ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Pharmacologic Treatment of Overactive Bladder

FINAL ENVIRONMENTAL SCAN REPORT

March 2016

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the treatment of Overactive Bladder Drug Class Review.

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Study Team

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Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

In Canada, there are six anticholinergics available for treatment of OAB: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium. In addition, mirabegron, a beta-3 adrenoreceptor agonist, is a recent addition to the armamentarium of treatment options. Botulinum toxin is approved for treatment of OAB in patients with inadequate response to, or who are intolerant to anticholinergic medications. Anticholinergics are available in various formulations including immediate release, long-acting preparations, transdermal and topical gel formulations. Mirabegron is available as an oral formulation. Oxybutynin immediate release, tolterodine extended release, tolterodine regular release and solifenacin are available as generic preparations.

In Ontario, all medications for the treatment of overactive bladder are listed on the public plan formulary, either as General Benefit or as Limited Use. Oxybutynin immediate release is considered “first-line” therapy in most jurisdictions in Canada, with other anticholinergics, mirabegron and/or onabotulinum toxin A considered second- or third-line therapy. Australia provides coverage through the public plan programs for oxybutynin immediate release tablet and oxybutynin patch only. No other product licensed for OAB is covered. In New Zealand, oxybutynin immediate release, tolterodine and solifenacin are covered under the public drug plan.

Part B: Guidelines for the treatment of overactive bladder

Seven guidelines on the treatment of OAB in adults were reviewed. All guidelines emphasize the role of non-pharmacologic therapy (e.g., lifestyle modifications, bladder retraining) prior to use of pharmacologic therapy. Anticholinergics (immediate or extended release) are recommended as second-line therapy if first-line treatment options are not successful. Mirabegron is recommended as an option in patients, either as an alternative to anticholinergics or in patients in whom anticholinergic drugs are contraindicated or clinically ineffective, or have unacceptable side effects. One guideline providing guidance for management of urinary incontinence in frail elderly persons suggests that oxybutynin should be avoided in the elderly, particularly at high doses; other antimuscarinics should be initiated at the lowest dose for tolerability.

Part C: Impact of different drug reimbursement schemes for treatment of overactive bladder

There is limited information regarding the impact of various reimbursement schemes (e.g., step therapy) for anticholinergics and mirabegron for treatment of OAB. One study showed no effect of copayment on adherence rates for medications for overactive bladder. Another study showed higher adherence rates for extended release medications compared with regular release medications, when cost was not a factor. Further research is required to assess the impact of various reimbursement schemes for medications for OAB.

Part D: Rapid review of selected topics

Pharmacology of anticholinergics and mirabegron: Although the anticholinergics used for OAB have different affinities for the various muscarinic receptors, this does not always translate into either efficacy differences or safety differences, as other factors may need to be considered such as penetration of the blood brain barrier. Beta3-adrenoceptor agonists do not bind to muscarinic receptors and as such are not associated with anticholinergic effects (e.g., dry mouth). However, beta3-adrenoceptors are located in other tissues such as heart and brain, and the long-term effects of mirabegron on cardiovascular function and cognition are not yet known.

Combination therapy: mirabegron and anticholinergics: There are limited studies evaluating the combination of mirabegron and anticholinergics for the treatment of OAB. Two RCTs assessed mirabegron in combination with solifenacin, and one open-label study also evaluated mirabegron in combination with solifenacin. Results from the two RCTs suggest that combination therapy with mirabegron and solifenacin may lead to improvement in symptoms compared to solifenacin as monotherapy; adverse effects with combination therapy do not appear to increase compared to monotherapy. Further studies are needed to elucidate which patients would be ideal candidates for combination therapy.

Cognitive function and use of anticholinergics: Most studies have concluded that prescribing drugs with anticholinergic adverse effects is associated with greater cognitive decline. Further research evaluating the cognitive effects of the anticholinergics (specifically oxybutynin versus other anticholinergics versus mirabegron) used in the treatment of OAB is needed.

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Introduction

Overactive bladder (OAB) is defined as "urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of infection or other proven pathology."[1] OAB is reported to affect 10-17% of women of all ages,[2;3] and 11-34% of men over the age of 65.[4-6] However, prevalence drastically increases in studies that examine older age groups, such as patients in nursing homes (43-77%)[2] or individuals with cognitive impairment/dementia (10-38%).[8] OAB can result in decreased work productivity, quality of sleep and mental health.[9;10] With the growth of the older population, there has been an increase of individuals experiencing OAB issues or urinary urgency/frequency, and subsequently the associated negative quality of life effects.

First line therapy for OAB includes lifestyle interventions such as weight loss, altering fluid intake, smoking cessation, regulating bowel function, bladder training and dietary modifications.[11;12] If conservative non-pharmacologic measures are not effective, pharmacologic interventions are often required. Anticholinergics (also known as antimuscarinics) are often used as first-line agents for patients with OAB; available agents in Canada are darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium. Mirabegron, a B-3 adrenoreceptor agonist, is an alternative to anticholinergics. Botulinum toxin injections are most often used in patients for whom oral medications are ineffective or are unable to tolerate anticholinergics.

The objectives of this report are:

- Part A: To summarize coverage of drug therapy for OAB through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- Part B: To summarize the guidelines for pharmacologic management of patients with OAB
- Part C: To review the evidence relating to the impact of different drug reimbursement schemes for drug treatment for OAB on patient access and/or utilization and costs
- Part D: To provide rapid reviews on selected topics

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability of Drugs used for Overactive Bladder in Canada

In Canada, there are eight medications commercially available that are approved for use of OAB: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium, mirabegron and botulinum toxin. All of these drugs are available as an oral formulation except for botulinum toxin, which is available as an injection only. Oxybutynin is also available as a transdermal preparation and topical gel, in addition to oral formulations. Oxybutynin (immediate release oral formulation), tolterodine (extended release formulation, immediate release) and solifenacin are available as generic products. Exhibit 1 outlines the dosage forms and costs (based on wholesale costs) for OAB drugs.

Summary

- There are six anticholinergics available in Canada for treatment of OAB: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium. In addition, mirabegron, a B-3 adrenoceptor agonist, is approved for the treatment of OAB.
- Botulinum toxin is approved for treatment of OAB in patients with inadequate response to or are intolerant to anticholinergic medications.
- Anticholinergics are available as long-acting preparations. In addition, oxybutynin is available as an immediate release, transdermal and topical gel formulation. Tolterodine is also available as an immediate release preparation.
- Oxybutynin (immediate release), tolterodine (extended release, immediate release) and solifenacin are available as generic preparations.

Exhibit 1: Commercially available medications for the treatment of overactive bladder in Canada

Drug Name	Brand name	Manufacturer	Availability	Dosage form	Usual daily dose	Generic available	30-day cost*	Date available in Canada**	Date listed on ODB formulary
Anticholinergics									
Darifenacin	Enablex	Merus Labs	7.5, 15 mg	Extended release tablet	7.5-15mg once daily	No	48.35	April 2006	Dec 15, 2011
Fesoterodine	Toviaz	Pfizer	4, 8mg	Extended release tablet	4-8mg once daily	No	45.00	April 2012	April 30, 2013
Oxybutynin	None	Generics	2.5, 5mg 1 mg/mL	Tablet Syrup	5mg 2-3 times daily	Yes	5.92	April 1997	Oct 01, 1996 Dec 31, 1998
	Ditropan XL	Janssen	5, 10mg	Extended release tablet	5-30mg daily	No	73.72[†]	June 2001	Not listed
	Oxytrol	Actavis	3.9mg/day	Transdermal	1 patch twice weekly	No	56.93[†]	August 2004	Available as EAP
	Gelnique	Actavis	100mg/g (10%)	Topical gel	10%: 1 sachet once daily	No	62.56[†]	Oct 2011	Not listed
Solifenacin	Vesicare	Astellas	5, 10mg	Tablet	5-10mg once daily	Yes	50.68	June 2006	Dec 15, 2011
	Various	Generics					12.67	July 2015	Sept 30, 2015
Tolterodine	Detrol	Pfizer	1, 2mg	Tablet	2mg twice daily	Yes	58.92	Nov 1998	Sept 15, 1999
	Tolterodine	Various					29.46	Dec 2015	Feb 25, 2016
	Detrol LA	Pfizer	2, 4mg	Extended release cap	4 mg once daily	Yes	58.93	March 2002	April 6, 2004
	Tolterodine ER	Various					14.73	Nov 2015	Dec 22, 2015
Trospium	Trosec	Sunovion	20mg	Tablet	20mg twice daily	No	48.38	April 2006	Dec 15, 2011
Beta 3-adrenoreceptor agonist									
Mirabegron	Myrbetriq	Astellas	25, 50mg	Extended release tablet	25-50mg once daily	No	43.80	March 2013	May 28, 2015
Neuromuscular blockers									
Botulinum toxin A	Botox	Allergan	50, 100, 200 units	Injection	100 units (usual interval 24 weeks) intradetrusor inj.	No	59.50	Dec 1992	May 28, 2015 (for OAB indication)

*Cost for the lowest daily dose based on prices obtained from the Ontario Drug Benefit Formulary (Accessed: February 29, 2016)
**Date obtained from Health Canada Database (http://webprod5.hc-sc.gc.ca/dpd-bdpp/newSearch-nouvelleRecherche.do?lang=eng)
[†]Wholesale acquisition cost for the lowest daily dose based on prices obtained from McKesson (Accessed: February 29, 2016)

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. No review was completed for oxybutynin (generic, Ditropan XL, Oxytrol) or tolterodine. For the agents that were reviewed by the CDR, a summary of recommendations is found in Exhibit 2 and Appendix A.

