



Treatment of Overactive Bladder

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. The drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing.

Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.

Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.

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Dean Elterman is part of the Speaker's Bureau for Astellas, Allergan and Pfizer.

Dana Sokora has been on advisory boards for Astellas.

No other 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 drug class review for treatment of overactive bladder.

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

List of abbreviations	
AB	Alberta
ACh	Anticholinergic
aHR	Adjusted hazard ratio
BC	British Columbia
CDR	Common Drug Review
CIHI	Canadian Institute for Health Information
DARF	Darifenacin
ER	Extended release
FEST	Fesoterodine
GB	General benefit
ICER	Incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
IR	Immediate release
LU	Limited Use
MB	Manitoba
MIRA	Mirabegron
MOHLTC	Ministry of Health and Long-Term Care
NB	New Brunswick
NIHB	Non-insured Health Benefits
NL	Newfoundland
NMA	Network meta-analysis
NS	Nova Scotia
NU	Nunavut
NW	Northwest Territories
OAB	Overactive bladder
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
ON	Ontario
OPDP	Ontario Public Drug Programs
OXYB	Oxybutynin immediate release
OXYB-ER	Oxybutynin extended release
OXYB-GEL	Oxybutynin gel
OXYB-Trans	Oxybutynin transdermal
PEI	Prince Edward Island
Q4	Fourth quarter
QALY	Quality adjusted life years
QC	Quebec
RCT	Randomized controlled trial
SK	Saskatchewan
SMH	St. Michael's Hospital
SOLF	Solifenacin
TOLT	Tolterodine immediate release

List of abbreviations	
TOLT-ER	Tolterodine extended release
TROS	Trospium
WDAE	Withdrawal due to adverse events
YK	Yukon Territories

Executive Summary

In Canada, there are six anticholinergics available for treatment of overactive bladder (OAB): darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium. In addition, mirabegron, a beta-3 adrenoceptor 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. In Ontario, most medications [exceptions oxybutynin extended release (Ditropan XL), oxybutynin transdermal (Oxytrol), oxybutynin gel (Gelnique)] used for the management of overactive bladder are listed on the Ontario Drug Benefit (ODB) formulary with Limited Use criteria. Oxybutynin immediate release (IR) is the only agent available as a General Benefit. Oxybutynin transdermal (Oxytrol) is available through the Exceptional Access Program.

OAB is a common condition that is more prevalent in the elderly. Clinical criteria for use of these medications in Ontario indicate that oxybutynin IR should be used as initial therapy; however, concern has been raised that the anticholinergic adverse effects of this drug may be harmful in the elderly population. As well, with the introduction of generic products and lower associated costs, an updated cost-effectiveness analysis of these agents was needed. As part of the formulary modernization review, an evaluation of drugs used in the management of OAB was undertaken to provide policy recommendations for these products in Ontario.

Key Considerations for Reimbursement Options

Efficacy

- Overall, the network meta-analysis (NMA) found that most agents, except for oxybutynin transdermal, were superior to placebo for most outcomes studied, including micturitions, incontinence, quality of life, urgency episodes and nocturia.
- The NMA also showed that for micturitions in 24 hours, solifenacin was superior to tolterodine, extended-release tolterodine and mirabegron. Additionally, for quality of life, solifenacin and fesoterodine were superior to mirabegron. No agent was significantly better than oxybutynin IR for any of the outcomes.

Safety

- Five safety outcome measures were analyzed in our systematic review: dry mouth, constipation, arrhythmias, withdrawals (all cause, due to adverse events, due to efficacy) and serious adverse events.
- For dry mouth, all agents had a significantly higher proportion of patients with dry mouth when compared to placebo, except for transdermal oxybutynin, oxybutynin gel and mirabegron. Overall, all agents were better tolerated than immediate-release oxybutynin. As well, based on our review, mirabegron was better tolerated than all other drugs, except transdermal and gel formulations of oxybutynin.
- For serious adverse events, no differences were observed amongst the agents when compared to each other or to placebo.
- In a rapid review of the observational literature comparing safety of OAB medications, only two studies were identified. Overall, there is a lack of evidence available on the real-world comparative safety, including falls, fractures and cognitive impairment, for OAB medications.

Accessibility

- No accessibility issues were identified in Ontario in our review of medications used in the treatment of OAB. All oral anticholinergics, mirabegron and botulinum toxin A are available on the ODB formulary, either as a General Benefit (oxybutynin IR), Limited Use or Exceptional Access Program (EAP) for Oxytrol.

Pharmacoeconomics

- An independent de novo economic model was developed to assess the cost effectiveness of alternative therapies for overactive bladder, as compared with each other or no therapy.
 - Based on this model, solifenacin is the most cost effective therapy for the treatment of OAB. Oxybutynin IR is cost-effective for patients who have failed on solifenacin, at \$27,000 per quality adjusted life year (QALY) gained compared with no therapy. All other agents, at current prices, are not cost effective based on a commonly used threshold of \$50,000 per QALY gained.
- With the introduction of generic solifenacin, but no other changes to current reimbursement for OAB medications, overall spending in 2018 for OAB medications is expected to decrease from current spending trends. In 2018, expenditure is expected to drop from \$6.2 million in 2014 to about \$6.0 million (↓2.7%) for patients aged less than 65 years and from \$31.3 million to approximately \$30.4 million (↓3.1%) for patients aged 65 years and older.
- Various reimbursement options were considered in the budget impact analysis, including step therapy (i.e., use of most cost-effective drug before receiving coverage for an alternative agent). The impact of enforcing step therapy is unclear as it is unknown whether this would lead to patients increasing their total time on all therapies (which would lead to increased expenditure) or decreasing their time on therapies other than oxybutynin (which would lead to decreased expenditure). Covering tolterodine ER and solifenacin under General Benefit was predicted to decrease expenditures.

Reimbursement Options

Given the similar efficacy of the OAB medications, the differences observed in adverse effects between the agents, and the differential cost effectiveness of these drugs, four main reimbursement options for treatment for OAB were considered. Final recommendations are based on results of our review, input from stakeholders and feedback from the ODPRN Citizen's Panel.

The following reimbursement option is recommended for consideration as a funding alternative for the Ontario Public Drug Programs:

Oxybutynin IR, tolterodine extended release or solifenacin as General Benefit, all other OAB medications Limited Use

- Oxybutynin IR, tolterodine ER and solifenacin listed as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine IR, trospium, mirabegron) listed as Limited Use.
 - Criteria for use include intolerance or failure to respond to oxybutynin IR OR tolterodine ER OR solifenacin

NOTE: Addition of generic tolterodine ER as General Benefit is considered based on price reduction to 25% of brand name costs. Availability of other medications (including tolterodine IR) as generic formulations priced at 25% of brand name costs should prompt re-evaluation of listing status, as these agents may become cost-effective alternatives.

Other Considerations

Recommendation 1: No listing is recommended for oxybutynin extended release (Ditropan XL).

Recommendation 2: For patients unable to swallow, recommend availability of oxybutynin gel (Gelnique) under Exceptional Access Program (but not oxybutynin transdermal [Oxytrol]).

Recommendation 3: It is recommended that a Therapeutic Note should be applied to all anticholinergics (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium) used for OAB, cautioning about the use of anticholinergics in the elderly. The therapeutic note does not apply to mirabegron, a beta-3 adrenoceptor agonist.

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Rationale for Review

In Canada, there are six anticholinergics available for treatment of overactive bladder: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium. In addition, mirabegron, a beta-3 adrenoceptor 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 immediate release and solifenacin are available as generic preparations.

In Ontario, most medications [exceptions oxybutynin extended release (Ditropan XL), oxybutynin transdermal (Oxytrol), oxybutynin gel (Gelnique)] used for the management of overactive bladder (OAB) are listed on the Ontario Drug Benefit (ODB) formulary as Limited Use. Oxybutynin immediate release (IR) is available as a General Benefit. Oxybutynin transdermal is available through the Exceptional Access Program (EAP). Clinical criteria for use of these medications indicate that oxybutynin IR should be used as initial therapy; however, concern has been raised that the anticholinergic adverse effects of this drug may be deleterious in the elderly population.¹ As well, with the introduction of generic products and lower associated costs, an updated cost-effectiveness analysis of these agents was needed. As part of the formulary modernization review, an evaluation of drugs, in particular the anticholinergics and mirabegron, used in the management of OAB was undertaken, in order to provide policy recommendations for these products in Ontario.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: <http://www.odprn.ca>

Background Information

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.”² OAB is reported to affect 10-17% of women of all ages^{3,4} and 11-34% of men over the age of 65.⁵⁻⁷ However, prevalence increases in studies that examine older populations, such as patients in nursing homes (43-77%)⁸ or individuals with cognitive impairment/dementia (10-38%).⁹ OAB can result in decreased work productivity, quality of sleep and mental health.^{10,11} As well, OAB can have a detrimental effect on the physical functioning, psychological well-being and health-related quality of life.¹² With the growth of the older population, there has been an increase of individuals experiencing OAB issues or urinary urgency/frequency.

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.^{13,14} 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. Tolterodine and oxybutynin are both available as short- and long-acting oral preparations; all

other agents are dosed once daily, except for trospium which is dosed twice daily. Mirabegron, a beta-3 adrenoceptor agonist, is an alternative to anticholinergics and is dosed once daily. Botulinum toxin injections are most often used in patients for whom oral medications are ineffective or are unable to tolerate anticholinergics.

