (B): The deprescribing cascade featuring the discontinuation of ChEIs, resolution of problematic side effects, and resulting lack of indication for anticholinergics.*[42]

Anticholinergic Drug Burden

- The anticholinergic drug burden is the cumulative anticholinergic activity a person is exposed to taking into consideration all the medications with anticholinergic effects they are taking. The burden increases as the number of anticholinergic medications prescribed increases.[1]
- Studies have shown that the higher the anticholinergic burden a person is exposed to, the higher their risk of experiencing anticholinergic adverse effects, cognitive impairment, and potentially mortality.[10,11,12,13,14]
  - A 2014 systematic review of 46 studies with a total of 60,944 participants reviewed the effect of anticholinergic medications on cognitive function, delirium, physical function, and mortality.[10] The results showed that patients with an increased anticholinergic burden experienced significant adverse effects.
    - 33 studies were analyzed for an impact on cognitive function; 23 of these studies showed a significant decline in cognitive function whereas 10 studies showed no significant associations.
    - 5 studies were analyzed for the risk of delirium. While only one study showed a significant association between anticholinergic medication and delirium, only one of the five studies analyzed had a population that consisted of nursing home residents and none of the studies considered anticholinergic burden scores.
    - 8 studies were analyzed for physical decline; 5 studies showed a decline in physical function and 3 studies showed no association at all.
    - 9 studies were analyzed for mortality risk; 3 studies showed an increase in mortality, while 6 studies showed that mortality was not statistically associated with anticholinergic use.
- A 2019 Australian cross-sectional study looked at the effects of anticholinergics on appetite and found a significant decrease in appetite with the use of anticholinergic medications.[14] This highlights a key adverse effect that can lead to frailty and weakness.

Anticholinergic Burden Scales

- The total anticholinergic burden score can be calculated by using published anticholinergic burden scales. Table 2: *Available Anticholinergic Burden scales* outlines some of the available anticholinergic burden scales[15]
- Anticholinergic burden scales were created to quantify the effects of medications with anticholinergic effects.
- These scales are generally formulated by an expert team combining results of research into anticholinergic properties of medications along with their own clinical expertise[5].
- These scales may include different medications and may vary in how scores were assigned; this illustrates that there is not universal agreement about anticholinergic burden and the impact on patients.[5]
- These lists may not include all medications with anticholinergic effects.[5]

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Anticholinergic Medications

Table 2: Available Anticholinergic Burden Scales[15]

Scale Name, Country of Origin, Year of Publication	Description	# of Medications Listed
1. The Anticholinergic Drug Scale (ADS), USA, 2006[52]	ADS is a four-point (0-3) scale that ranks anticholinergic drugs based on expert opinion	117
2. Anticholinergic Burden Classification (ABC), France, 2006[53]	ABC is a four-point scale (0-3) based on serum anticholinergic activity and expert opinion	27
3. Clinician-rated Anticholinergic Score (CrAS), USA, 2008[54]	CrAS is a four-point scale (0-3) based on pre-existing published anticholinergic scales and expert opinion	60
4. The Anticholinergic Risk Scale (ARS), USA, 2008[55]	ARS is a four-point scale (0-3) based on extensive literature review and expert opinion	49
5. Anticholinergic Cognitive Burden Scale (ACB), USA, 2008[56]	ACB is a four-point (0-3) scale developed based on published data and expert opinion	88
6. Anticholinergic Activity Scale (AAS), Norway, 2010[57]	AAS is a five-point scale (0-4) based on existing evidence and expert opinion	99
7. Anticholinergic Loading Scale (ACL), Australia, 2011[58]	ACL is a four-point (0-3) scale based on pre-existing published anticholinergic scales and expert opinion	49