Exhibit 2: Summary of Common Drug Review recommendations for overactive bladder drugs

Drug name (Generic/brand)	Recommendation (date of review)
Oxybutynin (Gelnique)	*Do not list (2012)*
Trospium (Trosec)	*List with criteria (2006)*
Darifenacin (Enablex)	*List with criteria (2009)*
Solifenacin (Vesicare)	*List with criteria (2009)*
Fesoterodine (Toviaz)	*List in a similar manner to extended-release tolterodine (2012)*
Mirabegron (Myrbetriq)	*List with criteria (2014)*
Onabotulinum toxin A (Botox)	*List with criteria (2014)*

Product listing in Ontario

All overactive bladder drugs (with the exception of Ditropan XL, Oxytrol and Gelnique) are funded by the Ontario Public Drug Programs, either as General Benefit or Limited Use.

Limited Use (LU)

Limited use (LU) drugs are drugs that have been deemed to have value in certain circumstances, although they may not be appropriate for general listing in the Formulary. Oxybutynin (generic) is the only drug offered as general benefit, while all other approved drugs are offered under Limited Use. The only drugs that are not listed are Ditropan XL, Oxytrol and Gelnique. Note that Oxytrol is available through the Exceptional Access Program.

The limited use criteria for all anticholinergics listed as LU as well as mirabegron is as follows:

> ***Code 290:*** For patients with urinary frequency, urgency or urge incontinence who have: Failed to respond to behavioral techniques AND an adequate trial of oxybutynin with gradual dose escalation has shown to be either ineffective or resulted in unacceptable side effects.
>
> NOTE: If after a trial of 2 weeks patients continue to experience similar side effects and no greater efficacy than oxybutynin, continued therapy with this more costly agent should be reassessed.
>
> *Antimuscarinic agents should be used with caution in the elderly due to potentially serious adverse effects (e.g. confusion, psychosis, acute urinary retention, constipation). Antimuscarinic agents should be avoided in older adults with pre-existing cognitive impairment (e.g. dementia) and those who are already using other drugs with significant*

anticholinergic effects (e.g. tricyclic antidepressants) in order to avoid a high overall anticholinergic drug burden.
LU Authorization Period: Indefinite.

The limited use criteria for botulinum toxin A is as follows:

Code 460: For adult patients with urinary frequency, urgency or urge incontinence due to overactive bladder who have:
Failed to respond to behavioral techniques AND had an inadequate response or intolerance to adequate trials (i.e., at least 2 weeks at the maximum tolerated dose) of at least two medications for overactive bladder (e.g. anticholinergics, mirabegron).
The recommended dose is 100U injected into the detrusor muscle.
NOTES:
Patients who fail to achieve a reduction of greater than 50 percent in the frequency of urinary incontinence episodes with 1 dose should not be retreated.
Maximum 3 doses per year in responders, at a frequency of no more than once every 12 weeks.
Patients must have a post-void residual (PVR) urine volume of less than 150mL.
LU Authorization Period: One year

The Exceptional Access Program criteria for Oxytrol are as follows:

The treatment of urinary frequency, urgency or urge incontinence in patients who are unable to take oral treatments (e.g. inability to swallow) or who are unable to absorb oral medications (e.g., short gut syndrome).
Adverse effects to oral therapy (e.g. dizziness) are not acceptable.
Duration of approval: 5 years

Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care's independent expert advisory committee on drug-related issues. In 2007, the CED recommended that darifenacin not be listed on the ODB formulary because it was not found to be more effective than already available drugs for OAB, and was more expensive. Similarly, in 2008, the CED reviewed trospium and recommended that it not be listed as it was not found to provide added therapeutic benefit over available alternatives. In 2011, solifenacin, darifenacin and trospium were added to the ODB formulary.

Summary

- In Ontario, all drugs used in the treatment of overactive bladder are listed on the ODB formulary. Oxybutynin (regular release tablet and syrup) is available as General Benefit.
- Darifenacin, fesoterodine, solifenacin, tolterodine, trospium, mirabegron and botulinum toxin A are available as Limited Use. Oxytrol is available through the Exceptional Access Program.
- Ditropan XL and Gelnique are not funded in Ontario.

Public Plan Listings in Canada

Part 1: Listing Status

In order to determine the listing of overactive bladder drugs across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix 2). In Canada, oxybutynin (generic) is available as full benefit (general benefit) in every jurisdiction. Eight of 12 jurisdictions restrict the use of other anticholinergics (or other dosage forms of oxybutynin) via special authorization ("active restriction"). Alberta, New Brunswick and Newfoundland have a "Step Therapy" program in place which adjudicates the prescription at the pharmacy level. Mirabegron is listed in nine jurisdictions. A summary of the various listings is available in Exhibit 3.

Restriction Criteria

Oxybutynin regular release is considered first-line therapy. Restriction criteria for anticholinergics include prior use of oxybutynin regular release with development of intolerance. For mirabegron, patients must also have been tried on oxybutynin with development of intolerance; in addition, most jurisdictions state that mirabegron is not to be used in conjunction with anticholinergic agents. Clinical criteria for each of the drugs is listed in Appendix C.

Exhibit 3: Public plan listings in Canada for overactive bladder drugs

Drug	Brand/ generic name	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB / NU/ NW
Darifenacin	Enablex	No	Step	Res	No	Pas	No	Step	Res	Res	Step	Res	Res
Fesoterodine	Toviaz	No	Step	Res	Res	Pas	Pas	Step	Res	Res	Step	No	No
Mirabegron	Myrbetriq	No	Step	Res	Res	Pas	Pas	Step	Res	No	Step	Res	No
Oxybutynin	Generic	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB
	Ditropan XL	No	No	No	Res	No	Pas	Res	Res	Res	Step	Res	No
	Oxytrol	No	No	No	Res	No	Pas	No	No	No	No	No	No
	Gelnique	No	No	No	No	No	No	No	No	No	No	No	No
Solifenacin	Vesicare	No	Step	Res	Res	Pas	Pas	Step	Res	Res	Step	Res	Res
	Generic	No	Step	Res	Res	Pas	Pas	Step	Res	Res	Step	Res	No
Tolterodine	Detrol	No	No	No	Res	Pas	Pas	Step	Res	Res	Step	FB	Res
	Generic	No	No	No	No	No	No	Step	Res	Res	No	FB	No
	Detrol LA	No	Step	Res	Res	Pas	Pas	Step	Res	Res	Step	Res	Res
	Generic LA	No	Step	Res	No	Pas	No	Step	Res	Res	Step	Res	No
Trospium	Trosec	No	Step	Res	Res	Pas	Pas	Step	Res	Res	Step	No	Res
Botulinum toxin A	Botox	No	FB	No	No	Pas	No	No	No	No	No	No	No

NO=not listed
RES=restricted listing-enforced
FB=unrestricted listing
PAS=restricted listing – passive (e.g., Limited Use in Ontario, Exceptional Medication with codes in Quebec)
Step=Step Therapy
Current as of February 17, 2016

Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program invited to participate in a 30 minute telephone interview (see Appendix D) to gather further information about formulary listing of drugs used in the treatment of OAB. Exhibit 4 summarizes the information obtained in the interviews.

Exhibit 4: Summary of interviews with representative from public drug program

Province	Listing	Information on listing
British Columbia	Oxybutynin IR (full benefit)	Therapeutic Review conducted in 2013. Only oxybutynin IR covered as other products have not been shown to be more effective. The Drug Benefit Council recommended adding one long-acting agent for patients with OAB who are unable to tolerate oxybutynin IR. In addition, the DBC recommends that mirabegron be considered for addition to the formulary.
Saskatchewan	Oxybutynin IR (full benefit) Long-acting anticholinergics (SA) Mirabegron (SA)	There is an online adjudication system at the pharmacy level ("step therapy") which checks to see whether oxybutynin has been used prior to long-acting anticholinergic. In addition, requests for long-acting anticholinergics can also be phoned in for approval.
Manitoba	Oxybutynin IR (full benefit) Long-acting anticholinergics (SA) Mirabegron (SA)	Prior use of oxybutynin required before approval for long-acting anticholinergics. Approval for long-acting drugs within 24 hours (telephone service).
New Brunswick	Oxybutynin IR (full benefit) Long-acting anticholinergics (Step therapy) Mirabegron (Step therapy)	Step therapy was initiated in December 2009. Some agents are not funded due to cost differential (similar efficacy/safety among the long-acting anticholinergic agents). Urologists have noted that oxybutynin IR is not a reasonable first-line therapy for the elderly, due to anticholinergic adverse events.
Nova Scotia, PEI	Oxybutynin IR (full benefit) Long-acting anticholinergics (SA) Mirabegron (SA-Nova Scotia but not PEI)	Clinical review concluded that efficacy of products is similar. Although oxybutynin IR has greater incidence of anticholinergic effects, the clinical relevance of this finding is questionable. Some physician groups have indicated that oxybutynin IR is not appropriate for initiating therapy in the elderly.
NIHB	Oxybutynin IR (full benefit) Long-acting anticholinergics (SA)	Prior approval required for long-acting anticholinergics; patients must have failed on or are intolerant of therapy with oxybutynin IR.
Yukon	Oxybutynin IR, tolterodine IR (full benefit) Long-acting anticholinergics (SA) Mirabegron (SA)	Use of short-acting (including oxybutynin and tolterodine) prior to use of long-acting anticholinergic.