Public plan reimbursement of drugs used in treatment of OAB

Canada

All public drug plans in Canada provide coverage for oxybutynin IR as general benefit. Oxybutynin ER (Ditropan XL) is listed with clinical criteria in 7 jurisdictions, and oxybutynin transdermal (Oxytrol) in 2 jurisdictions (Exhibit 1). No public plan in Canada provides coverage for oxybutynin gel (Gelnique). Other anticholinergic agents as well as mirabegron are listed with criteria (either requiring special authorization or through a step therapy program adjudicated at the pharmacy level) across Canada. British Columbia has the most strict listing only providing coverage for oxybutynin immediate release.

Exhibit 1: 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

The Common Drug Review (CDR), established in 2003, 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.¹⁵ Seven medications (oxybutynin-Gelnique, trospium, darifenacin, solifenacin, fesoterodine, mirabegron and onabotulinum toxin A) were reviewed; other products were not reviewed as they were available prior to establishment of the CDR. The recommendation for oxybutynin (Gelnique) was not to list, because of lack of randomized controlled trials comparing it directly with other medications for OAB. The recommendation for all other agents reviewed was to list with criteria.

Ontario

All overactive bladder drugs (with the exception of Ditropan XL and Gelnique) are funded by the Ontario Public Drug Programs. Oxybutynin immediate release is listed as General Benefit. All other funded agents (darifenacin, fesoterodine, solifenacin, tolterodine, trospium, mirabegron, botulinum toxin A) are listed as Limited Use. Oxytrol is available through Exceptional Access Program for 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).

The Limited Use (LU) 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 objective of the drug class review for treatment of overactive bladder is to provide evidence-informed policy recommendations for these drugs in Ontario.

Components of the Drug Class Review

The treatment of OAB drug class review is comprised of:

- qualitative analyses of perspectives of patients and prescribers
 - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for drug therapy for OAB; completion of online survey by patients
- environmental scans of:
 - national and international drug policies
 - considerations relating to health equity
- analysis of real-world drug utilization using:
 - administrative claims data from Ontario and across Canada (where available)
 - summaries of relevant observational literature
- systematic review and network meta-analysis (NMA) of the literature
- cost-effectiveness analysis and reimbursement-based economic analyses

Results from all of the above components were reviewed and consolidated into a set of policy recommendations.

Overview of Findings

Qualitative Research Team: Perspectives of Patients and Physicians

Findings of the qualitative study represented common experiences and perceptions described across patient and physician groups (primary care physicians, urologist, urogynecologists, geriatricians). Seventeen semi-structured telephone interviews with patients and physicians were conducted and online surveys were completed by 42 patients.

Diagnosis of OAB

- Participants described various strategies for diagnosing OAB such as collecting detailed information on symptoms, performing a physician exam, and doing formal testing (e.g. cystoscopy, post void residual bladder ultrasound, and urinalysis).
- In addition, they described that OAB is not a condition that many patients like to bring up on their own, so more physicians are being educated to ask patients about OAB symptoms during annual check-ups.

Management of OAB

- Most physician participants stated that non-pharmacological strategies are recommended prior to the use of pharmacological strategies (either alone or in combination).

- Physician participants prefer long-acting agents over short-acting agents for the management of OAB.
 - The main factors participants considered before prescribing anticholinergics are the agent's side effect profile, patient's drug coverage, patient physiology, current medication use, and frequency of dosing.
 - In general, they believed the long-acting anticholinergic agents are better tolerated by most OAB patients because they have fewer side effects and are dosed once daily.
- Participants generally reserved beta-3 agonists for patients who do not respond to anticholinergics and botulinum toxin A injections for patients who do not respond to either class of medications.

"They [non-pharmacologic strategies] help somewhat but I don't think they help a lot. You know it's an adjunct, and it's important, but it probably isn't going to change things enough to significantly affect quality of life and symptoms. You know so it's good to do and in some people it really does the trick but for most people it's an adjunct to pharmacologic measures" –specialist physician

Accessibility to OAB medications on the Ontario Drug Benefit formulary

- Physician participants are satisfied with updated ODB coverage but do not agree with the Limited Use criteria (i.e., use of oxybutynin prior to initiation of long-acting anticholinergic agents).
- Physician participants unanimously expressed that they feel the criteria do not align with their preferences for OAB management. The criteria dictate that all patients should start on oxybutynin immediate release; however physicians prefer to start with a newer long-acting agent because they perceive oxybutynin immediate release is not tolerated well by most patients.
 - Some participants admitted to using the LU code without following the criteria and others started patients on a range of samples to determine which product is the most helpful.

"I think it denies people access to drugs that are clearly better, I mean for example, oxybutynin, very old OAB agent, clearly associated with delirium and cognitive impairment versus a new drug like fesoterodine or mirabegron, you know so what would you want your father who has got some mild cognitive problems to go on? But according to the letter to the law, they are supposed to be tried on a crappy agent and get side effects before they go on an agent that is clearly a drug of choice if you just cared about caring for patients." –specialist physician

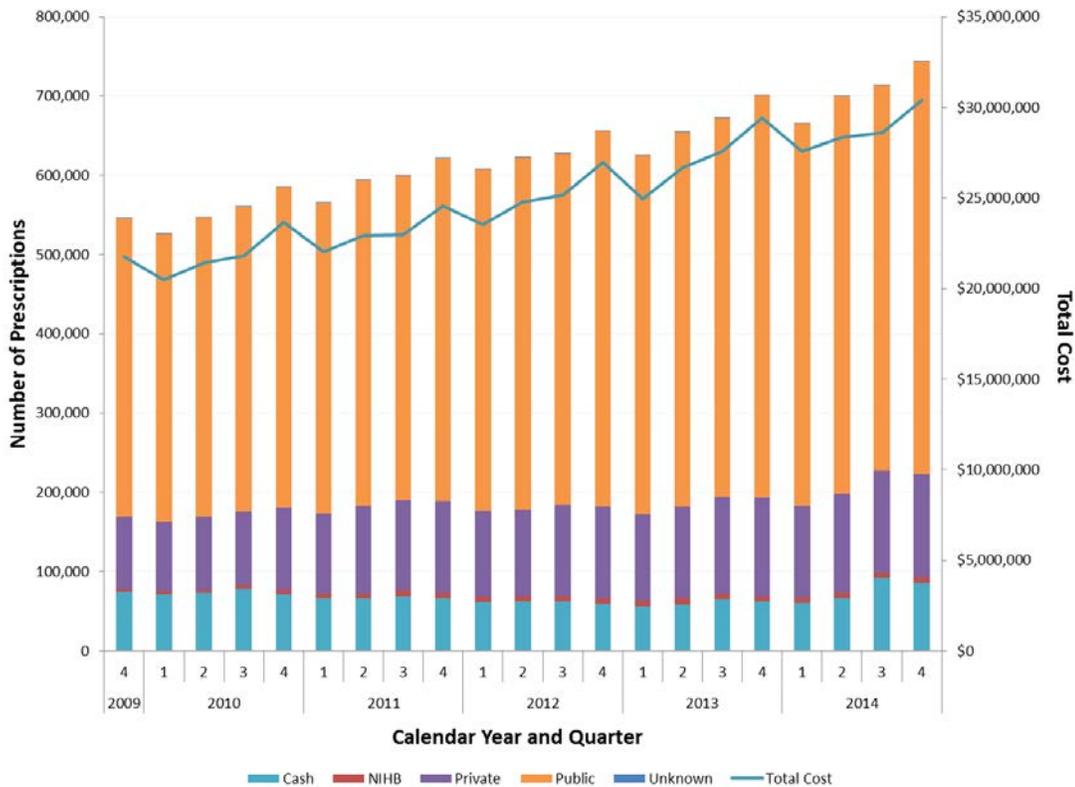
Pharmacoepidemiology Team

Various data sources were used to examine trends in national and provincial prescribing of OAB medications including IMS Geographic Prescription Monitor, Canadian Institute for Health Information National Prescription Drug Utilization Information System (CIHI-NPDUIS) and administrative databases in Ontario. Several limitations are associated with the analysis of the data including: codes used to flag OAB diagnosis have not been validated are likely to underestimate diagnosis rates; data presented are based on prescriptions filled (unable to verify that the patient took the medication); IMS Geographic Prescription Monitor does not collect patient-level data and information for privately funded prescriptions only available at the prescription (not patient) level. In addition, this analysis did not include utilization for botulinum toxin A claims, due to the small sample size.

Current Utilization across Canada

Quarterly dispensing of prescriptions for overactive bladder medications in Canada has increased by 36.2% over the past 4 years, from 545,985 prescriptions dispensed in the fourth quarter (Q4) of 2009 to 743,653 prescriptions in Q4 2014 (Exhibit 2). In line with the increase in the number of prescriptions is a nearly 40% increase in costs observed between Q4 2009 and Q4 2014 (\$21.4 million to \$30.4 million). In Q4 2014 public payers accounted for the majority (69.9%; N=519,807 of 743,653) of all OAB medication prescriptions in Canada.