- Medications with scores of 0 or 1 are preferred to limit the overall anticholinergic burden.
- A burden score of 3 or greater has been associated with increased cognitive impairment and mortality.[1,4]
- While there are multiple different scoring systems, the German Anticholinergic Burden score and the Anticholinergic Cognitive Burden (ACB) Scale have been demonstrated to show most validity and reliability.[5]
- Anticholinergic burden scales are not a replacement for clinical assessment. They can be used as tools to help identify medications with high anticholinergic effects within classes of treatment and assess if viable alternatives with less anticholinergic effects are available.[4]
- Medications are scored as having no, weak, moderate, or strong anticholinergic effects (e.g., 0 = no anticholinergic effect; 3 = strong anticholinergic effect)
- A 2020 systematic review and meta-analysis analyzed 20 articles which included 18 cohort studies to assess the association of anticholinergic burden and mortality.[11]
    - It was concluded that there was an association between anticholinergic burden and higher risk of mortality. The calculators used in these studies were the Anticholinergic Cognitive Burden (ACB) Scale, Anticholinergic Drug Scale (ADS), and Anticholinergic Risk Scale (ARS) with the majority of studies using the Anticholinergic Cognitive Burden Scale.
- A 2020 retrospective cohort study looked at the impact of anticholinergic burden on fall risk and fall-related injuries in 10,698 participants with mild cognitive impairment or dementia and at least two additional chronic conditions.[12]
    - Among participants with a total anticholinergic drug burden (ADB) score of 5 or greater, those taking a combination of medications with an ADB score of 2 and an ADB score of 3 had the highest fall risk or fall-related injury.
    - Exposure to medications with an ADB score of 2 posed higher risks than exposure with medications having an ACB score of 1 or 3.
    - Participants exposed to multiple medications each having an ADB score of 1 were also at higher risk of fall or fall-related injuries.
- A 2021 systematic prognostic reviewed eight cohort and case-control studies with participants aged 65 or older taking anticholinergic medications with falls being the primary outcome.[13]
    - All eight studies showed a significant association between increased ADB and increased falls particularly when the total ACB score was 4 or greater.
    - Most studies used the ACB Scale, however the review found that no conclusion could be made regarding which ADB scale provided the best value in older individuals.

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Anticholinergic Medications

Online Anticholinergic Burden Calculators

ACB Calculator (www.acbcalc.com)[5]

- Utilizes the German Anticholinergic Burden score and the Anticholinergic Cognitive Burden Scale (for any score discrepancies, the higher value is used).
- Several medications can be added to provide a total anticholinergic burden score
- The list of medications included with this online calculator is limited to medications with known anticholinergic effects.

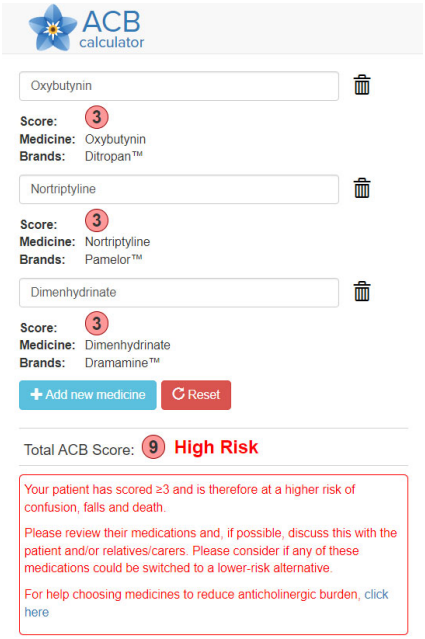

Figure 4: Example of the ACB Calculator Online Tool[5]

Medichec (www.medichec.com)[6]
Refers to "AEC" score (Anticholinergic Effect on Cognition)

Pros:

- Developed by the NHS (UK)
- Has a large list of medications in its database
- Includes medications with AEC scores of 0
- Calculates a total AEC score
- Includes a visual aid and explanation on other side effects including hyponatremia, dizziness, constipation, QTc prolongation, bleeding risk, and drowsiness
- Can be exported as a pdf or emailed

Cons:

- Longer webpage which requires more scrolling to get the information you want
- Colour coded visual aids and score correlations not always intuitive (need to read descriptions)