IR: immediate release
SA: special access

Summary

- All public drug plans in Canada provide coverage for oxybutynin regular release (generic) as general benefit. Ditropan XL is listed with clinical criteria in 7 jurisdictions, and Oxytrol in 2 jurisdictions. No public plan in Canada provides coverage for Gelnique.
- British Columbia only provides coverage for oxybutynin regular release.
- Other anticholinergic agents are listed with criteria (either requiring special authorization or through a step therapy program adjudicated at the pharmacy level) across Canada.
- Mirabegron is currently listed on nine public plan formularies.

Selected International Jurisdictions

United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list ("formulary") has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.[3] Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.[4] In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix E and Exhibit 5 for examples of copayments with tiered formulary systems).

Exhibit 5: Listing of drugs for treatment of OAB for select plans in the United States

	Darifenacin	Fesoterodine	Mirabegron	Oxybutynin				Solifenacin	Tolterodine		Trospium	Botulinum toxin A
	Enablex	Toviaz	Myrbetriq	Generic	Ditropan XL	Oxytrol	Gelnique	Vesicare	Detrol	Detrol LA	Trosec	Botox
AETNA Three-Tier Open Formulary (www.aetna.com)	Tier 3	Tier 3	Tier 2	G: Tier 1	Tier 3	NC For women - Tier 1	Tier 3	Tier 2	G: Tier 1 B: Tier 3	Tier 3	G: Tier 1	Tier 3
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Non-preferred	Non-preferred	Non-preferred	G: Preferred	Non-preferred	Non-preferred	Preferred	Preferred	G: Preferred B: Non-preferred	Non-preferred	G: Preferred	Non-preferred
Blue Cross Blue Shield of Texas Standard Preferred Drug List (April 2015) (www.bcbstx.com)	Non-preferred	Non-preferred	Non-preferred	G: Preferred	Preferred	Non-preferred	Non-preferred	Preferred	G: Preferred B: Preferred	Preferred	G: Non-preferred	Non-preferred
Connecticut Medicaid Preferred Drug List (www.ctdssmap.com)	Non-preferred	Preferred	Non-preferred	G: Preferred	Non-preferred	Non-preferred	Non-preferred	Preferred	G: Non-preferred B: Non-preferred	Non-preferred	G: Non-preferred	Preferred
Idaho Medicaid Preferred Drug List (www.healthandwelfare.idaho.gov)	Non-preferred	Preferred	Non-preferred	G: Preferred	Not listed	Non-preferred	Non-preferred	Preferred	G: Non-preferred B=Not listed	Not listed	G: Non-preferred	Preferred
Illinois Medicaid Preferred Drug List (http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf)	Non-preferred	Non-preferred	Non-preferred	G: Preferred	Preferred	Non-preferred	Non-preferred	Non-preferred	G: Non-preferred B: Non-preferred	Non-preferred	G: Non-preferred	Non-preferred
Kaiser Permanente 2014 Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserper	Tier 4	Tier 4	Tier 4	G: Tier 2	Tier 4	Tier 4	Tier 4	Tier 4	G: Tier 2 B: Tier 4	Tier 4	G: Tier 2	Tier 3

	Darifenacin	Fesoterodine	Mirabegron	Oxybutynin				Solifenacin	Tolterodine		Trospium	Botulinum toxin A
	Enablex	Toviaz	Myrbetriq	Generic	Ditropan XL	Oxytrol	Gelnique	Vesicare	Detrol	Detrol LA	Trosec	Botox
manente.org)												
Kentucky Preferred Drug List 2015 (www. ubsidiz.magellan **medicaid**.com)	Non-preferred	Non-preferred	Tier 4	G: Preferred	Not listed	Non-preferred	Non-preferred	Preferred	G: Preferred B=Not listed	Non-preferred	G: Preferred	Tier 4
Oregon Fee-for-Service Enforceable Physical Health Preferred Drug List 2015 (http://www.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx)	Non-preferred	Preferred	Non-preferred	G: Preferred	Non-preferred	Non-preferred	Non-preferred	Non-preferred	G: Preferred B: Non-preferred	Non-preferred	G: Non-preferred	Non-preferred
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/)	Non-preferred	Preferred	Non-preferred	G: Preferred	Non-preferred	Non-preferred	Non-preferred	Preferred	G: Non-Preferred B: Non-preferred	Non-preferred	G: Non-preferred	Not listed
WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) (https://www.wellcare.com/medicare_formulary/new_york)	Non-preferred	Non-preferred	Non-preferred	G: Tier 2	Non-preferred	Non-preferred	Non-preferred	Tier 3	G: Non-Preferred B: Non-preferred	Non-preferred	G: Tier 2	Non-preferred
Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Tier 4	Tier 4	Tier 4	G: Tier 1	Tier 1	Tier 4	Tier 4	Tier 4	G: Tier 1 B: Tier 1	Tier 1	G: Tier 1	Specialty drug

G= generic B= brand NC= not covered

Other Countries

Australia: In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts oxybutynin (patch/tablet) (see Exhibit 6) by offering it as Restricted Benefit.[5] Restricted benefit means that the drug is available for certain therapeutic indications or patient populations only, and prescribers are responsible for checking whether their patients meet these criteria, similar to Limited Use in Ontario. No other drugs are listed on the PBS for treatment of OAB.

Exhibit 6: Drugs for treatment of Overactive Bladder (Australia, publically funded)

Product	Dosage form	Criteria (Authority required)
Oxybutynin	patch	Detrusor overactivity in a patient who cannot tolerate oral oxybutynin, or who cannot swallow oral oxybutynin
	tablet	Detrusor overactivity

New Zealand[6]*:* In New Zealand, the Pharmaceutical management Agency (PHARMAC) is the agency that decides which medicines, medical devices and related products are subsidized. Exhibit 7 outlines the funding of drugs for the treatment of OAB.

Exhibit 7: Drugs for the treatment of Overactive Bladder (New Zealand, publically funded)

Product	Criteria (Authority required)
Oxybutynin, oral	Listed without criteria
Tolterodine	Patient has overactive bladder and a documented intolerance of, or is non-responsive to oxybutynin
Trospium	Not listed
Darifenacin	Not listed
Solifenacin	Patient has overactive bladder and a documented intolerance of, or is non-responsive to oxybutynin
Fesoterodine	Not listed
Mirabegron	Not listed
Onabotulinum toxin A	Not listed

Scotland[7]: Several drugs were reviewed by the Scottish Medicines Consortium and accepted for use within NHS Scotland.

Exhibit 8: Drugs for the treatment of Overactive Bladder Drugs (Scotland)

Product	Criteria (Authority required)
Oxybutynin, patch	Restricted to patients who derive clinical benefit from oral oxybutynin but who experience intolerable anticholinergic side effects
Oxybutynin, IR	Listed (no review)
Oxybutynin, long-acting	Listed (no review)
Tolterodine (short- and long-acting)	Listed (no review)
Trospium	Accepted
Darifenacin	Accepted; restricted to second-line use due to increased expense
Solifenacin	Not recommended
Fesoterodine	Accepted; restricted to second-line use due to increased expense
Mirabegron	Accepted
Onabotulinum toxin A	Accepted; restricted to patients who have failed oral treatments

IR: immediate release

Summary

- In the United States, all drug plans reviewed provide coverage for oxybutynin immediate release (considered a “preferred drug” or “Tier 1” drug). In addition, select other anticholinergics are listed in most plans as “preferred”.
- Australia provides coverage through the public plan programs for oxybutynin immediate release tablet and oxybutynin patch only. No other product licensed for OAB is covered.
- In New Zealand, oxybutynin immediate release, tolterodine and solifenacin are covered under the public drug plan.

Part B: Guidelines for the use of pharmacotherapy in treatment of OAB

Various guidelines are available for the management of patients with overactive bladder. Seven guidelines were reviewed including the Canadian Urological Association (CUA), Society of Obstetricians and Gynaecologists of Canada (SOGC), American Urological Association (AUA/SUFU), American College of Physicians (ACP), European Association of Urology (EAU), International Consultation on Incontinence, and NICE.

In general, guidelines recommend lifestyle interventions, behavioural therapies and pelvic floor muscle training as first-line treatment. Anticholinergics are recommended as second-line therapy if these treatment options are not successful. Most guidelines (exception American Urological Association) do not specify whether an immediate or extended release anticholinergic should be used as first-line pharmacotherapy. Oxybutynin transdermal is recommended as an option for patients who are unable to tolerate oral medication in four guidelines. As well, most guidelines do not specify a particular anticholinergic as first-line therapy; however NICE recommends oxybutynin IR, tolterodine IR or darifenacin as first-line medications. Note that the two Canadian guidelines were published prior to the introduction of some of the newer agents, including mirabegron. A summary of the guidelines is found in Exhibit 9.

NICE recommends mirabegron as a third-line oral therapy option in patients who have failed a trial of at least two anticholinergics; other guidelines recommend mirabegron as an option for treatment. Immediate release oxybutynin is not recommended for the frail elderly; as well, caution is advised in prescribing antimuscarinics in the elderly.