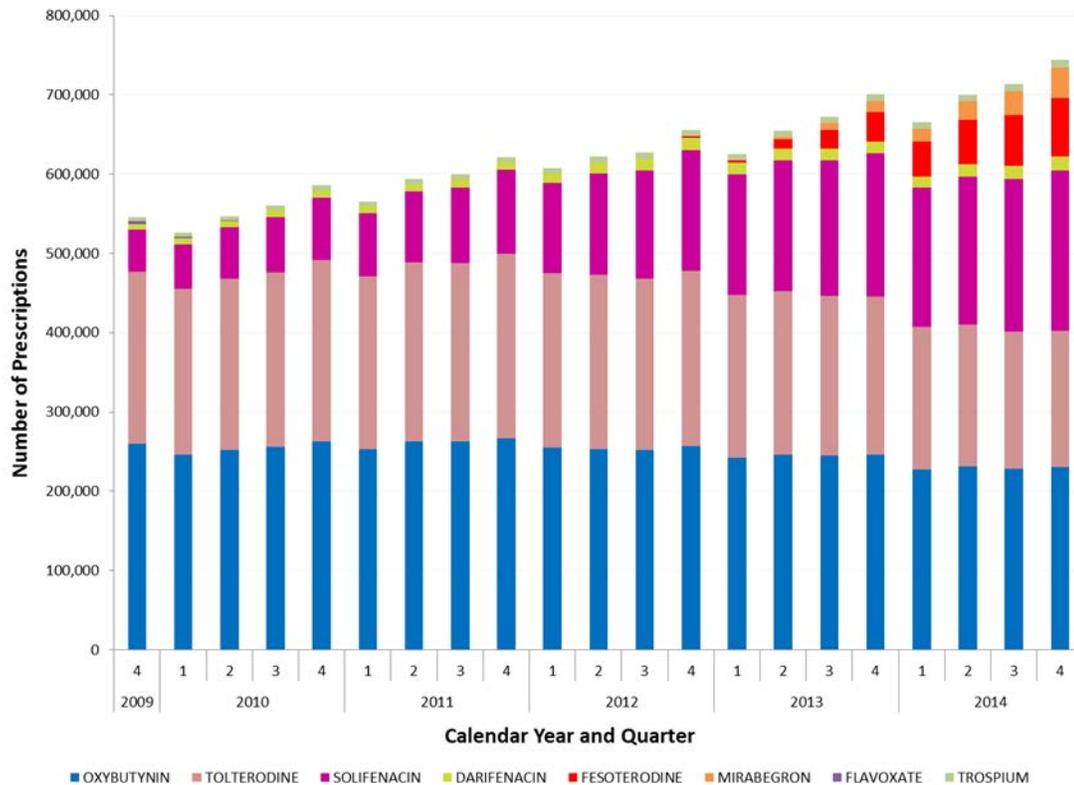
Exhibit 2: Total number of prescriptions for OAB medications dispensed to all individuals in Canada, by payer and quarter (Source: IMS data)



Oxybutynin was found to be the most commonly dispensed OAB medication between Q4 2009 (47.5%; N=260,091 prescriptions) and Q4 2014 (31.0%; N=230,340 prescriptions) but

has seen a decrease in its total market share of OAB medications (Exhibit 3). This reduction is likely due to expanded reimbursement of other available agents (i.e., tolterodine and solifenacin) and the introduction of new treatment options (i.e., darifenacin, fesoterodine, and mirabegron).

Exhibit 3: Prescriptions for publicly funded OAB medications dispensed in Canada, by province and drug in 2014 (Source: IMS data)



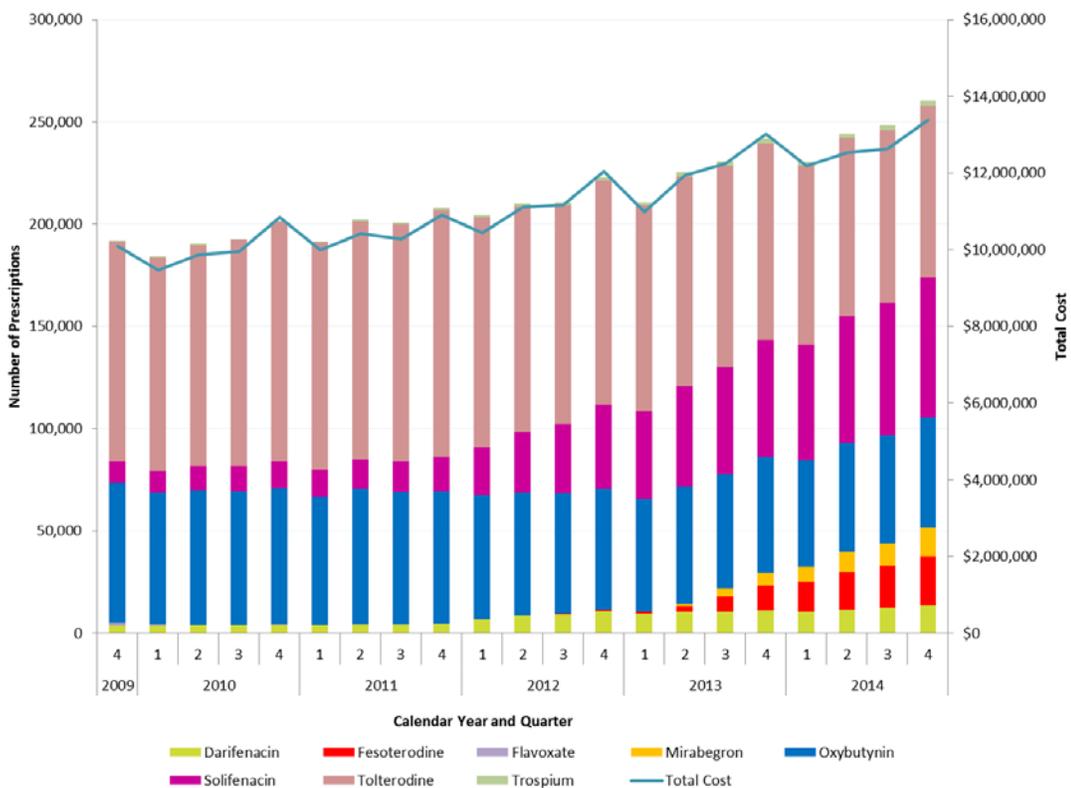
The rate of OAB medication users among public drug plan beneficiaries has increased across all provinces studied (with the exception of British Columbia), but varies widely by province (range of 4 users per 1,000 eligible population in British Columbia to 27 users per 1,000 eligible population in New Brunswick). Oxybutynin was the most commonly used provincially-funded OAB medication among all studied provinces (with the exception of Ontario where tolterodine is most commonly used), which may be due to the general listing status of the generic formulation in all provinces. British Columbia had the lowest average provincially funded cost per user (\$100-150) due to its strict listing. Listing in British Columbia highly restricts access to all agents except for oxybutynin (974 users per 1,000 eligible). In contrast, Ontario had the second highest cost per user (\$400-450) among provinces examined.

Patterns of OAB Medication Use in Ontario

The use of OAB medications in Ontario has increased over time, with the total number of prescriptions dispensed, regardless of payer, having increased by 35.6% from 192,030 prescriptions in Q4 2009 to 260,446 prescriptions in Q4 2014. Consequently, costs also increased by approximately 32.6% from \$10.1 million to \$13.4 million between Q4 2009 and Q4 2014, respectively (Exhibit 4).

Among all prescriptions in Q4 2014 for OAB medications in Ontario, regardless of payer, over half (56%; N=107,691 prescriptions) of prescriptions were for tolterodine, followed by oxybutynin (35.7%; 68,553 prescriptions), solifenacin (5.3% N=10,213 prescriptions), darifenacin (1.9%; N=3,743 prescriptions) and trospium (0.3%; N=556 prescriptions). In Q4 2014, three quarters (75.3%; N=196,113 prescriptions) of OAB medications dispensed in Ontario were paid for by public payers. Among provincially-funded users in Ontario, there has been a large shift in trends of OAB medication use over the last 14 years. At the start of 2000 only three OAB medications were available. Oxybutynin was the most commonly used OAB medication. This trend changed as tolterodine saw a 10-fold increase from approximately 3,000 users to over 34,000 users between Q1 2000 and Q4 2011, respectively. By Q3 2015, with the introduction of four newer agents to the formulary, tolterodine use dropped close to 40% but remained the most utilized publicly funded OAB medication in Ontario. Solifenacin was the second most utilized treatment followed by oxybutynin, mirabegron, fesoterodine, darifenacin, and trospium in Q3 2015.

Exhibit 4: Total number of prescriptions and cost for OAB medications dispensed in Ontario by all payers, by drug and quarter (Source: IMS data)



Characteristics of Publically-funded OAB Medication Users in Ontario

In fiscal years 2012 and 2013, there were a total of 113,980 publicly-funded OAB medication users in Ontario. The majority of users were treated with tolterodine (43.3%; N=49,447), followed by oxybutynin (28.3%; N=32,347), solifenacin (20.8%; N=23675) darifenacin (4%; N=4613), fesoterodine (2.7%; N=3071), trospium (0.6%; N=658), and dual therapy users (0.1%; N=169). Users of OAB medications in Ontario were on average 73 years of age,

approximately one-third (38.8%) were males (N=36,682), 4.1% (N=4,663) lived in long-term care, and 66.9% (N=76,196) had a diagnosis of OAB.

In fiscal years 2012 and 2013, we identified 43,184 users, of whom 23,221 filled 2 or more prescriptions, aged 66+ who newly initiated an OAB medication in Ontario. Most new users (who received at least two OAB prescriptions) initiated solifenacin (36.6%; N=8509), followed by tolterodine (31.7%; N=7365), oxybutynin (17.4%; N=4044), darifenacin (6.9%; N=1603), fesoterodine (6.4%; N=1484), and trospium (0.9%; N=216). The median age of new users of OAB agents who received 2 or more prescriptions was 77 years. Only 8.9% of oxybutynin initiators (N=358), compared to over half of fesoterodine (55.1%, N=817) and trospium initiators (50.9%, N=110), received their initial prescription from a urologist. A high proportion of new users of oxybutynin had only one prescription over the period of continuous use (59.6%, N=5,963). A small proportion of users (10.8% to 20.3%) in Q3-2015 had any previous oxybutynin use despite the current Limited Use criteria which limits the use of these medications to users who have failed or could not tolerate oxybutynin.