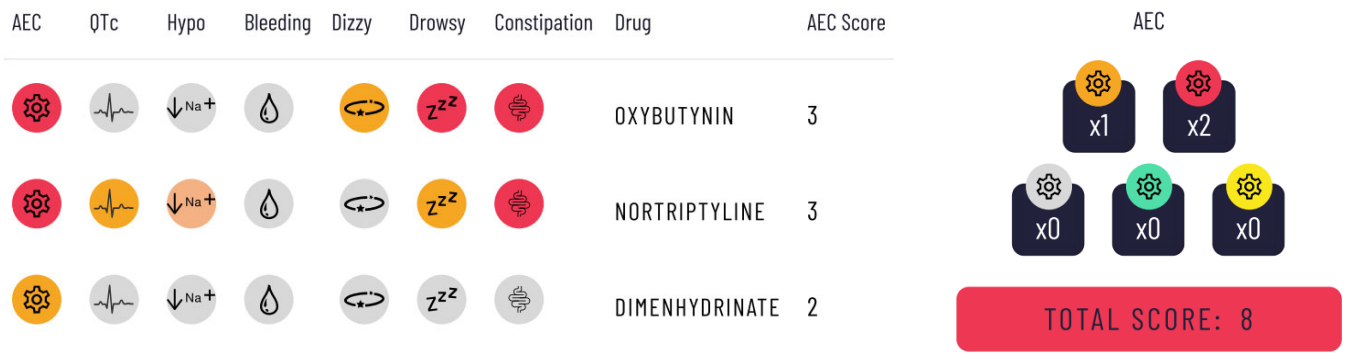

Figure 5: Example of the Medichec Online Tool[5]

Quarterly Medication Review Deprescribing Focus

Anticholinergic Medications

Anticholinergic Medications

- There are lists of medications with anticholinergic effects available, including the *Reference List of Drugs with Potential Anticholinergic Effects* developed by RxFiles (attached).[16]
- Antihistamines, analgesics, and medications for the treatment of hypersalivation are medications with anticholinergic effects in LTC where treatment alternatives with lower anticholinergic burdens exist.[5,6,16]
- Some long-acting muscarinic-antagonists (LAMAs) (e.g., ipratropium, tiotropium, aclidinium, umeclidinum) used for the treatment of COPD have an anticholinergic mechanism, however their systemic absorption and subsequent anticholinergic effects can be minimized by avoiding overuse and by using a spacer device such as an Aerochamber®.

Antihistamines

- First-generation antihistamines (e.g., diphenhydramine) have high anticholinergic activity (see Table 3 below).
- Consider using a second-generation antihistamine (e.g., cetirizine, loratadine) which have lower anticholinergic activity.
- Cetirizine is on the PCH Medication Standing Orders for mild allergic reactions and is a preferred option when an antihistamine is required.

Table 3: Antihistamine Anticholinergic Burden[5,6,16]

MEDICATION	ANTICHOLINERGIC BURDEN SCORE
DIPHENHYDRAMINE	3
DOXYLAMINE	3
CETIRIZINE	1
LORATADINE	1
HYDROXYZINE	1

Hypersalivation

- Scopolamine and atropine have high anticholinergic activity (see Table 4 below).

Table 4: Anticholinergic Burden of Medications Used in the Treatment of Hypersalivation[5,6,16]

MEDICATION	ANTICHOLINERGIC BURDEN SCORE
SCOPOLAMINE	3
ATROPINE	3
GLYCOPYRROLATE/GLYCOPYRRONIUM	1

- For treatment of hypersalivation or increased secretions at end-of-life, consider using glycopyrrolate.

Analgesics/Muscle Relaxants

Table 5: Anticholinergic Burden of Common Pain Medications[5,6,16]

MEDICATION	ANTICHOLINERGIC BURDEN SCORE
METHOCARBAMOL	3
CYCLOBENZAPRINE	2
BACLOFEN	1
TRAMADOL	2
MEPERIDINE	2

- Baclofen has lower anticholinergic activity among the muscle relaxants compared to methocarbamol and cyclobenzaprine
- The majority of opioids have low anticholinergic activity except

LTC Quarterly Medication Review Deprescribing Focus

Anticholinergic Medications

Deprescribing Anticholinergic Medications[7]

- Candidates for deprescribing anticholinergic medications include:
  - Residents who have continued use of medication without improvement.
  - Residents with a high total anticholinergic burden score (of 3 or higher).
  - Residents prescribed a variety of anticholinergic medications for treatment of concomitant health conditions.
  - Planned or concurrent treatment with cholinesterase inhibitors for dementia.
  - Residents experiencing adverse effects, refer to Figure 2.