Exhibit 9: Summary of guidelines for treatment of overactive bladder

Recommendation	Guideline supporting recommendation
Anticholinergics as second-line treatment (after conservative measures)	CUA, AUA/SUFU, ACP, EAU, NICE
Similar efficacy between oral anticholinergics	SOGC, EAU
Use IR formulations for initial therapy (ER if ineffective)	EAU, NICE (first-line: oxybutynin IR, tolterodine IR, darifenacin ER)
ER preferred to IR due to lower rates of dry mouth	AUA/SUFA
Trial of 4-12 weeks to assess efficacy of drugs	CUA
Consider dose modification, or trial of another anticholinergic (or mirabegron), if one agent not effective, or not tolerated	SOGC, AUA/SUFA, CUA, NICE
Transdermal oxybutynin as an option in patients unable to tolerate oral agents	SOGC, AUA/SUFA, EAU
Mirabegron as an alternative to anticholinergics	EAU, AUA/SUFA

Recommendation	Guideline supporting recommendation
Mirabegron as an option for patients for whom anticholinergic drugs are contraindicated or clinically ineffective, or have unacceptable side effects	NICE

Canadian Urological Association (2012)[8]: Adult Urinary Incontinence

- Conservative therapy should be considered prior to the initiation of medical or surgical treatment of urgency urinary incontinence.
- Antimuscarinics are appropriate as first- or second-line treatment. Choice of agent depends on physician experience and preference, formulary coverage and/or patient preference and insurance coverage. In clinical practice, patients are considered to have refractory symptoms if they have failed at least two adequate treatments (4 to 12 weeks) of antimuscarinic drugs.
- Onabotulinumtoxin A, neuromodulation and surgical interventions are acceptable options for a small percentage of patients who do not respond to conservative and drug therapies.

Society of Obstetricians and Gynaecologists of Canada (2012)[9]: Overactive bladder treatment

- Behavioural management protocols and functional electrical stimulation should be offered in the spectrum of effective primary treatments for overactive bladder syndrome.
- Oral oxybutynin, immediate and extended release, as well as transdermal oxybutynin, may be offered as treatment of OAB, as they are associated with significant objective clinical improvement at 12 weeks. Oxybutynin immediate release has superior cost-effectiveness but more side effects than other anticholinergics. Adverse events associated with transdermal oxybutynin are fewer than with oral oxybutynin.
- Other agents such as tolterodine, trospium, solifenacin and darifenacin, may be offered as treatment for OAB, as there are associated with significant objective clinical improvement at 12 weeks.
- Trospium is an adequate anticholinergic choice for overactive bladder syndrome patients with pre-existing cognitive impairment and for OAB patients taking concurrent CYP450 inhibitors. Solifenacin may be an adequate anticholinergic choice for elderly OAB patients or patients with pre-existing cognitive dysfunction. Darifenacin is an adequate anticholinergic choice for OAB patients with pre-existing cardiac concerns or cognitive dysfunction.
- The choice of anticholinergic therapy should be guided by individual patient comorbidities, as objective efficacy of anticholinergic drugs is similar. Dose escalation does not improve objective parameters and causes more anticholinergic adverse effects. It is, however, associated with improved subjective outcomes. To decrease side effects, switching to a lower dose or using an extended release formulation or transdermal delivery mechanism should be considered.
- Intravesical botulinum toxin injection and sacral nerve and posterior tibial nerve stimulation are clinically effective options for OAB patients unresponsive to conservative options or pharmacotherapy.

American Urological Association (2014)[10]: Overactive bladder (non-neurogenic)

- First line treatment:
  - Behavioural therapies, including bladder training and control strategies, pelvic floor muscle training and fluid management
  - Combination behavioural and pharmacologic management
- Second-line treatment
  - Oral anti-muscarinics: if an immediate and an extended release formulation are available, then ER formulations should be preferentially prescribed over IR formulations because of lower rates of dry mouth.
  - Oral beta3-adrenoceptor agonists
  - Transdermal oxybutynin
  - Dose modification or drug change for inadequate symptoms control or unacceptable adverse events
  - Management of side effects
  - Considerations in prescribing to frail or elderly patients
- Third-line treatment in carefully selected patient populations
  - Intradetrusor onabotulinumtoxin A
  - Scaral neuromodulation
  - Peripheral tibial nerve stimulation

American College of Physicians (2014)[11]: Urinary incontinence in women

- Behavioural therapies and pelvic floor muscle training recommended as first-line treatment.
- Pharmacologic treatment recommended if bladder training not successful. Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use and cost of medication.

European Association of Urology (2015)[12]: Urinary incontinence

- Antimuscarinic drugs:
  - Offer IR or ER formulations for adults with urgency urinary incontinence.
  - If IR formulations are unsuccessful, offer ER formulations or longer-acting antimuscarinic agents.
  - Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.
- Antimuscarinic drugs in the elderly
  - In older people, every effort should be made to employ non-pharmacological treatments first.
  - Use antimuscarinic with caution in elderly patients who are at risk of, or have, cognitive dysfunction.

- Mirabegron
    - Offer mirabegron to people with urgency urinary incontinence, but warn patients receiving mirabegron that the possible long-term side effects remain uncertain.

Report from the 5th International Consultation on Incontinence: Urinary incontinence in frail elderly persons[13]

Summary of evidence for pharmacological management in the frail elderly:

- Short-term treatment with oxybutynin-IR has small to moderate efficacy in reducing urinary frequency and urgency urinary incontinence when added to behavioural therapy in long-term care residents
- Low-dose oxybutynin-ER does not cause delirium in cognitively impaired nursing home residents
- Oxybutynin IR has been associated with cognitive adverse effects in people with dementia and/or Parkinson's disease and the incidence and prevalence are unknown
- Oxybutynin has been associated with tachycardia but not associated with QTc prolongation or ventricular arrhythmia
- Oxybutynin is less effective in people with impaired orientation, cerebral cortical under-perfusion and reduced bladder sensation
- Oxybutynin is less well tolerated than solifenacin in older people
- Fesoterodine is effective in ameliorating the symptoms of OAB in frail older people, identified by VES-13
- There is insufficient evidence to determine the efficacy, tolerability and safety of the following agents in the frail elderly: intravesical oxybutynin, transdermal oxybutynin, trospium, tolterodine, darifenacin, solifenacin, mirabegron, duloxetine, oral and topical estrogen
- Tolterodine is associated with cognitive impairment and tachycardia, and the incidence and prevalence of this are unknown
- Solifenacin (5 mg/day) is associated with no impairment of cognition in older people with mild cognitive impairment versus placebo

NICE guidance (2013)[14]: Urinary incontinence in women

- Offer bladder training lasting for a minimum of 6 weeks as a first-line treatment to women with urgency or mixed urinary incontinence.
- When offering antimuscarinic drugs take into account, woman's coexisting conditions, use of other existing medications, risk of adverse effects.
- Before starting treatment, discuss with women the likelihood of success and associated common adverse effects, that some adverse effects may indicate that treatment is starting to have an effect and that they may not see the full benefits until they have been taking the treatment for 4 weeks.
- Do not use flavoxate, propantheline and imipramine for the treatment of urinary incontinence or OAB in women
- Do not offer oxybutynin (immediate release) to frail older women.
- Offer one of the following choices first to women with OAB or mixed UI:

    - Oxybutynin (immediate release) OR
    - Tolterodine (immediate release) OR
    - Darifenacin (once daily preparation)
- If the first treatment for OAB is not effective or well-tolerated, offer another drug with the lowest acquisition cost.
- Offer a transdermal OAB drug to women unable to tolerate oral medication.
- Mirabegron can be offered as an option in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects.

Summary

- Seven guidelines were reviewed that provided recommendations for pharmacologic management of patients with OAB.
- Guidelines recommend behavioural therapies and bladder training as first-line therapy.
- Anticholinergics (immediate or extended release) are recommended as second-line therapy if first-line treatment options are not successful.
- Oxybutynin transdermal is recommended as an option for patients who are unable to tolerate oral medication in four guidelines.
- Mirabegron is recommended as an option in patients, either as an alternative to anticholinergics or in patients in whom anticholinergic drugs are contraindicated or clinically ineffective, or have unacceptable side effects.
- One guideline providing guidance for management of urinary incontinence in frail elderly persons suggests that oxybutynin should be avoided in the elderly, particularly at high doses; other antimuscarinics should be initiated at the lowest dose for tolerability.

Part C: Impact of different drug reimbursement schemes for treatment of adults with overactive bladder

Methods

A literature search was conducted in Pubmed using the terms: (oxybutynin or darifenacin or solifenacin or fesoterodine or tolterodine or trospium or mirabegron or muscarinic antagonists) AND (healthcare services accessibility OR health policy OR reimbursement incentive OR cost sharing OR deductibles and coinsurance OR insurance coverage OR health benefit plans employee OR insurance pharmaceutical service OR managed care programs) AND (overactive bladder or urinary bladder overactive). Bibliographies of identified articles were scanned for additional relevant articles.

Results

Despite the use of step therapy (i.e., trial of one medication, usually immediate release oxybutynin, before coverage of second-line agent) in many jurisdictions for medications for overactive bladder, there is a lack of information in the literature detailing the impact of different drug reimbursement schemes. A retrospective cohort study compared the persistence, adherence and switch rates for oxybutynin IR and ER, and tolterodine ER.[25] The

study included 1,117 individuals who were privately insured, on Medicare or had coverage through self-insured employers. Overall, only 13.2% persisted with treatment for at least one year (15% for tolterodine ER; 15.3% for oxybutynin ER and 6.5% for oxybutynin IR). Medication compliance measures were higher for ER formulations (35.2% for tolterodine ER, 36.1% for oxybutynin ER, and 14.8% for oxybutynin IR, p<0.001). The increased adherence rate was noted despite significant differences in the median copay (tolterodine ER-$16.74; oxybutynin ER-$15.00; oxybutynin IR-$5.85). In this study, the lack of influence of copay suggests that other factors are more important predictors of persistence (e.g., adverse effect profile).