Patterns of OAB Medication Use and Discontinuation

We identified 23,221 elderly patients aged 66 years and older who newly initiated an OAB medication in Ontario between 2011 and 2013, and who continued treatment with at least one prescription refill. Most users were prescribed only one OAB medication type throughout their period of continuous use (83.5%, N=19,399). Over half (57.9%) of users (N=13,439) were still on therapy at 6 months and 39.9% (N=9,276) were still on therapy at 1 year. Users remained on any OAB therapy for a median of 251 days. A relatively high proportion of users of oxybutynin discontinued use or switched to a different OAB agent within 6 months after initiation (24-26%) compared to other drug groups (14% or less). The median time to discontinuation of a user's initial drug significantly differed by drug initiated. The median time to discontinuation was lowest for oxybutynin users (110-120 days) and highest for solifenacin users (240-250 days).

Systematic Review Team

The objective of the systematic review was to determine the comparative clinical efficacy and safety of pharmacologic treatments (excluding botulinum toxin A) for overactive bladder (OAB) in adults, by use of a systematic review and Bayesian network meta-analysis.

A total of 105 unique randomized controlled trials (RCTs) reported in 168 publications met the inclusion criteria. A total of 79 studies reported outcomes of interest. These studies were published between 1997 and 2015, and the total number of participants in each study ranged from 18 to 2,417. RCTs included in the analyses were all parallel design, except for one crossover study which reported data for the first period. Study duration ranged from 2 to 52 weeks, although median study duration was 12 weeks. Study participants were predominantly female (range 50 to 100%) and had varying treatment experience with anticholinergic agents. Mean age ranged from 40.2 years to 75.3 years.

Efficacy

Outcome measures used for assessment of treatment of OAB include micturitions in 24 hours, incontinence in 24 hours, quality of life, urgency episodes and nocturia. See Exhibit 5 for an overall summary of efficacy results for the outcomes reported in this review.

Overall, most agents, except for oxybutynin transdermal, were superior to placebo for most outcomes studied, including micturitions, incontinence, quality of life, urgency episodes and nocturia. No agent was significantly better than oxybutynin IR for any of the outcomes.

- *Micturitions in 24 Hours (at 12 weeks study duration)*
 - All agents were superior to placebo except for the oxybutynin transdermal formulation.
 - When compared to each other, extended-release oxybutynin was superior to transdermal oxybutynin, tolterodine, extended-release tolterodine and mirabegron.
 - Solifenacin was superior to tolterodine, extended-release tolterodine and mirabegron.
- *Incontinence in 24 Hours (at 12 weeks study duration)*
 - All agents were superior to placebo except for the oxybutynin transdermal formulation and trospium.
 - When compared to each other, extended-release oxybutynin and solifenacin were superior to tolterodine, extended-release tolterodine, darifenacin, fesoterodine, and mirabegron.
- *Quality of Life (at end of study)*
 - Tolterodine ER, solifenacin, trospium, fesoterodine and mirabegron significantly improved quality of life when compared with placebo.
 - When compared to each other, extended-release tolterodine significantly improved quality of life compared to solifenacin and fesoterodine.
 - Solifenacin and fesoterodine were superior to mirabegron.
 - No studies reported quality of life outcomes for the oxybutynin gel formulation.
- *Urgency Episodes (at end of study)*
 - All agents significantly reduced mean urgency episodes when compared to placebo.
 - When compared to each other, only one comparison showed statistically superior efficacy. Fesoterodine significantly reduced mean urgency episodes when compared to mirabegron.
 - No studies reported urgency episode outcome data for the oxybutynin gel or transdermal formulations.
- *Nocturia (at end of study)*
 - Extended-release tolterodine, solifenacin, fesoterodine and mirabegron significantly reduced nocturia when compared with placebo.
 - No differences were seen amongst the OAB agents when they were compared to each other.

Exhibit 5: Summary of efficacy outcomes for overactive bladder agents

	PLB												
OXYB	●●●○	OXYB											
OXYB-ER	●●●●	○○○○○	OXYB-ER										
OXYB-TRANS	○○○●●	○○○●●	●○○●●	OXYB-TRANS									
OXYB-GEL	●●●●○	○○●●○	○○●●●	○○●●●	OXYB-GEL								
TOLT	●●●●○	○○○○○	●●○○○	○○○●●	○○○●●	TOLT							
TOLT-ER	●●●●●	○○○○○	●●○○○	○○○●●	○○○●●	○○○○○	TOLT-ER						
DARF	●●●●○	○○○○○	●○○○	○○○●●	○○○●●	○○○○○	○○○○○	DARF					
SOLF	●●●●●	○○○○○	○○○○○	○○○●●	○○○●●	●●○○○	●●●●○	●●○○○	SOLF				
TROS	●○○●○	○○○○○	○○○○○	○○○●●	○○○●●	○○○○○	○○○○○	○○○○○	○○○○○	TROS			
FEST	●●●●●	○○○○○	●○○○	○○○●●	○○○●●	○○○○○	●○○●○	○○○○○	○○○○○	●○○○	○○○○○	FEST	
MIRA	●●●●●	○○○○○	●●○○○	○○○●●	○○○●●	○○○○○	○○○○○	○○○○○	○○○○○	●●●○○	○○○○○	○○●●○	MIRA
<p>The 5 contiguous circles correspond, respectively, to the five efficacy outcomes: Micturitions in 24 hours, Incontinence in 24 hours, Quality of Life, Urgency Episodes in 24 hours, and Nocturia in 24 hours.</p> <ul style="list-style-type: none"> • The GREEN circle indicates that the 'row' OAB medication is significantly better than the 'column' OAB medication. • The RED circle indicates that the 'row' OAB medication is significantly worse than the 'column' OAB medication. • The WHITE circle indicates that there is no significant difference between the 'row' and 'column' OAB medication. • A GREY circle indicates that the outcome was not available for analysis. <p>Note micturitions and incontinence outcomes were measured at 12 weeks, while the rest of the outcomes were measured at end of study.</p>													

Additional reviews: Use of combination therapy (anticholinergics + mirabegron)

There are limited studies evaluating the combination of mirabegron and anticholinergics for the treatment of OAB. Two randomized controlled trials assessed mirabegron in combination with solifenacin^{16,17}, and one open-label study also evaluated mirabegron in combination with solifenacin¹⁸. Results from the two RCTs suggest that combination therapy with mirabegron and solifenacin may lead to improvement in symptoms compared to solifenacin as monotherapy; however, no increase in adverse effects are noted with combination therapy compared to monotherapy. Further studies are needed to elucidate which patients would be ideal candidates for combination therapy.

Safety

Five safety outcome measures were used in the systematic review: dry mouth, constipation, arrhythmias, withdrawals (all cause, due to adverse events, due to efficacy) and serious adverse events. See Exhibit 6 for an overall summary of safety and tolerability results for the outcomes reported in this review.

- ***Dry mouth***
 - All agents had significantly higher proportion of patients with dry mouth, except for transdermal oxybutynin, oxybutynin gel and mirabegron when compared to placebo.
 - When compared to each other, all agents were better tolerated than immediate-release oxybutynin.
 - Mirabegron was better tolerated than other agents except the transdermal and gel formulations of oxybutynin.
 - Extended-release tolterodine was better tolerated than darifenacin, tolterodine, extended-release oxybutynin and fesoterodine.
- ***Constipation***
 - All agents had significantly higher proportion of patients with constipation compared to placebo except the oxybutynin formulations, including immediate- and extended-release, transdermal and gel.
 - When compared to each other, oxybutynin (including immediate- and extended-release, transdermal but not gel formulations) were better tolerated (in terms of constipation) compared to the other agents, with few exceptions.
 - Mirabegron and tolterodine were better tolerated than darifenacin, solifenacin, and fesoterodine.
- ***Withdrawals due to adverse events (WDAE)***
 - All agents were similar to placebo with respect to WDAE except for immediate-release oxybutynin, solifenacin and fesoterodine which had significantly higher WDAE.
 - Extended-release oxybutynin, tolterodine, extended-release tolterodine, solifenacin and mirabegron had significantly fewer WDAE compared to immediate-release oxybutynin.
 - Fesoterodine had significantly more WDAE when compared to tolterodine and extended-release tolterodine.

- *Withdrawals due to lack of efficacy*
 - Tolterodine, extended-release tolterodine, solifenacin, fesoterodine and mirabegron had significantly fewer withdrawals due to a lack of efficacy when compared to placebo.
 - No differences amongst the OAB agents were found when they were compared in the NMA.
- *Serious adverse events*
 - No differences amongst the agents when compared to each other or to placebo.