Treatment of Overactive Bladder (OAB)

Types or Urinary Incontinence:

1. *Stress Urinary Incontinence*
   - Incontinence generally occurs with physical activity, no incontinence when physically inactive or when supine
2. *Urge Urinary Incontinence or Overactive Bladder (OAB)*
   - Increased urinary frequency (more than 8 micturitions per day)
   - Urgency with or without incontinence
   - Nocturia (1 or more micturition per night) and enuresis may also be present
3. *Overflow Incontinence (Chronic Urinary Incontinence)*
   - Usually due to enlarged prostate in men; cystocele formation or surgical overcorrection of stress incontinence in women.
   - Incontinence occurs from bladder underactivity, which results in the retention of urine in the bladder and overflow of urine
4. *Functional Incontinence*
   - Involuntary incontinence due to environmental or physical barriers to using the bathroom.

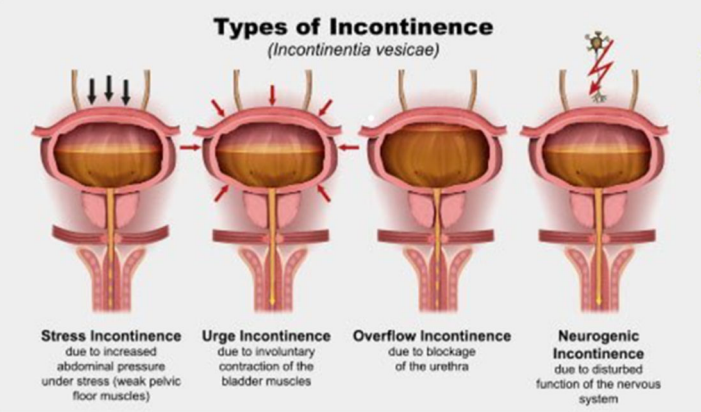

Figure 6: Visual Representation of the Types of Incontinence.[22]

- Per the Canadian Urological Association's 2017 guidelines on adult OAB[23] and the American Urological Association's 2019 guidelines on adult OAB (2019)[25, 26] first-line treatment should consist of behavioural therapies and lifestyle changes.
  - This may provide limited benefit in LTC residents with dementia or those who are not able to follow instructions.
- Second line therapy includes oral antimuscarinics which act on the detrusor smooth muscle in the bladder (e.g., oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, darifenacin) or oral beta3-adrenergic receptor agonists which increase bladder capacity (e.g., mirabegron). [23,25,26] Refer to table of *Medications for Overactive Bladder* attached.
- Clinicians should use caution in prescribing antimuscarinics or beta3-adrenergic receptor agonists in the frail OAB patient.[25,26]
- The selected agent should be trialed at the lowest recommended dose followed by dose increases to obtain best clinical response with minimal side effects.[23]
- The risk of adverse effects versus benefits of therapy should be assessed when considering pharmacological treatment of OAB in the elderly.[23]