Another study evaluated medication adherence of overactive bladder drugs in a healthcare system in which patients do not pay for medication.[15] The two most commonly prescribed medications were tolterodine extended release (4,716 patients or 60%) and oxybutynin immediate release (2,003 or 25.5%). A greater proportion of patients on tolterodine ER and oxybutynin ER were adherent (39.2% and 42.6%, respectively) compared with oxybutynin IR (24.7%).

Summary

- One study showed no effect of copayment on adherence rates for medications for overactive bladder. Another study showed higher adherence rates for extended release medications compared with regular release medications, when cost was not a factor.
- Further research is required to assess the impact of various reimbursement schemes for medications for OAB.

Part D: Rapid Review of Selected Topics

Pharmacology of anticholinergics and mirabegron

Anticholinergic (also known as antimuscarinic) agents alleviate the symptoms of OAB through inhibition of muscarinic receptors in the urothelium and detrusor muscle, reducing detrusor contraction and sensations associated with urgency. Muscarinic receptors are distributed in cardiac muscle, smooth muscle, the CNS, on presynaptic autonomic nerves and at autonomic ganglia. There are five muscarinic receptor subtypes (M1 to M5) that are found in various tissues throughout the body. In the bladder, 80% are M2, although normal human detrusor contraction is mediated by M3. The M2 receptor may contribute to the abnormal detrusor pathology.[16] In addition to the effects on the bladder, antagonism of muscarinic receptors affects other tissues and functions. For example, antagonism of the M1 receptor has the greatest impact on cognitive function, although M2 and M4 receptors may also play a role. The M2 receptor has a functional role in mediating heart rate, while the M3 receptor mediates vasodilation. M3 receptors are involved in contraction of the gastrointestinal smooth muscle, saliva production and iris sphincter function.[17, 18]

Newer antimuscarinics have greater affinity for the M2 and M3 versus the M1 receptors.

Darifenacin is considered to be selective for the M3 receptor; M3 selectivity is believed to minimize some anticholinergic effects, primarily dry mouth. However, M3 selectivity may be associated with higher rates of other adverse events such as constipation. Other available agents do not display any selectivity or have greater M3 selectivity vs. M2 selectivity (e.g., solifenacin).[19] Although M2 and M3 receptors play a role in cardiovascular function, in clinical practice, the potential effects of anticholinergic agents on heart rate and blood pressure are unlikely to be of clinical significance. [20]

An anticholinergic agent that spares that M1 receptor would be expected to have less impact on CNS functioning than an M1-selective agent. In addition, the extent to which an anticholinergic medication impairs CNS function depends on its ability to cross the blood brain barrier (BBB). All agents have the potential to cross the BBB, and their ability is dependent on chemical properties such as molecular weight, lipophilicity and polarity. Drugs such as darifenacin, tolterodine and trospium are unlikely to cross the BBB, whereas oxybutynin is more likely to cross the BBB.[21]

Beta3-adrenoceptor (along with the beta1- and beta2-adrenoceptors) is located in the bladder detrusor muscle and urothelium. The beta3-adrenoceptor is thought to be the main subtype mediating relaxation of detrusor smooth muscle during the storage phase in humans; stimulation of this receptor results in increased bladder capacity. All of the beta-adrenergic receptor subtypes are important regulators of human cardiac function so there is a potential for cardiovascular side effects.[17, 22] However, a systematic review of the cardiovascular safety of mirabegron (beta3-adrenoceptoragonist) did not identify any significant CV adverse effects. Small increases in blood pressure and pulse rate versus placebo were observed (≤1 mm Hg and 1 bpm, respectively).[23] The function of beta3-receptors in the human CNS is unclear and observational studies of mirabegron use on cognitive function are in progress.[24]

Summary

- Although the anticholinergics used for OAB have different affinities for the various muscarinic receptors, this does not always translate into either efficacy differences (see report from systematic review team www.odprn.ca) or safety differences, as other factors may need to be considered such as penetration of the blood brain barrier.
- Beta3-adrenoceptor agonists do not bind to muscarinic receptors and as such are not associated with anticholinergic effects (e.g., dry mouth). However, beta3-adrenoceptors are located in other tissues such as heart and brain, and the long-term effects of mirabegron on cardiovascular function and cognition are not yet known.

Combination therapy: mirabegron and anticholinergics

Although guidelines recommend non-pharmacologic therapies for initial treatment of OAB, most patients will require the use of pharmacotherapy, usually an anticholinergic (also known as an antimuscarinic) agent.[18;19] These agents decrease bladder afferent activity by blocking muscarinic acetylcholine receptors in the urothelium and suburothelial myofibroblasts, thereby improving symptoms.[22] Mirabegron, a beta3-adrenoreceptor agonist, is a new addition to the armamentarium of treatment options. It activates beta-3 adrenergic receptors in the bladder, resulting in relaxation of detrusor smooth muscle during the storage phase of the fill-void cycle and an increase in bladder capacity.[25] Since mirabegron and anticholinergic medications have different mechanisms of action, combination therapy with these two drug classes has been suggested to possibly increase efficacy and help to improve the tolerability of the anticholinergics. A review of published trials evaluating mirabegron in combination with an anticholinergic medication for patients with OAB was completed.

A total of 2 randomized controlled trials (RCTs) were identified, both of which investigated the combination treatment with mirabegron and solifenacin.[37;38] In the first trial, sponsored by the manufacturer of mirabegron, a total of 1306 patients (mean age: 54.1 yo to 56.5 yo across all groups) were randomised to 12 weeks of treatment in 1 of 12 groups: combination therapy with solifenacin 2.5, 5 or 10 mg + mirabegron 25 or 50mg), monotherapy (solifenacin 2.5, 5 or 10mg, or mirabegron 25 or 50mg) or placebo. Primary outcome measure was change from baseline to end of treatment in mean volume voided per micturition (MVV). Other outcomes were number of micturitions per 24 hr, number of incontinence episodes per 24 hr, and number of urgency episodes per 24 hr. Compared with solifenacin 5 mg used as monotherapy, all combinations with solifenacin 5 or 10mg significantly improved MVV ranging from 18 mL (95% CI 5.4-30.0) to 26.3 mL (95% CI, 12.0-41.0), respectively for solifenacin 5mg + mirabegron 25mg and solifenacin 10mg + mirabegron 50mg. For number of micturitions per 24 hours, statistically significant differences compared with solifenacin were observed with solifenacin 5 mg + mirabegron 50mg, solifenacin 10 mg + mirabegron 25 mg, and solifenacin 10mg + mirabegron 50mg. In terms of treatment-emergent adverse events leading to discontinuation, there was no difference between any of the groups. Anticholinergic adverse effects (e.g., dry mouth, constipation) showed a dose-response relationship with solifenacin but did not increase with combination therapy, except for constipation.

In the second study, the efficacy and safety of solifenacin and mirabegron (combination and monotherapy) were evaluated in 239 patients with OAB (mean age: 71.2 yo) over a 6 week period.[26] Patients were randomized to receive mirabegron 50mg/day, solifenacin 10mg/day, mirabegron 50mg/day + solifenacin 10 mg/day, or placebo. Patients completed OAB-questionnaires, bladder diaries and underwent urodynamic examinations. Upon completion of the study, a decrease in the number of episodes of incontinence decreased in all active groups from baseline (mirabegron 2.3/day, solifenacin 2.2/day, solifenacin+mirabegron 3.8/day, placebo no change). The change in episodes of incontinence was significantly different in the combination group compared to mirabegron or solifenacin as monotherapy. In patients treated with mirabegron alone, 3 of 63 (4.8%) patients discontinued therapy because of adverse effects compared to 1/52 (1.9%) patients receiving solifenacin alone and 3/65 (4.6%) in the combination group.

A multicenter, open-label study assessed the safety and efficacy of mirabegron as an add-on

therapy in patients treated for OAB with solifenacin.[39] A total of 223 patients continued to be treated with solifenacin 2.5 or 5 mg once daily and additional mirabegron 25 mg once daily for 16 weeks; mirabegron dose could be increased to 50 mg if the patient's symptom improvement was not sufficient after 8 weeks. Efficacy endpoints included changes from baseline in overactive bladder symptom score (OABSS) total score, mean number of micturitions/24 hours, mean number of urgency episodes/24 hr, and mean number of urinary incontinence episodes/24 hours. Significant improvements from baseline were observed in efficacy endpoints from baseline to end of treatment in all treatment groups. The mean changes for OABSS ranged from -3.4 to -4.0 for the different treatment groups, all exceeding the minimal clinically important difference (score of three points).[27] The most common treatment-emergent adverse event was constipation, with incidences ranging from 5.4% (solifenacin 2.5mg+mirabegron 50mg and solifenacin 5 mg + mirabegron 50 mg) to 8.6% (solifenacin 5mg + mirabegron 25 mg). Dry mouth was only reported in one patient. A total of three patients withdrew from the study due to adverse events (aggravation of irritable bowel syndrome, chest discomfort, dysuria).

Summary

- There are limited studies evaluating the combination of mirabegron and anticholinergics for the treatment of OAB. Two RCTs assessed mirabegron in combination with solifenacin, and one open-label study also evaluated mirabegron in combination with solifenacin.
- Results from the two RCTs suggest that combination therapy with mirabegron and solifenacin may lead to improvement in symptoms compared to solifenacin as monotherapy; adverse effects with combination therapy do not appear to increase compared to monotherapy.
- Further studies are needed to elucidate which patients would be ideal candidates for combination therapy.