Other safety studies

Observational studies

A rapid review of the observational literature was done to investigate the comparative safety, specifically falls and cognitive effects, of OAB medications. Although there were several studies that explored the class effect of anticholinergic agents^{19;20}, only two studies were identified that conducted comparative safety assessments within this class of medications.^{21;22}

In the first retrospective cohort study conducted in Ontario in patients 66 years and older, there were no significant differences between oxybutynin and tolterodine for risk of falls (adjusted hazard ratio 1.04, 95% CI 0.95 to 1.14), fractures (aHR 0.90, 95% CI 0.66 to 1.23) or delirium (aHR=0.90, 95% CI 0.66 to 1.23).²¹ The second study explored the relative risk, resource utilization, and costs related to new users of OAB medications using US claims data. No difference in the rates of fracture was observed between tolterodine and oxybutynin ER ($p=0.11$) and oxybutynin IR ($p=0.14$). Oxybutynin IR users were found to have higher risk of depression ($P=0.01$) than tolterodine, while no difference was found with Oxybutynin ER ($p=0.41$).²²

Summary: Only two comparative observational studies of the safety of OAB medications were found. No studies were found studying newer agents. Overall, due to the limited evidence available, no conclusive statements can be made regarding differences in safety or between OAB medications based on observational data.

Exhibit 6: Summary of safety and tolerability outcomes for overactive bladder agents

	PLB											
OXYB	●○○●○○	OXYB										
OXYB-ER	●○○○○○	●●●○○○	OXYB-ER									
OXYB-TRANS	○○○○○○	●○○○○○	●○○○○○	OXYB-TRANS								
OXYB-GEL	○○○○○○	●○○○○○	○○○○○○	○○○○○○	OXYB-GEL							
TOLT	●●●○○○	●●●○○○	○○○○○○	●○○○○○	○○○○○○	TOLT						
TOLT-ER	●●●○○○	●●●○○○	●○○○○○	●○○○○○	○○○○○○	●○○○○○	TOLT-ER					
DARF	●●●○○○	●●●○○○	●○○○○○	●●●○○○	○○○○○○	●○○○○○	●●●○○○	DARF				
SOLF	●●●○○○	●●●○○○	●○○○○○	●○○○○○	○○○○○○	●○○○○○	●○○○○○	○○○○○○	SOLF			
TROS	●●●○○○	●●●○○○	○○○○○○	●○○○○○	○○○○○○	○○○○○○	○○○○○○	○○○○○○	○○○○○○	TROS		
FEST	●●●○○○	●●●○○○	●○○○○○	●●●○○○	○○○○○○	●○○○○○	●○○○○○	○○○○○○	●○○○○○	○○○○○○	FEST	
MIRA	●○○○○○	●○○○○○	●○○○○○	●○○○○○	○○○○○○	●○○○○○	●○○○○○	●○○○○○	●○○○○○	●○○○○○	●○○○○○	MIRA
<p>The 5 contiguous circles correspond, respectively, to the five efficacy outcomes: Dry mouth, Constipation, Withdrawals due to adverse events, Withdrawals due to lack of efficacy, Serious adverse events. All outcomes were measured at end of study.</p> <ul style="list-style-type: none"> • The GREEN circle indicates that the 'row' OAB medication is significantly better than the 'column' OAB medication. • The RED circle indicates that the 'row' OAB medication is significantly worse than the 'column' OAB medication. • The WHITE circle indicates that there is no significant difference between the 'row' and 'column' OAB medication. • A GREY circle indicates that the outcome was not available for analysis. 												

Pharmacoeconomics Team

Cost-Effectiveness Literature Review

A systematic review of the literature was conducted to summarize the current published evidence on the comparative cost-effectiveness of pharmacologic treatments in the management of adults with OAB. Of the 26 published economic evaluations identified in this review, most studies were conducted across a range of European settings; three Canadian economic analyses were also identified²³⁻²⁵. The majority of included economic evaluations expressly cited financial support from the pharmaceutical industry or had authors who were affiliated with industry, and study findings consistently favoured the sponsor's product. Additionally, limitations of existing economic analyses included issues related to the derivation of utility values, as well as modeling of treatment discontinuation and adverse events. Furthermore, the inclusion of costs related to incontinence pad use in studies' base case analyses limits generalizability to the Canadian context, as most public jurisdictions do not provide funding for incontinence pads.

Two of the three Canadian studies were published more than 10 years ago and their findings do not accurately reflect current clinical evidence or cost data; all three studies received industry funding. Moreover, all three evaluations were limited by their narrow research questions, and had issues related to the extrapolation of short-term efficacy data from single clinical trials, the handling of treatment discontinuation rates and adverse events, and the inclusion of costs of incontinence pads.²³⁻²⁵ Therefore, although these economic evaluations may reflect the context of the Canadian health care decision maker, drawbacks related to their analytic approach and choice of comparators weaken the applicability of the results.

Two independent analyses^{26;27} were also included in this review. While the applicability of the study findings was strengthened by their consideration for a broad range of treatment comparators and the absence of industry sponsorship or affiliation, a number of limitations similar to those identified within all studies were identified, including analytic approach, choice of comparators and lack of Canadian perspective. Accordingly, these analyses are not sufficiently useful in aiding decision making within the Canadian context.

The paucity of well conducted independent analyses from the Canadian perspective precluded any inferences regarding the cost-effectiveness of drug therapies for OAB treatment in Canada.

De novo Economic Evaluation

An independent de novo economic model was developed to assess the cost effectiveness of OAB therapies (not including botulinum toxin A) in the Canadian context. The costs and quality adjusted life years (QALYs) of oxybutynin IR, oxybutynin ER, oxybutynin gel, oxybutynin transdermal, tolterodine IR, tolterodine ER, solifenacin, fesoterodine, trospium, darifenacin, mirabegron and no drug treatment (no therapy) were compared. A Markov model was developed to compare the therapies over a twelve month period with monthly cycles using data obtained from the systematic review of clinical studies.

Based on this model, solifenacin is the most cost effective therapy for the treatment of OAB. Oxybutynin IR is cost-effective for patients who have failed on solifenacin, at an incremental cost of \$27,000 per quality adjusted life year (QALY) gained, as compared with no therapy (see Exhibit 7). All other agents are not cost effective based on a commonly used threshold of \$50,000 per QALY gained; this analysis was done prior to the introduction of generic tolterodine. A sensitivity analysis was done using a reduced price of tolterodine ER (25% of current branded price); at this price, tolterodine ER was cost effective compared to no therapy (with an incremental cost per QALY gained of \$26,000 but was dominated by solifenacin). Thus, solifenacin remained the optimal therapy.

Exhibit 7: Incremental cost per quality adjusted life years for medications used for overactive bladder

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.6836	\$0.00	\$0.00	\$0.00
Solifenacin	0.6935	\$187.78	\$19,049.70	\$19,049.70
Dominated				
Oxybutynin IR	0.6889	\$145.36	\$27,442.19	Subject to extended dominance through no therapy and Solifenacin
Mirabegron	0.6927	\$464.08	\$51,197.47	Dominated by Solifenacin
Trospium	0.6920	\$442.69	\$53,170.58	Dominated by Solifenacin
Fesoterodine	0.6915	\$442.24	\$56,168.19	Dominated by Solifenacin
Darifenacin	0.6909	\$476.93	\$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.6934	\$645.17	\$66,168.22	Dominated by Solifenacin
Oxybutynin transdermal	0.6911	\$524.62	\$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.6911	\$553.56	\$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.6909	\$539.81	\$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.6908	\$539.74	\$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Budget Impact Analysis and Reimbursement-based Economic Evaluation

- For the period Q4/2014 to Q3/2015, the average number of users <65 years per quarter was 13,492. For OAB patients 65+, the total average number of users was 60,402. Based on data from the OPDP, expenditure is expected to drop from \$6.2 million in 2014 to about \$6.0 million (↓2.7%) in 2018 for patients aged less than 65 years and from \$31.3 million to approximately \$30.4 million (↓3.1%) for patients aged 65 years and older. A slight decrease in expenditures is anticipated due to the availability of several agents as generic formulations (solifenacin, tolterodine IR, tolterodine ER).
- An independent de novo economic model was developed to assess the cost effectiveness of alternative therapies for overactive bladder, as compared with each other or no therapy.

- Based on this model, solifenacin is the most cost effective therapy for the treatment of OAB. Oxybutynin IR is cost-effective for patients who have failed on solifenacin, at \$27,000 per quality adjusted life year (QALY) gained compared with no therapy. All other agents, at current prices, are not cost effective based on a commonly used threshold of \$50,000 per QALY gained.
- Various reimbursement options were considered in the budget impact analysis, including step therapy (i.e., use of most cost-effective drug before receiving coverage for an alternative agent). The impact of enforcing step therapy is unclear as it is unknown whether this would lead to patients increasing their total time on all therapies (which would lead to increased expenditure) or decreasing their time on therapies other than oxybutynin (which would lead to decreased expenditure). Covering tolterodine ER and solifenacin under General Benefit was predicted to decrease expenditures.
- In addition, there are limitations with the current ODB pharmacy system that do not allow for step therapy to be enforced.
- Note that dual therapy (i.e., mirabegron + anticholinergic medications) was not considered in this model.
- For the reimbursement-based economic evaluation, a strategy whereby solifenacin and oxybutynin IR are considered as first line therapies with enforcement of step therapy is the optimal reimbursement strategy.