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Anticholinergic Medications

Treatment of Overactive Bladder continued…

- Pharmacologic treatment with antimuscarinics and selective beta3-adrenergic receptor agonists are effective for the treatment of stress and urge urinary incontinence.[10] Combination therapy may be appropriate when single drug failure occurs.
  - Choice of medication depends on factors such as:
    - Resident's history of antimuscarinic use (e.g., Was it effective? Should an alternate antimuscarinic therapy be used at this time?) [25,26]
    - Adverse effects experienced in the past and potential impact of adverse effects on the resident
    - Resident preferences
    - Comorbidities
    - Current medication history (e.g., is the resident also using other medications with anticholinergic properties)
- If an immediate release (IR) and an extended release (ER) formulation are available, ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth.[25,26]
  - The rate for the oxybutynin ER formulation was 40% (95% CI: 28% to 53%) and was statistically significantly lower than the oxybutynin IR rate of 69% (95% CI: 60.6% to 76.5%) [25,26] However, oxybutynin ER tablets (Ditropan XL®) are no longer marketed in Canada.
  - ER formulations can not be crushed so may not be appropriate for older adults with difficulty swallowing tablets or capsules whole.
- LUTS-FORTA 2014[45]
  - Medications used to treat lower urinary tract symptoms (LUTS) regularly in older persons were systematically reviewed to classify appropriate and inappropriate drugs based on efficacy, safety and tolerability by using the Fit fOR The Aged (FORTA) classification.
  - No medications were rated at the FORTA A level (indispensable).
  - Only three medications were assigned to FORTA B (beneficial): dutasteride, fesoterodine and finasteride.
  - The majority of medications were rated FORTA C (questionable): darifenacin, mirabegron, extended release oxybutynin, silodosin, solifenacin, tadalafil, tamsulosin, tolterodine and trospium.
  - FORTA D (avoid) was assigned to alfuzosin, doxazosin, immediate release oxybutynin, propiverine and terazosin
  - In older people, the majority of these drugs, in particular those from the group of **α-**blockers and antimuscarinics, should either be used with caution or be avoided.
  - The evidence base for the use of these drugs in older people is limited.
- A 2022 retrospective cohort study found that tolterodine and oxybutynin led to higher risk of cognitive decline compared to other antimuscarinic medications, but further research is necessary to determine if oxybutynin and tolterodine are significantly more likely to cause cognitive decline.[30]
- Some antimuscarinics such as solifenacin and darifenacin are more selective for the M3 receptors in the bladder, which may make them a better option than other antimuscarinic that have affinity for all muscarinic receptors to limit cognitive adverse anticholinergic effects.[27]
  - Short-term clinical studies have shown that solifenacin, which has high affinity for the M3 receptor but also binds to the M1 receptor, did not cause cognitive decline. However, there are no long-term randomized controlled trials that prove the safety of this medication for the CNS. [29]
- Studies have shown that darifenacin, a M3-selective medication, did not cause cognitive decline.[28]
- In a retrospective cohort study using linked administrative data involving patients over the age of 66 newly started on an OAB medication. When compared to treatment with a β_3-adrenergic receptor agonist, continuous use of newer anticholinergics such as fesoterodine, solifenacin and tolterodine for over 30 days was associated with an increased risk of delirium (HR 1.13, 95% CI 1.02-1.26) and continuous use of oxybutynin had an increased risk of falls/fracture (HR 1.13, 95% CI 1.02-1.24) primarily in those over 77 years of age [31]
  - This equates to one extra fall/fracture for every 45 person-years of use of oxybutynin and one extra case of delirium for every 246 person years of newer anticholinergics use instead of β_3-adrenergic receptor agonists[31]
- *Mirabegron*:
  - Systematic literature review and network meta-analysis of randomized controlled trials assessed the efficacy and tolerability of mirabegron 50 mg versus antimuscarinic monotherapies and combination therapies.[32]
    - Mirabegron 50 mg was as effective as antimuscarinic therapy, with fewer common, bothersome side effects such as dry mouth, constipation, and urinary retention.
    - The risk of constipation with mirabegron 50 mg was similar to that with placebo (OR: 0.79 [95% CI: 0.60, 1.05]).

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Anticholinergic Medications

Treatment of Overactive Bladder continued...

- ◊ The risk of constipation was significantly lower for mirabegron 50 mg compared with nine active treatments (darifenacin 7.5 and 15 mg, fesoterodine 8 mg, propiverine 20 mg, solifenacin 5 mg combined with mirabegron 25 or 50 mg, solifenacin 5 and 10 mg, and trospium 60 mg).
- ◊ Combination treatment of solifenacin 5 mg plus mirabegron 25 or 50 mg was more effective than mirabegron 50 mg alone, but with more anticholinergic side effects.
- ◊ Combination therapy may be beneficial for patients with OAB who do not respond adequately to first-line pharmacological treatment.

- SYNERGY trial[46]
  - All active treatment groups had greater improvements in the mean numbers of micturitions per 24 hours versus placebo, with effect sizes for the combined therapy groups (solifenacin/mirabegron 25 mg: -0.85; solifenacin/mirabegron 50 mg: -0.95) higher than with mirabegron monotherapy (25 mg: -0.36; 50 mg: -0.39) and solifenacin 5 mg monotherapy (-0.56).
  - Researchers noted that the combined solifenacin/mirabegron 50 mg group was statistically significantly superior to both monotherapies at end of treatment for urge urinary incontinence episodes, urgency episodes and nocturia, with effect sizes that appeared to be additive.
  - Adverse events including dry mouth, constipation, and dyspepsia, were slightly increased in the combination therapy groups compared to monotherapies.
  - Urinary retention was reported more frequently in the combination groups compared to monotherapy and placebo.
- Mirabegron is not without its own risks:
  - Contraindications include: severe uncontrolled hypertension (systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg) and hypersensitivity to mirabegron or its components.[35]
  - Mirabegron should be discontinued if angioedema of the tongue, oropharynx, or larynx occurs.
  - The dose of mirabegron needs to be adjusted for renal impairment.[35]
  - Other known side effects include: tachycardia, diarrhea or constipation, cystitis, influenza, nasopharyngitis, and sinusitis.[3]