Cognitive function and use of anticholinergics

Studies investigating the effects of anticholinergics on cognitive function, in particular in the elderly, are scarce. In a literature review, only one of 72 clinical trials enrolling adults with OAB specifically addressed cognitive function (using Mini-Mental State Examination-MMSE).[28] A review of observational trials was done to evaluate the association between anticholinergic medications (specifically used for treatment of overactive bladder) and development of dementia/cognitive impairment.

Results

Several studies have concluded that prescribing drugs with anticholinergic adverse effects (not specifically used for the treatment of OAB) is associated with greater cognitive decline.[42-44] A recent meta-analysis evaluated possible associations between drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults.[29] A total of 18 studies (including randomized controlled trials, prospective and retrospective cohort and case-control studies) were identified. For cognitive impairment, three studies were included. Overall, exposure to drugs with anticholinergic effects as a class was associated with increased odds of cognitive impairment (OR 1.45, 95% CI 1.16-1.73).

In a 2-year longitudinal study, 13,004 participants aged 65 years and older were enrolled in a Medical Research Council Cognitive Function and Ageing Study.[30] After adjusting for various factors such as age, educational level, social class and cognitive performance at baseline, use of medication with definite anticholinergic effects was associated with a 0.33 point greater decline in MMSE score than not taking anticholinergics over the 2-year study period (95% CI 0.03-0.64, p=0.03).

A prospective cohort study investigated the relationship between cumulative exposure to anticholinergic medications and memory and executive function in older men.[31] A total of 544 community-dwelling men aged 65 and older were followed for a 2-year period. Cumulative exposure to anticholinergic medications over the preceding 12 months was associated with poorer performance on several measures, including the Hopkins Verbal Recall Test (assessing short-term memory) and the instrumental activity of daily living scale (IADL).

A longitudinal cohort study followed 297 people aged >60 years without dementia and on no anticholinergic drug and 30 patients who were taking at least one anticholinergic drug.[46] Compared with non-users, patients taking at least one anticholinergic drug had poorer performance on reaction time, attention, delayed non-verbal memory, narrative recall, visuospatial construction and language tasks, but not on tasks of reasoning, immediate and delayed recall of wordlists and implicit memory. Anticholinergic drug use was a strong predictor of mild cognitive impairment (OR 5.12, p=0.001).

Another prospective population-based cohort study evaluated whether cumulative anticholinergic use is associated with a higher risk for incident dementia.[32] A total of 3434 participants 65 years and older with no dementia at study entry were included. The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics. Over a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia. For dementia, adjusted hazard ratios for cumulative anticholinergic use compared with nonuse were 0.92 (95% CI, 0.74-1.16) for total standardized daily doses (TSDD) of 1 to 90; 1.19 (95% CI, 0.94-1.51) for TSDDs of 91 to 365; 1.23 (95% CI, 0.94-1.62) for TSDDs of 366 to 1095; and 1.54 (95% CI, 1.21-1.96) for TSDDs greater than 1095. Two other studies have examined anticholinergic use and incident dementia risk. In a study conducted among primary care patients 75 years and older, anticholinergic use during the 54-month study period was associated with an increased risk for dementia (adjusted HR, 2.08) compared with non-use.[47] Another cohort study of individuals 65 years or older found that long-term anticholinergic use was associated with an increased risk for dementia (adjusted HR, 1.65) during 4 years of follow-up.[33] Note that none of these studies specifically evaluated medications used for the treatment of OAB.

OAB-specific studies:
A prospective observational study enrolling 168 patients with OAB evaluated the effect of anticholinergic treatment on cognitive functions, depression and quality of life.[49] MMSE scores did not decline after anticholinergic treatment, even in patients with Alzheimer's disease.

Summary

- Most studies have concluded that prescribing drugs with anticholinergic adverse effects (not specifically drugs used for treatment of OAB) is associated with greater cognitive decline.
- Further research evaluating the cognitive effects of the anticholinergics (specifically oxybutynin versus other anticholinergics versus mirabegron) used in the treatment of OAB is needed.

Health Canada Warnings

- No warnings or advisories have been issued by Health Canada for the solifenacin, trospium, tolterodine, darifenacin, oxybutynin, fesoterodine, mirabegron or onabotulinum toxin A.

Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- There are six anticholinergics available in Canada for treatment of OAB: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium. In addition, mirabegron, a beta-3 adrenoceptor agonist, has been recently approved for the treatment of OAB.
- Botulinum toxin is approved for treatment of OAB in patients with inadequate response to, or who are intolerant to anticholinergic medications.
- Anticholinergics are available in various formulations including immediate release, long-acting, transdermal and topical gel formulation. Mirabegron is available as an oral formulation.
- Oxybutynin (immediate release), tolterodine (extended release, immediate release) and solifenacin are available as generic preparations.

Public Plan Listing in Ontario

- In Ontario, drugs used in the treatment of overactive bladder are listed on the ODB formulary. Oxybutynin (regular release tablet and syrup) is available as General Benefit.
- Darifenacin, fesoterodine, solifenacin, tolterodine, trospium, mirabegron and botulinum toxin A are available as Limited Use.
- Ditropan XL, Oxytrol and Gelnique are not funded in Ontario.

Public Plan Listing in Canada

- All public drug plans in Canada provide coverage for oxybutynin regular release (generic) as general benefit. Ditropan XL is listed with clinical criteria in 7 jurisdictions, and Oxytrol in 2 jurisdictions. No public plan in Canada provides coverage for Gelnique.
- British Columbia only provides coverage for oxybutynin regular release.
- Other anticholinergic agents are listed with criteria (either requiring special authorization or through a step therapy program adjudicated at the pharmacy level) across Canada.
- Mirabegron is currently listed on nine public plan formularies.

Selected International Jurisdictions

- In the United States, all drug plans reviewed provide coverage for oxybutynin immediate release (considered a “preferred drug” or “Tier 1” drug). In addition, select other anticholinergics are listed in most plans as “preferred”.
- Australia provides coverage through the public plan programs for oxybutynin immediate release tablet and oxybutynin patch only. No other product licensed for OAB is covered.
- In New Zealand, oxybutynin immediate release, tolterodine and solifenacin are covered under the public drug plan.

Part B: Guidelines for the treatment of patients with overactive bladder

- Seven guidelines were reviewed that provided recommendations for pharmacologic management of patients with OAB.
- Guidelines recommend behavioural therapies and bladder training as first-line therapy.
- Anticholinergics (immediate or extended release) are recommended as second-line therapy if first-line treatment options are not successful.
- Oxybutynin transdermal is recommended as an option for patients who are unable to tolerate oral medication in four guidelines.
- Mirabegron is recommended as an option in patients, either as an alternative to anticholinergics or in patients in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects.
- One guideline providing guidance for management of urinary incontinence in frail elderly persons suggests that oxybutynin should be avoided in the elderly, particularly at high doses; other antimuscarinics should be initiated at the lowest dose for tolerability.

Part C: Impact of different drug reimbursement schemes for drugs used in the treatment of overactive bladder

- One study showed no effect of copayment on adherence rates for medications for overactive bladder. Another study showed higher adherence rates for extended release medications compared with regular release medications, when cost was not a factor.
- Further research is required to assess the impact of various reimbursement schemes for medications for OAB.

Part D: Rapid Reviews of Selected Topics

Pharmacology of anticholinergics and mirabegron: Although the anticholinergics used for OAB have different affinities for the various muscarinic receptors, this does not always translate into either efficacy differences or safety differences, as other factors may need to be considered such as penetration of the blood brain barrier. Beta3-adrenoceptor agonists do not bind to muscarinic receptors and as such are not associated with anticholinergic effects (e.g., dry mouth). However, beta3-adrenoceptors are located in other tissues such as heart and brain, and the long-term effects of mirabegron on cardiovascular function and cognition are not yet known.

Combination therapy: mirabegron and anticholinergics: There are limited studies evaluating the combination of mirabegron and anticholinergics for the treatment of OAB. Two RCTs assessed mirabegron in combination with solifenacin, and one open-label study also evaluated mirabegron in combination with solifenacin. Results from the two RCTs suggest that combination therapy with mirabegron and solifenacin may lead to improvement in symptoms compared to solifenacin as monotherapy; adverse effects with combination therapy do not appear to increase compared to monotherapy. Further studies are needed to elucidate which patients would be ideal candidates for combination therapy.

Cognitive function and use of anticholinergics: Most studies have concluded that prescribing drugs with anticholinergic adverse effects is associated with greater cognitive decline. Further research evaluating the cognitive effects of the anticholinergics (specifically oxybutynin versus other anticholinergics versus mirabegron) used in the treatment of OAB is needed.

Health Equity

In Ontario, drugs used in the treatment of OAB are available on the Ontario Drug Benefit formulary. Oxybutynin immediate release is considered “first-line” therapy, and should be used as initial therapy for patients with OAB.

Conclusion

In Ontario, medications for the treatment of overactive bladder are listed on the public plan formulary, either as General Benefit or as Limited Use. Oxybutynin immediate release is considered “first-line” therapy in most jurisdictions in Canada, with other anticholinergics, mirabegron and/or onabotulinum toxin A considered second- or third-line therapy.

Seven guidelines on the treatment of OAB in adults were reviewed. All guidelines emphasize the role of non-pharmacologic therapy (e.g., lifestyle modifications, bladder retraining) prior to use of pharmacologic therapy.

Reference List

1. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61(1):37-49.

2. Offermans MP, Du Moulin MF, Hamers JP, Dassen T, Halfens RJ. Prevalence of urinary incontinence and associated risk factors in nursing home residents: a systematic review. Neurourol Urodyn 2009;28(4):288-294.

3. Ovsag K, Hydery S, Mousa S. Preferred drug lists: potential impact on healthcare economics. Vascular health and risk management 2008;4:403-413.