Exhibit 8: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged 65 years and older (assuming no change in mirabegron prescribing)

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	Ach¹	MIRA²	TOTAL	Net Budget Impact	%
Status quo (base case): No change to current GB listing for OXYB and LU for currently covered agents					
	\$26,358,701	\$4,008,829	\$30,367,530	N/A	N/A
Status quo + LU listing for Ditropan XL, Gelnique, Oxytrol⁵					
	\$27,499,304	\$4,008,829	\$31,508,133	\$1,140,603	4%↑
Enforced step therapy for ACh medications (no increase in overall time on all OAB agents)³					
	\$18,358,309	\$2,534,816	\$20,893,125	-\$9,474,405	-31%
Enforced step therapy for Ach medications (no increase in overall time on all OAB agents)³ + LU listing for Ditropan XL, Gelnique, Oxytrol⁵					
	\$19,953,114	\$2,534,816	\$22,487,930	-\$7,879,600	-26%↓
Enforced step therapy for Ach medications (no change in time on individual OAB therapy⁴)					
	\$28,437,606	\$4,008,829	\$32,446,435	\$2,078,905	7%↑
Enforced step therapy for Ach medications (no change in time on individual OAB therapy⁴) + LU listing for Ditropan XL, Gelnique, Oxytrol⁵					
	\$30,306,518	\$4,008,829	\$34,315,347	\$3,947,817	13%↑
GB listing for generic products (OXYB, TOLT IR⁶, SOLF) and LU listing for all other currently covered agents⁶					
	\$28,076,600	\$4,008,829	\$32,085,429	\$1,717,899	6%↑
GB listing for generics, LU for other currently covered agents + LU listing for Ditropan XL, Gelnique, Oxytrol⁵					
	\$29,148,712	\$4,008,829	\$33,157,541	\$2,790,011	9%↑
GB listing for OXYB AND SOLF and LU listing for other currently covered agents⁶					
	\$26,715,003.85	\$4,008,829.13	\$30,723,832.99	\$356,303.08	1%↑
GB listing for SOLF and LU listing for all other currently covered agents⁶					
	\$27,038,332.72	\$4,008,829.13	\$31,047,161.85	\$679,631.94	2%↑
<p>¹ ACh = Anticholinergic OAB medications, includes darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium</p> <p>² MIRA = mirabegron (beta-3 adrenergic agonist)</p> <p>³ In this scenario, the total time on OAB medications is the same (based on rates obtained from OPDP data).</p> <p>⁴ In this scenario, the total time on other (non-oxybutynin IR) OAB medications is the same, but there is also additional time added for oxybutynin IR.</p> <p>⁵ Assume 5% of current users of anticholinergic medications will move to Ditropan XL, Gelnique and Oxytrol (equal amongst them)</p> <p>⁶ Tolterodine IR was modeled at current prices (not 25% of branded name product price).</p>					

Health Equity Issues

No major health equity issues were identified in this review. See Appendix A for Health Equity Considerations.

Accessibility of Medications for OAB

No accessibility issues were identified in Ontario in our review for medications use in the treatment of OAB. All oral anticholinergics, mirabegron and botulinum toxin A are available on the ODB formulary, either as a General Benefit (oxybutynin regular release) or Limited Use. For patients unable to swallow, oxybutynin transdermal is available through the Exceptional Access Program.

Recommendations for Consideration

Key Considerations

Efficacy

- In our review, outcome measures used for assessment of treatment of OAB included micturitions in 24 hours, incontinence in 24 hours, quality of life, urgency episodes and nocturia.
- Overall, the network meta-analysis (NMA) found that most agents, except for oxybutynin transdermal, were superior to placebo for most outcomes.
- The NMA also showed that for micturitions in 24 hours, solifenacin was superior to tolterodine, tolterodine ER and mirabegron. Additionally, for quality of life, solifenacin and fesoterodine were superior to mirabegron. No agent was significantly better than oxybutynin IR for any of the outcomes.

Safety

- Five safety outcome measures were used in the systematic review: dry mouth, constipation, arrhythmias, withdrawals (all cause, due to adverse events, due to efficacy) and serious adverse events.
- For dry mouth, all agents had significantly higher proportion of patients with dry mouth, except for transdermal oxybutynin, oxybutynin gel and mirabegron when compared to placebo. Overall, all agents were better tolerated than immediate-release oxybutynin. As well, mirabegron was better tolerated than all other drugs, except transdermal and gel formulations of oxybutynin.
- For constipation, all agents had significantly higher proportion of patients compared to placebo except the oxybutynin formulations, including immediate- and extended-release, transdermal and gel.
- For withdrawals due to adverse events, all agents were similar to placebo except for immediate-release oxybutynin, solifenacin and fesoterodine which had significantly higher number of events. However, when compared to immediate-release oxybutynin, extended-release oxybutynin, tolterodine, tolterodine ER, solifenacin and mirabegron had significantly fewer number of withdrawals due to adverse events.
- For serious adverse events, no differences were observed amongst the agents when compared to each other or to placebo.

- In a rapid review of the observational literature comparing safety of OAB medications, only two studies were identified. The limited evidence does not indicate a difference in the rate of fractures between oxybutynin and tolterodine. Overall, there is a lack of evidence available on the real-world comparative safety, including falls and cognitive impairment, for OAB medications.

Accessibility

- No accessibility issues were identified in Ontario in our review for medications use in the treatment of OAB. All oral anticholinergics, mirabegron and botulinum toxin A are available on the ODB formulary, either as a General Benefit (oxybutynin regular release) or Limited Use.

Pharmacoeconomics

- *Cost effectiveness literature review:* A systematic review of the literature was done to highlight the current published evidence on the comparative cost-effectiveness of pharmacologic treatments in the management of adults with OAB. Of the 26 published economic evaluations identified in this review, most studies were conducted across a range of European settings; three Canadian economic analyses were also identified. Most studies (88%) cited financial support or affiliation with the pharmaceutical industry, and all such studies favored the sponsoring company's drug. The availability of well-designed independent analyses from the Canadian perspective is lacking; as such, a de novo model was developed to address the research question.
- *De novo economic evaluation:* An independent de novo economic model was developed to assess the cost effectiveness of alternative therapies for overactive bladder, as compared with each other or no therapy. A Markov model was developed which modelled the impact of treatment on the frequency of micturitions and incontinence episodes over a 12 month period. Based on this model, solifenacin is the most cost effective therapy for the treatment of OAB. Oxybutynin IR is cost-effective for patients who have failed on solifenacin, at \$27,000 per quality adjusted life year (QALY) gained compared with no therapy. All other agents, at current prices, are not cost effective based on a commonly used threshold of \$50,000 per QALY gained.
- *Budget impact analysis and reimbursement-based economic evaluation:* For the period Q4/2014 to Q3/2015, the average number of users <65 years per quarter was 13,492. For OAB patients 65+, the total average number of users was 60,402. Based on data from the OPDP, spending on OAB medications for those aged 65 and older was \$31.3 million and for those under 65 years \$6.2 million in 2014; total expenditures are projected to be approximately \$36.4 million by 2018 for all age groups.
 - Mirabegron is a new addition to the ODB formulary, and as such, there is limited data available for utilization of this product. If mirabegron prescribing were to increase by either 10% or 20% per annum from 2016 to 2018, limited effect on overall OAB medication expenditure is expected if there were no change to current coverage ("status quo").

Reimbursement Options

Given the similar efficacy of the OAB medications, the differences observed in adverse effects between the agents, and the differential cost effectiveness of these drugs, four main

reimbursement options for treatment for OAB are proposed. Since botulinum toxin A was not included in our analysis, no new listing recommendations for this product have been made; it is currently listed on the ODB formulary as Limited Use.

Option A (status quo): Oxybutynin IR as General Benefit, all other OAB medications Limited Use

- Oxybutynin IR as General Benefit
- All other currently listed products (darifenacin, fesoterodine, solifenacin, tolterodine, trospium, mirabegron) listed as Limited Use
 - Criteria for use include intolerance or failure to respond to oxybutynin IR

Rationale:

- No agent has been found to be more efficacious than oxybutynin IR.
- Although solifenacin is the most cost-effective medication, oxybutynin IR is also cost-effective for patients who have failed on solifenacin at \$27,000 per QALY gained compared with no therapy. All other OAB medications are not cost effective at a threshold of \$50,000/QALY.

Limitations:

- Overall, oxybutynin is not as well tolerated as other agents. Clinicians prefer the use of long-acting agents in order to minimize potential adverse effects.
- More users of oxybutynin IR discontinued or switched to other medications, compared to other drugs.

Option B1: Oxybutynin IR, tolterodine ER and solifenacin as General Benefit, all other OAB medications Limited Use

- Oxybutynin IR, solifenacin and tolterodine ER listed as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine IR, trospium, mirabegron) listed as Limited Use.
 - Criteria for use include intolerance or failure to respond to oxybutynin IR AND solifenacin AND tolterodine ER

NOTE: Addition of generic tolterodine ER as General Benefit is considered based on price reduction to 25% of brand name costs. Availability of other medications (including tolterodine IR) as generic formulations priced at 25% of brand name costs should prompt re-evaluation of listing status, as these agents may become cost-effective alternatives.

Rationale:

- All agents (including solifenacin, tolterodine and oxybutynin IR) are superior to placebo.
- Addition of solifenacin and tolterodine ER as first-line therapy provides options that are better tolerated than oxybutynin.
- Clinicians prefer use of long-acting agents, such as solifenacin and tolterodine ER. This reimbursement option provides three first-line options.
- Over 92% of all current users are on solifenacin, tolterodine and oxybutynin.
- Solifenacin has been shown to have the greatest persistence in therapy.

- Solifenacin is the most cost-effective medication for OAB. Oxybutynin IR is cost-effective for patients who have failed on solifenacin, at \$27,000 per quality adjusted life year (QALY) gained compared with no therapy. In a sensitivity analysis, tolterodine ER (at 25% of branded cost) was cost-effective compared to no therapy, but was dominated by solifenacin. All other OAB medications are not cost effective at a threshold of \$50,000/QALY.