Deprescribing Medications for Overactive Bladder

- Identify residents who may be candidates for deprescribing medications for overactive bladder:
  - Residents using 2 or more medications for OAB. Consider if one or more medications can be reduced or discontinued.
  - Residents using medications for OAB who start showing signs of overflow incontinence due to urinary retention [47]
  - Residents with cardiovascular conditions; antimuscarinics and mirabegron can effect the QT interval and heart rate
  - Residents using mirabegron with blood pressure that becomes difficult to control
  - Residents using incontinence products:
    - ◊ Continued benefit and risks of pharmacologic treatment of OAB in residents wearing incontinence products should be reassessed.
    - ◊ There are no specific guidelines or studies that investigated the usefulness of pharmacological treatment of OAB in patients wearing incontinence products.
    - ◊ Medications that relax the bladder may still be helpful for reducing episodes of urge incontinence which could be distressing to the resident.
    - ◊ If the resident is not bothered by the symptoms, then deprescribing can be trialed.
- A discussion of the risks and benefits of continued treatment should take place with the resident and/or their substitute decision maker.
- When tapering antimuscarinic medications for OAB, it has been recommended to decrease the dose by 25-50% every 1-4 weeks. Consider slower weaning of 12.5% when reducing to the final lowest dose and stop treatment 2 weeks after starting the lowest dose. [7]
- Monitor for withdrawal symptoms which can occur within 1-3 days of dose reductions. Withdrawal symptoms such as irritability, anxiety, insomnia, sweating, GI effects such as nausea are usually mild and can last up to 6-8 weeks.
  - If severe withdrawal symptoms such as severe anxiety, tachycardia, orthostatic hypotension, and severe insomnia occur, restart medication at lowest tolerated dose and retry deprescribing in 6-12 weeks.
  - Previous or new symptoms of OAB (e.g., urinary urgency, increased urinary frequency, nocturia, incontinence) may return within 1-2 weeks of dose reduction and these should be monitored as well.

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Anticholinergic Medications

Antipsychotics

- Olanzapine and quetiapine have high anticholinergic activity compared to risperidone or aripiprazole (see Table 6 below).
- For antipsychotic guidelines and deprescribing recommendations, please refer to the LTC QMR Deprescribing Focus for Jul-Sep 2022

Table 6: Anticholinergic Burden of Antipsychotics[5,6,16]

MEDICATION	ANTICHOLINERGIC BURDEN SCORE
OLANZAPINE	3
QUETIAPINE	3
HALOPERIDOL	2
METHOTRIMEPRAZINE	2
ARIPIRAZOLE	1
RISPERIDONE	1
PALIPERIDONE	1

Antidepressant for Depression or Pain

- Tricyclic antidepressants and paroxetine have high anticholinergic activity[5,6,16]
- Antidepressants with the lowest risk of anticholinergic side effects should be considered (see Table 7 below).[39]
- The Canadian Guidelines on Prevention, Assessment and Treatment of Depression Among Older Adults (2021) recommends:
  - Duloxetine or sertraline be considered as first-line agents for acute episodes of major depression in older adults.[39]
  - Escitalopram and citalopram may also be considered, but the risk of QTc elevation may limit dosage to sub-therapeutic levels.[39]
- For pain, tricyclic antidepressants, such as amitriptyline and nortriptyline, have similar efficacy and side effect profiles due to their high anticholinergic burden.[32]
  - Imipramine also has a high anticholinergic burden and is associated with cognitive decline, which may limit its use.[40]
  - Desipramine has a high anticholinergic burden, but its safety with respect to cognitive decline has not been studied.
  - Duloxetine may be a safer medication to use, but should be monitored due to increase fall risk.[3,41]

Table 7: Anticholinergic Burden of Antidepressants[5,6,16]

MEDICATION	ANTICHOLINERGIC BURDEN SCORE
AMITRIPTYLINE	3
NORTRIPTYLINE	3
DESIPRAMINE	3
IMIPRAMINE	3
PAROXETINE	3
CITALOPRAM	1
ESCITALOPRAM	1
FLUOXETINE	1
SERTRALINE	1
BUPROPION	1
MIRTAZAPINE	1
TRAZADONE	1
VENLAFAXINE	1
DULOXETINE	0

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Anticholinergic Medications

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