4. Motheral B, Fairman K. Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. Med Care 2001;39:1293-1304.

5. Australian Government Department of Health. Pharmaceutical Benefits Scheme. Australian Government Department of Health, 2013http://www.pbs.gov.au/browse/body-system).

6. PHARMAC. PHARMAC: Pharmaceutical Management Agency for New Zealand. http://www pharmac health nz/, 2014.

7. Scottish Medicines Consortium. SMC Advice Directory. http://www scottishmedicines org uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory?ds=Y&searchtext=symbicort&category=&submissionType=&fromDate=From%3A&toDate=To%3A&acceptedForUseCheck=Y&acceptedForRestrictedUseCheck=Y&notRecommendedForUseCheck=Y, 2013.

8. Bettez M, Tu lM, Carlson K et al. 2012 update: guidelines for adult urinary incontinence collaborative consensus document for the canadian urological association. Can Urol Assoc J 2012;6(5):354-363.

9. Geoffrion R. Treatments for overactive bladder: focus on pharmacotherapy. J Obstet Gynaecol Can 2012;34(11):1092-1101.

10. Gormley EA, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2015;193(5):1572-1580.

11. Qaseem A, Dallas P, Forclea M, et al. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2014;161:429-440.

12. Lucas M, Bedretdinova D, Berghmans L, et al. Guidelines on urinary incontinence (European Association of Urology). https://uroweb.org/guideline/urinary-incontinence/?type=summary-of-changes . 2015.
Ref Type: Online Source

13. Wagg A, Gibson W, Ostaszkiewicz J, et al. Urinary incontinence in frail elderly persons: report from the 5th International Consultation on Incontinence. Neurourol Urodynam 2015;34:398-406.

14. NICE guidance. Urinary incontinence in women: management. http://www.nice.org.uk/guidance/cg171/chapter/1-recommendations#assessment-and-investigation . 2013.
Ref Type: Online Source

15. Sears C, Lewis C, Noel K, et al. Overactive bladder medication adherence when medication is free to patients. J Urology 2009;183:1077-1081.

16. Giglio D, Tobin G. Muscarinic receptor subtypes in the lower urinary tract. Pharmacology 2009;83:259-269.

17. Wagg A, Nitti V, Kelleher C, et al. Oral pharmacotherapy for overactive bladder in older patients: mirabegron as a potential alternative to antimuscarinics. Curr Med Res 2016;published ahead of print:1-18.

18. Jayarajan J, Radomski S. Pharmacotherapy of overactive bladder in adults: a review of efficacy, tolerability and quality of life. Res Rep Urol 2014;6:1-16.

19. Department of Veterans Affairs Pharmacy Benefits Management Services. Anticholinergic agents for overactive bladder syndrome: VA drug class review. www.pbm.va.gov . 2011.
Ref Type: Online Source

20. Rosa G, Baucknehtt M, Scala C, et al. Cardiovascular effects of antimuscarinic agents in overactive bladder. Expert Opin Drug Saf 2013;12:815-827.

21. Kay G, Granville L. Antimuscarinic agents: implications and concerns in the management of overactive bladder in the elderly. Clin Ther 2005;27:127-138.

22. Giarenis I, Robins D, Cardozo L. Overactive bladder and the beta3-adrenoreceptor agonists: current strategy and future prospects. Drugs 2015;75:1707-1713.

23. Rosa G, Ferrero S, Nitti V, et al. Cardiovascular safety of beta3-adrenoceptor agonists for the treatment of patients with overactive bladder syndrome. Eur Urology 2015;69:311-323.

24. Orme S, Morris V, Gibson W, et al. Managing urinary incontinence in patients with dementia: pharmacological treatment options and considerations. Drugs Aging 2015;32:559-567.

25. Anon. Mirabegron (Myrbetriq) for overactive bladder. Med Lett Drugs Ther 2013;55:13-15.

26. Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. A randomized, controlled trial of effectiveness and safety of management of OAB symptoms in elderly men and women with standard-dosed combination of solifenacin and mirabegron. Arch Gerontol Geriatr 2015;61(2):212-216.

27. Gotoh M, Homma Y, Yokoyama I, et al. Responsiveness and minimal clinically important change in overactive bladder symptom score. Urology 2011;78:768-773.

28. Paquette A, Gou P, Tannenbaum C. Systematic review and meta-analysis: do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous sytem adverse events? J Am Geriatr Soc 2011;59:1332-1339.

29. Ruxton K, Woodman R, Mangoni A. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: a systematic review and meta-analysis. Br J Clin Pharm 2015;80:209-220.

30. Fox C, Richardson K, Maidment I, et al. Anticholinergic medication use and cognitive impairment in the older population: the Medical Research Council Cognitive Function and Ageing STudy. J Am Geriatr Soc 2011;59:1477-1483.

31. Han L, Agostini J, Allore H. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc 2008;56:2203-2210.

32. Gray S, Anderson M, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern MEd 2015;175:401-407.

33. Carriere I, Fourrier-Reglat A, Dartigues J, et al. Drugs with anticholinergic properties, cognitive decline and dementia in an elderly general population. JAMA Int Med 2009;169:1317-1324.

Appendix A: Common Drug Review Recommendations

Oxybutynin Chloride Gel (Gelnique) (May 2012)

The Canadian Drug Expert Committee (CDEC) recommends that oxybutynin chloride gel not be listed.

Reasons for the Recommendation:

- The Committee considered the comparative clinical benefit of oxybutynin chloride gel to be uncertain because of the absence of any randomized controlled trials (RCTs) that directly compare it with other pharmacological treatments for overactive bladder.
- There are no RCTs comparing the incidence of anticholinergic adverse effects (such as cognitive and neurological) between oxybutynin chloride gel and other oxybutynin products, particularly in the elderly.

Solifenacin (Vesicare) Resubmission (June 2009)

The Canadian Expert Drug Advisory Committee recommends that solifenacin be listed for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and in a similar manner as drug plans list tolterodine.

Reasons for the Recommendation:

- There is insufficient evidence that solifenacin provides clinically important differences in outcomes compared with oxybutynin or tolterodine.
- Since the initial solifenacin submission reviewed by the Committee, the price has been reduced and this was an important consideration in making this recommendation. The daily cost of solifenacin xxxxxxx is less than tolterodine immediate-release and extended-release formulations ($1.82), but more than oxybutynin immediate release formulations ($0.40 to $0.59). The manufacturer has requested that the submitted price of solifenacin remain confidential pursuant to the Confidentiality Guidelines of the Procedure for Common Drug Review.

Trospium (Trosec) (August 2006)

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that trospium be listed for patients who cannot tolerate immediate-release oxybutynin and in a similar manner as drug plans list tolterodine.

Reasons for the Recommendation:

- The Committee reviewed 12 randomized controlled trials (RCTs) of trospium in the treatment of overactive bladder. Nine of these RCTs were of short duration (2-4 weeks) and seven used urodynamic outcome measures. Therefore, the Committee focused its review on two 12-week, placebo controlled RCTs and one 52 week RCT comparing trospium with oxybutynin, all of which used clinical outcome measures. Trospium was found to be superior to placebo and equivalent to oxybutynin as assessed by the number of episodes of urge incontinence and number of voids per day. In the two placebo-controlled RCTs, the number of voids per day was reduced,

from a baseline of approximately 13, by a mean of 2.4 to 3 with trospium compared with 0.6 to 1.8 for placebo.
- Trospium causes typical anticholinergic side effects such as dry mouth, constipation and visual disturbances. Trospium offers the potential of a reduction in central nervous system side effects compared with oxybutynin (due to reduced penetration of the blood-brain barrier), but this purported advantage has not yet been proven in clinical trials in elderly patients in whom this adverse effect is most important.
- Trospium costs $1.50 per day which is more expensive than immediate-release oxybutynin ($0.50 – 0.75 per day) but less expensive than extended-release oxybutynin and tolterodine ($1.75 per day).

Darifenacin (Enablex) Resubmission (April 2009)

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that darifenacin be listed for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and in a similar manner as drug plans list tolterodine.

Reason for the Recommendation:

- The daily cost of darifenacin ($1.46) is less than tolterodine immediate-release and extended-release formulations ($1.82), but more than oxybutynin immediate release formulations ($0.40 to $0.59).

Fesoterodine (Toviaz) (October 2012)

The Canadian Drug Expert Committee (CDEC) recommends that fesoterodine be listed in a similar manner to extended-release tolterodine.

Reasons for the Recommendation:

- In three double-blind, randomized controlled trials (RCTs) in patients with overactive bladder, compared with extended-release tolterodine, fesoterodine produced similar reductions in daily urinary urge incontinence and micturition events.
- At the submitted price, the daily cost of fesoterodine (4 mg to 8 mg daily*, [confidential price removed at manufacturer's request]*) is less expensive than extended-release tolterodine (4 mg daily, $1.91). The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Mirabegron (Myrbetriq) (November 2014)

The Canadian Drug Expert Committee (CDEC) recommends that mirabegron be listed for the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence, and urinary frequency, if the following clinical criteria and conditions are met:

Clinical Criteria:

- Intolerance or inadequate response to an adequate trial of an anticholinergic therapy.

Conditions:

- List in a manner similar to other pharmacological treatments for use after oxybutynin.
- Not to be used in combination with other pharmacological treatments for OAB.