Limitations:

- In order to access other long-acting agents, patients need to have been tried on oxybutynin IR, tolterodine ER and solifenacin. This would result in patients who are unable to tolerate solifenacin or tolterodine ER being switched to oxybutynin IR, which has significantly greater adverse effects than solifenacin or tolterodine ER.
- In addition, more users of oxybutynin IR discontinued or switched to other medications, compared to other drugs.

Option B2: Oxybutynin IR, tolterodine ER or solifenacin as General Benefit, all other OAB medications Limited Use

- Oxybutynin IR, tolterodine ER and solifenacin listed as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine IR, trospium, mirabegron) listed as Limited Use.
 - Criteria for use include intolerance or failure to respond to oxybutynin IR OR tolterodine ER OR solifenacin

Rationale:

- All agents (including solifenacin, tolterodine and oxybutynin IR) are superior to placebo.
- Addition of solifenacin and tolterodine ER as first-line therapy provides options that are better tolerated than oxybutynin IR. Patients need to be tried on only one of oxybutynin OR solifenacin OR tolterodine ER before being tried on other agents. This allows for prescribers to choose another agent based on patient's previous response and tolerability.
- Clinicians prefer use of long-acting agents, such as solifenacin and tolterodine ER. This reimbursement option provides three first-line options, two of which are long-acting (i.e., solifenacin, tolterodine ER).
- Over 92% of all current users are on solifenacin, tolterodine or oxybutynin. Solifenacin has been shown to have the greatest persistence in therapy.
- Solifenacin is the most cost-effective medication for OAB. Oxybutynin IR is cost-effective for patients who have failed on solifenacin, at \$27,000 per quality adjusted life year (QALY) gained compared with no therapy. In a sensitivity analysis, tolterodine ER (at 25% of branded cost) may be cost-effective compared to no therapy, but was dominated by solifenacin. All other OAB medications are not cost effective at a threshold of \$50,000/QALY.

Limitations:

- This option may result in use of a less cost-effective agent as second-line therapy than either solifenacin, tolterodine ER or oxybutynin.

Option C1: Enforced use of oxybutynin IR, tolterodine ER AND solifenacin as initial therapy, all other OAB medications Limited Use

- Oxybutynin IR, tolterodine ER and solifenacin as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine IR, trospium, mirabegron) listed as Limited Use.
 - Criteria for use include intolerance or failure to respond to oxybutynin IR AND solifenacin AND tolterodine ER; system would require that the patient had prior use of oxybutynin IR, tolterodine ER and solifenacin before approval granted for other agent

Rationale:

- Similar to Option B1 except ENFORCED Limited Use (e.g., have the pharmacy system perform a look-back to see if the patient has had previous use of first-line therapy before allowing access to second-line options).
- Only 10-20% of patients currently meet Limited Use criteria; enforced Limited Use would help to address this issue.
- Several provinces have adopted “step therapy” (i.e., use of oxybutynin IR prior to coverage of alternative agent) that is adjudicated at the pharmacy level.

Limitations

- In order to access other long-acting agents, patients need to have been tried on oxybutynin IR, tolterodine ER and solifenacin. This would result in patients who are unable to tolerate solifenacin and tolterodine ER being switched to oxybutynin IR, which has significantly greater adverse effects than solifenacin.
- In addition, more users of oxybutynin IR discontinued or switched to other medications, compared to other drugs.
- Current pharmacy systems are not able to perform “look-back” for previous therapy.

Option C2: Enforced use of oxybutynin IR, tolterodine ER OR solifenacin as initial therapy, all other OAB medications Limited Use

- Oxybutynin IR, tolterodine ER and solifenacin as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine IR, trospium, mirabegron) listed as Limited Use.
 - Criteria for use include intolerance or failure to respond to oxybutynin IR OR solifenacin OR tolterodine ER; system would require that the patient had prior use of oxybutynin IR, tolterodine ER OR solifenacin before approval granted for other agent

Rationale:

- Similar to Option B2 except ENFORCED Limited Use (e.g., have the pharmacy system perform a look-back to see if the patient has had previous use of first-line therapy before allowing access to second-line options).

- Only 10-20% of patients currently meet Limited Use criteria; enforced Limited Use would help to address this issue.
- Several provinces have adopted “step therapy” (i.e., use of oxybutynin IR prior to coverage of alternative agent) that is adjudicated at the pharmacy level.

Limitations

- This option may result in use of a less cost-effective agent as second-line therapy than either solifenacin, tolterodine ER or oxybutynin.
- Current pharmacy systems are not able to perform “look-back” for previous therapy.

Option D: Solifenacin as General Benefit, all other OAB medications Limited Use

- Solifenacin as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine ER/IR, trospium, mirabegron, oxybutynin IR) listed as Limited Use.
 - Criteria for use for include intolerance or failure to respond to solifenacin
 - Additional criteria for use for oxybutynin IR include use in patients with neurogenic bladder. Since Limited Use criteria are only based on approved indications, off-label indications for oxybutynin IR (e.g., hyperhidrosis, enuresis) will not be added.

Rationale:

- Solifenacin is equal to or more efficacious than other agents.
- Addition of solifenacin as first-line therapy provides an option that is better tolerated than oxybutynin. Adverse effects (in particular dry mouth) are more common with oxybutynin IR than with other OAB medications.
- Clinicians prefer use of long-acting agents, such as solifenacin.
- Solifenacin has been shown to have the greatest persistence in therapy.
- Solifenacin is the most cost-effective medication for OAB. Oxybutynin IR is cost-effective for patients who have failed on solifenacin, at \$27,000 per quality adjusted life year (QALY) gained compared with no therapy. All other OAB medications are not cost effective at a threshold of \$50,000/QALY.

Limitations

- In order to access other long-acting agents, patients need to have been tried on solifenacin.
- This option limits oxybutynin IR for use in approved indications only; however, oxybutynin is also used off-label for other indications such as hyperhidrosis and enuresis.

Considerations for other recommendations

Recommendation 1: No listing is recommended for oxybutynin extended release (Ditropan XL).

- Oxybutynin ER was no more effective than solifenacin, trospium or oxybutynin IR, although oxybutynin ER was more effective than tolterodine, darifenacin, fesoterodine and mirabegron for some outcomes.

- From a tolerability standpoint, there are no advantages of oxybutynin ER over other available OAB medications, except for oxybutynin IR (for dry mouth and constipation) and darifenacin, solifenacin and fesoterodine (for constipation).
- Oxybutynin ER does not provide any advantages over other currently available OAB medications for patients who are unable to swallow.
- At current prices, oxybutynin ER is not cost effective.

Recommendation 2: For patients unable to swallow, recommend availability of oxybutynin gel (Gelnique) under Exceptional Access Program (but not oxybutynin transdermal [Oxytrol]).

- Oxybutynin transdermal is no more effective than placebo or any oral anticholinergic medication, although it is better tolerated than oral medications. However, oxybutynin transdermal is associated with localized application site reactions (e.g., itchiness).
- Oxybutynin gel is more effective than placebo but no more effective than other OAB medications; as well, fewer patients experience dry mouth with oxybutynin gel than with other agents.
- Both oxybutynin transdermal and gel provide options for patients unable to take oral medications.
- At current prices, oxybutynin transdermal and oxybutynin gel are not cost effective.
- However, coverage of oxybutynin gel through EAP should be considered for patients who are unable to swallow or who are unable to absorb oral medications. Inclusion of oxybutynin gel is recommended over oxybutynin patch since there are no significant differences in efficacy for the two products but oxybutynin patch is associated with localized application site reactions.

Recommendation 3: It is recommended that a Therapeutic Note should be applied to all anticholinergics (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium) used for OAB, cautioning about the use of anticholinergics in the elderly. The therapeutic note does not apply to mirabegron, a beta-3 adrenoceptor agonist.

- There is currently a note in the Limited Use criteria (code 290) cautioning about the use of antimuscarinics (anticholinergics) in the elderly. However, this note is not included in the listing for oxybutynin IR.
- The note should be added as a “Therapeutic Note”, rather than being part of the Limited Use criteria.
 - *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.*

Stakeholder Review

Findings from the stakeholder review contributed to selection of final policy recommendations, and include feedback solicited from an open call for review, comments received during a workshop for stakeholders, as well as results from the ODPRN Citizen's Panel.

Findings from the ODPRN Citizens' Panel

Citizens' Panel (CP) members considered each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. Panel members completed a survey prior to the meeting, as well as following the meeting.

- Panel members found option B2 (solifenacin, tolterodine OR oxybutynin IR as General Benefit, all other agents as Limited Use) the most acceptable option in both pre- and post- surveys.
“A logical option, to ease the access to these 3 drugs by virtue of their GB status, and not require a patient to try all 3 before potentially changing to a LU-status product if necessary; while still keeping costs to ODB reasonable”
- The least acceptable options were options A and C.
For Option A: *“Denies people easier access to drugs that are clearly more effective and [also] as cost effective.”*
- Panel members agreed with recommendation 1 (no listing is recommended for oxybutynin ER) and recommendation 3 (inclusion of Therapeutic Notes for all anticholinergics). For recommendation 2 (inclusion of oxybutynin gel under EAP), the majority of members agreed with this but questioned if LU should be used instead of EAP.

Exhibit 9: Overall option ranking

	Mean Ranking (1 = Most Acceptable 7 = Least Acceptable)
	Post-meeting
Option A: (status quo) Oxybutynin IR as GB, all other OAB medications LU	6.5 (0.6)
Option B1: Oxybutynin IR, solifenacin and tolterodine (immediate and extended release) as GB, all other OAB medications LU	4.8 (0.5)
Option B2: Oxybutynin IR, solifenacin or tolterodine (immediate and extended release) as GB, all other OAB medications LU	1.0 (0.0)
Option B3*: Oxybutynin IR and solifenacin as GB, all other OAB medications LU	4 (0.8)
Option B4*: Oxybutynin IR, solifenacin as GB, all other OAB medications LU	2.8 (0.5)
Option C: Enforced use of oxybutynin IR OR solifenacin as initial therapy, all other OAB medications Limited Use	6.5 (0.6)
Option D: Solifenacin as General Benefit, all other OAB medications Limited Use	2.5 (1.0)

*Options presented to the Citizen's Panel prior to the price reduction of generic tolterodine.

Final Policy Recommendations and Conclusion

Final recommendations for the OAB drug class review are based on results of our review (patient and prescriber perspectives, efficacy and safety data, utilization data in Ontario and across Canada, cost-effectiveness analysis), input from stakeholders and feedback from the ODPRN Citizen's Panel.

The following reimbursement option is recommended for consideration as a funding alternative for the Ontario Public Drug Programs:

Oxybutynin IR, tolterodine ER or solifenacin as General Benefit, all other OAB medications Limited Use

- Oxybutynin IR, tolterodine ER and solifenacin listed as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine IR, trospium, mirabegron) listed as Limited Use.
 - Criteria for use include intolerance or failure to respond to oxybutynin IR OR tolterodine ER OR solifenacin

NOTE: Addition of generic tolterodine ER as General Benefit is considered based on price reduction to 25% of brand name costs. Availability of other medications (including tolterodine IR) as generic formulations priced at 25% of brand name costs should prompt re-evaluation of listing status, as these agents may become cost-effective alternatives.

Considerations for other recommendations

Recommendation 1: No listing is recommended for oxybutynin extended release (Ditropan XL).

Recommendation 2: For patients unable to swallow, recommend availability of oxybutynin gel (Gelnique) under Exceptional Access Program (but not oxybutynin transdermal [Oxytrol]).

Recommendation 3: It is recommended that a Therapeutic Note should be applied to all anticholinergics (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium) used for OAB, cautioning about the use of anticholinergics in the elderly. The therapeutic note does not apply to mirabegron, a beta-3 adrenoceptor agonist.

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Appendix A: Health Equity Considerations for Medications used for Treatment of Overactive Bladder

Identify populations that may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.	Proposed OAB medication recommendations
Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)	No accessibility issues identified. Coverage of medications, including medications for OAB, for Aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.
Age-related groups (e.g., children, youth, seniors, etc.)	Elderly: No restrictions for OAB medications were identified.
Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)	No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage through ODB.
Ethno-racial communities (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)	No accessibility issues identified.
Francophone (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)	No accessibility issues identified.
Homeless (including marginally or under-housed, etc.)	Not eligible for ODB coverage.
Linguistic communities (e.g., uncomfortable using English or French, literacy affects communication, etc.)	No accessibility issues identified.
Low income (e.g., unemployed, underemployed, etc.)	No accessibility issues identified; low income individuals who receive public drug coverage will have access to OAB medications through ODB.
Religious/faith communities	No accessibility issues identified.
Rural/remote or inner-urban populations (e.g., geographic or social isolation, under-served areas, etc.)	No accessibility issues identified.
Sex/gender (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)	No accessibility issues identified for sex/gender in the review.
Sexual orientation , (e.g., lesbian, gay, bisexual, etc.)	No accessibility issues identified.
Other: please describe the population here.	None identified.

(based on Health Equity Impact Assessment <http://www.health.gov.on.ca/en/pro/programs/hea>)

Appendix B: Assessment of Reimbursement Options

	Option A (status quo): Oxybutynin IR GB; LU for other drugs	Option B1: GB Oxybutynin IR, tolterodine ER AND solifenacin; LU for other drugs	Option B2: GB Oxybutynin IR, tolterodine ER OR solifenacin; LU for other drugs	Option C: Enforced use of oxybutynin IR, tolterodine ER AND solifenacin GB; LU for other drugs	Option D: Solifenacin GB; LU for other drugs
Efficacy	<ul style="list-style-type: none"> Most agents were superior to placebo for most outcomes. 				
Safety concerns	<ul style="list-style-type: none"> Oxybutynin associated with the greatest incidence of dry mouth (but not constipation); withdrawals due to adverse events more common with oxybutynin IR Dry mouth: all agents had significantly higher proportion of patients with dry mouth, except for transdermal oxybutynin, oxybutynin gel and mirabegron when compared to placebo. <p>Beers criteria (2015)¹ recommends that all anticholinergics be avoided in patients with dementia or cognitive impairment. No data is available for mirabegron in patients with dementia.²⁸</p>				
Accessibility	No change in number of patients currently receiving OAB medications	No change in number of patients currently receiving OAB medications	No change in number of patients currently receiving OAB medications	No change in number of patients currently receiving OAB medications	No change in number of patients currently receiving OAB medications; accessibility may be limited in patients currently using oxybutynin IR off-label (e.g., hyperhidrosis, enuresis)
Budget Impact (2018 annual expenditures estimated \$36.4 million)	No change	↑1% (increase \$356,000) (based on enforced listing for solifenacin and oxybutynin IR only)	BIA not available	↓30% (savings of \$11 million) to ↑14% (increase \$5.1 million) (based on enforced listing for solifenacin and oxybutynin IR only)	↑2% (increase \$680,000)
Alignment with other jurisdictions	Quebec (Exceptional Medication with codes in Quebec)	None (Except for Yukon Territory, no jurisdiction currently lists solifenacin or tolterodine as GB)	None (Except for Yukon territory, no jurisdiction currently lists solifenacin or tolterodine as GB)	None (no jurisdiction currently lists solifenacin or tolterodine as GB)	None (no jurisdiction currently lists solifenacin as GB)
Feasibility concerns	No concerns identified	No concerns identified	No concerns identified	May be difficult to implement based on current ODB pharmacy computer system	No concerns identified
Prescribing Criteria	LU criteria for use include intolerance or failure to respond to oxybutynin IR	LU criteria for use include intolerance or failure to respond to oxybutynin IR, tolterodine ER AND solifenacin	LU criteria for use include intolerance or failure to respond to oxybutynin IR OR solifenacin or tolterodine ER	Enforced LU criteria used for use include intolerance or failure to respond to oxybutynin IR, tolterodine AND solifenacin	LU criteria for use include intolerance or failure to respond to solifenacin
Indication creep	Oxybutynin has been used for other indications such as hyperhidrosis and enuresis (based on its anticholinergic profile) Other anticholinergic agents have been used for management of benign prostatic hyperplasia				NOTE: with this option, oxybutynin IR would be available as LU for other approved indications (i.e., neurogenic bladder)

GB: General benefit; LU: Limited Use; IR: immediate release; ER: extended release

Appendix C: Proposed LU Criteria for Drugs for Overactive Bladder

Drugs included

- Darifenacin (Enablex)
- Fesoterodine (Toviaz)
- Trospium (Trosec)
- Mirabegron (Myrbetriq)
- Tolterodine IR (Detrol and generics)

Criteria for Coverage

1. Patient with overactive bladder and symptoms of urinary frequency, urgency or urge incontinence
AND
2. Patient has failed to respond to behavioural techniques
AND
3. Patient has not responded or has experienced unacceptable side effects following a 4-week trial of oxybutynin immediate release **OR** a 4-week trial of solifenacin **OR** a 4-week trial of tolterodine extended release, or has contraindications to the use of oxybutynin immediate release, solifenacin and tolterodine ER

LU Authorization Period

Indefinite

Therapeutic Notes (to be included with ALL anticholinergic OAB agents available on the ODB formulary):

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.

Explanation of Limited Use Criteria

Current criteria	Proposed criteria	Rationale
Patient with urinary frequency, urgency or urge incontinence	Patient with overactive bladder and symptoms of urinary frequency, urgency or urge incontinence	<ul style="list-style-type: none"> Includes patients with overactive bladder who are symptomatic
Failed to respond to behavioural techniques	Failed to respond to behavioural techniques (no change)	<ul style="list-style-type: none"> Guidelines on management of OAB emphasize the role of non-pharmacologic therapy (e.g., lifestyle modifications, bladder retraining) prior to the use of pharmacologic therapy
<p>An adequate trial of oxybutynin with gradual dose escalation has shown to be either ineffective or resulted in unacceptable side effects</p> <p>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.</p>	Patient has not responded or has experienced unacceptable side effects following a 4-week trial of oxybutynin immediate release OR a 4-week trial of solifenacin or a 4-week trial of tolterodine ER, or has contraindications to the use of oxybutynin immediate release, tolterodine and solifenacin	<ul style="list-style-type: none"> Solifenacin is cost-effective and oxybutynin IR may be cost-effective in patients who have failed on solifenacin. Tolterodine ER priced at 25% brand name price (i.e., generic pricing) may be cost-effective at \$26,000 per QALY gained compared to solifenacin. NICE guidance (Urinary incontinence in women, 2013) suggests that full benefits of treatment may not be apparent until 4 weeks of treatment
LU Authorization Period: indefinite	LU Authorization Period: indefinite (no change)	<ul style="list-style-type: none"> No change proposed for LU authorization period.