Reasons for the Recommendation:

- Nine double-blind randomized controlled trials (RCTs) and a network meta-analysis demonstrated that mirabegron was superior to placebo and similar to other anticholinergic drugs for improving the symptoms of OAB. The incidence of dry mouth, a clinically important side effect to patient groups, appeared lower with mirabegron than with comparator anticholinergic drugs.
- At the submitted price ($vvvv per day), mirabegron is more costly than generic oxybutynin immediate release (IR) ($0.20 to $0.30 per day), but less costly than other anticholinergic drugs currently funded by most Common Drug Review (CDR)–participating drug plans as second-line options for the treatment of OAB ($1.50 to $2.28 per day).

Of Note:

CDEC noted that patients with OAB may benefit from behavioural training or lifestyle modification, and non-pharmacological approaches should be considered before initiating any drug therapy.

Onabotulinum toxin A (Botox) (November 2014)

The Canadian Drug Expert Committee (CDEC) recommends that onabotulinumtoxinA (Ona A) be listed for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication, if the following clinical criterion and conditions are met:

Clinical Criterion:

- Patients have had an adequate trial with at least two other pharmacologic treatments for OAB.

Conditions:

- Prescribing and administration is restricted to urologists.
- Funding should be limited to treatment with one dose to establish efficacy, and it should be discontinued in non-responders (i.e., those who fail to achieve a reduction of at least 50% in the frequency of urinary incontinence episodes with one dose).
- Limit to a maximum of three doses per year in responders, at a frequency of no more than once every 12 weeks.
- Reduction in price to improve the cost-effectiveness to an acceptable level.

Reason for the Recommendation:

- Two phase 3 randomized controlled trials (RCTs) (study 095 [N = 557] and study 520 [N = 548]) conducted in adults with symptoms of idiopathic OAB who had not been adequately controlled with anticholinergic medications demonstrated that treatment with Ona A resulted in statistically significantly greater reductions from baseline in incontinence episodes, urge incontinence episodes, urgency episodes, micturition, and nocturia episodes compared with placebo.

- Based on the Common Drug Review's (CDR) estimated incremental cost per quality-adjusted life-year (QALY) of $59,388 for Ona A, CDEC concluded that Ona A is not a cost- effective treatment option for OAB at the submitted price ($3.57 per unit).

Of Note:
CDEC noted that patients with OAB may benefit from behavioural training or lifestyle modification, and non-pharmacological approaches should be considered prior to the initiation of any drug therapy.

Appendix B: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961:::::
NIHB (Non-insured Health Benefits) Program	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php

Appendix C: Restriction Criteria for Drug used in the Treatment of Overactive Bladder

Drug	Criteria
Alberta	
darifenacin, fesoterodine, solifenacin, tolterodine long-acting, trospium	For patients who are intolerant to oxybutynin. Special authorization may be granted for 24 months.
mirabegron	For patients who are intolerant to oxybutynin. Special authorization may be granted for 24 months. Coverage cannot be provided for mirabegron when this medication is intended for use in combination with other overactive bladder agents.
Saskatchewan	
darifenacin, fesoterodine, solifenacin, tolterodine long-acting, trospium	For treatment of patients intolerant to oxybutynin chloride
mirabegron	For treatment of overactive bladder for patients intolerant to, or with an inadequate response to oxybutynin. NOTE: should not be used in combination with other pharmacologic treatments for OAB.
Manitoba	
fesoterodine, mirabegron, Ditropan XL, Oxytrol, solifenacin, tolterodine, trospium	Urinary incontinence in patients unable to tolerate or failing immediate release oxybutynin (e.g. headache, dry mouth, dyspepsia)
Quebec	
fesoterodine, solifenacin, tolterodine, trospium	For treatment of vesical hyperactivity in persons for whom oxybutynin is poorly tolerated, contraindicated or ineffective
Ditropan XL, Oxytrol	For treatment of vesical hyperactivity in persons for whom immediate-release oxybutynin is poorly tolerated
mirabegron	For treatment, as monotherapy, of vesical hyperactivity in persons for whom oxybutynin is poorly tolerated, contraindicated or ineffective
New Brunswick	
darifenacin, tolterodine, fesoterodine, solifenacin, trospium	For the treatment of overactive bladder with symptoms of urinary frequency, urgency and/or urge incontinence in patients who have not tolerated a reasonable trial of immediate-release oxybutynin." Clinical Note: Requests for the treatment of stress incontinence will not be considered. Claim Notes: If the beneficiary has had a claim for oxybutynin in the previous 24 months, the adjudication system will recognize this. Information and the claim for the drug will be automatically reimbursed without the need for a written special authorization request. Written special authorization will continue to be available as an option for patients who may not have the relevant first line agent on history due to changes in drug coverage or other factors.
mirabegron	For the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence, and urinary frequency, in patients who have an intolerance or inadequate response to an adequate trial of immediate-release oxybutynin. Clinical Notes: Requests for the treatment of stress incontinence will not be considered. of OAB

Drug	Criteria
Ditropan XL	For the treatment of overactive bladder with symptoms of urinary frequency, urgency and/or urge incontinence in patients who have not tolerated a reasonable trial of immediate release oxybutynin. Clinical Note: Requests for the treatment of stress incontinence will not be considered.
Nova Scotia	
darifenacin, tolterodine, fesoterodine, solifenacin, trospium	For the treatment of over-active bladder (not stress incontinence) for patients who cannot tolerate or have insufficient response to an adequate trial of immediate release oxybutynin (e.g. 3 months) - a three month trial will be approved initially with assessment of the effectiveness of this therapy required if further coverage is considered
Ditropan XL	For the treatment of over-active bladder (not stress incontinence) for patients who cannot tolerate immediate release oxybutynin after an adequate trial (e.g. 3 months) - a three month trial will be approved initially with assessment of the effectiveness of this therapy required if further coverage is considered
mirabegron	For the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence, and urinary frequency if the patient has had an intolerance or inadequate response to an adequate trial of an anticholinergic therapy - not to be used in combination with other pharmacological treatments of OAB - a three month trial will be approved initially with assessment of the effectiveness of this therapy required if further coverage is considered
Prince Edward Island	
darifenacin, tolterodine, fesoterodine, solifenacin, trospium	For the treatment of over-active bladder (not stress incontinence) in patients who cannot tolerate or have an insufficient response to an adequate trial (e.g. 3 months) of immediate release oxybutynin.
Ditropan XL	For the treatment of over-active bladder (not stress incontinence) after a reasonable trial (e.g. 3 months) of Oxybutynin immediate release is not tolerated.
Newfoundland	
darifenacin/ solifenacin	For the treatment of urinary frequency, urgency, or urge incontinence when a patient has had to discontinue oxybutynin immediate release due to intolerable side effects. *an appropriate trial is considered to be of 12 weeks duration. Please note that coverage may be considered WITHOUT a Special Authorization request as long as the beneficiary's medication history in the NLPDP database shows the prior use of a benefit regular release oxybutynin or any long-acting urinary agent (Detrol LA, Uromax, Trosec, Ditropan XL, Vesicare) DIN within the past year. If there is no history of a previous benefit regular release oxybutynin, or any long-acting urinary agent (Detrol LA, Uromax, Trosec, Ditropan XL, Vesicare) claim, the normal Special Authorization Process will be required.
Fesoterodine/ tolterodine/ trospium	For the treatment of overactive bladder (not stress incontinence) after a reasonable trial, titrated, and of appropriate length* of oxybutynin IR is not tolerated. *an appropriate trial is considered to be of 12 weeks duration. Please note that coverage may be considered WITHOUT a Special Authorization request as long as the beneficiary's medication history in the NLPDP database shows the prior use of a benefit regular release oxybutynin or any long-acting urinary agent (Detrol LA, Uromax, Trosec, Ditropan XL, Vesicare, Toviaz) DIN within the past year. If there is no history of a previous benefit regular release oxybutynin, or any long-acting urinary agent (Detrol LA, Uromax, Trosec, Ditropan XL, Vesicare, Toviaz) claim, the normal Special Authorization Process will be required.
Ditropan XL	For the treatment of urinary frequency, urgency, or urge incontinence when a patient has had to discontinue oxybutynin immediate release due to intolerable side effects. Please note that coverage may be considered WITHOUT a Special

Drug	Criteria
	Authorization request as long as the beneficiary's medication history in the NLPDP database shows the prior use of a benefit regular release oxybutynin or any long-acting urinary agent (Detrol LA, Uromax, Trosec, Ditropan XL, Vesicare, Toviaz) DIN within the past year. If there is no history of a previous benefit regular release oxybutynin, or any long-acting urinary agent (Detrol LA, Uromax, Trosec, Ditropan XL, Vesicare, Toviaz) claim, the normal Special Authorization Process will be required.
NIHB	
darifenacin, solifenacin, tolterodine, trospium	For the symptomatic relief of overactive bladder in patients: ¨ with symptoms of urinary frequency, urgency or urge incontinence; AND ¨ who have failed on or are intolerant to therapy with immediate-release oxybutynin
Yukon	
darifenacin, Ditropan XL, solifenacin, tolterodine (long-acting)	For patients who have insufficient response to immediate release formulations
mirabegron	For the treatment of overactive bladder (OAB) for patients intolerant to, or with an inadequate response to an adequate trial of oxybutinin. Not to be used in combination with other pharmacological treatments for OAB.

Appendix D: Interview Questions

How long have you listed drugs for OAB on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list these agents this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain drugs for OAB NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?
Do you have any special restrictions regarding the use of drugs for OAB?

Appendix E: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	$5	$28	$55	25%
Plan B	$2	$20	$40	N/A
Plan C	$10	$25	50%	25%
Plan D	$4	$17	75%	25%

Adapted from:
http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage