

# Treatments for Overactive Bladder

## FINAL PHARMACOEPIDEMIOLOGY REPORT

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**Study Team: Mina Tadrous, Wayne Khuu, Dean Elterman, Samantha Singh, Kimberly Fernandes, Diana Martins, David Juurlink, Mike Paterson, Muhammad Mamdani, Tara Gomes**

## Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada. Tara Gomes, Muhammad Mamdani, and David Juurlink have received grant funding from the Ministry of Health and Long-term Care. 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 Treatments for Overactive Bladder (OAB) Drug Class Review.

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## Study Team

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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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website ([www.odprn.ca](http://www.odprn.ca)).

## Contents

Executive Summary.....	5
Introduction .....	8
IMS Geographic Prescription Monitor (GPM <sup>12</sup> ) .....	8
Canadian Institute for Health Information NPDUIS .....	8
Administrative Databases in Ontario .....	9
Ontario Drug Benefit Database .....	9
Other Health Administrative Databases .....	9
Methods .....	9
National and Provincial Trends in OAB Medication Use .....	9
Cross-Provincial Comparisons of Publicly-Funded OAB Medication Use .....	10
Characteristics of Provincially-Funded OAB Medication Users in Ontario in Fiscal Years 2012-2013 .....	10
Patterns of OAB Medication Use among Adult New Users in Ontario.....	10
Exhibits and Findings .....	11
National Trends in Use of OAB Medications .....	11
Exhibit 1: Total Number of Prescriptions for OAB Medications Dispensed to All Individuals in Canada, by Payer and Quarter .....	11
Exhibit 2: Total Number of Prescriptions for OAB Medications Dispensed to All Individuals in Canada, by Drug and Quarter.....	12
Exhibit 3: Total Number of Prescriptions for OAB Medications Dispensed to All Individuals in Canada in 2014, by Drug and Payer.....	13
Cross Provincial Trends in Use of OAB Medications among Adults.....	14
Exhibit 6: Proportion of Spending for OAB Medications Dispensed in Canada, by Province and Payer in 2014 .....	18
Exhibit 7: Prescriptions for Publicly Funded OAB Medications Dispensed in Canada, by Province and Drug in 2014.....	19
Exhibit 8: Prescriptions for Non-publicly Funded OAB Medications Dispensed in Canada, by Province and Drug in 2014.....	19
Cross Provincial OAB Medication Use among Public Drug Plan Beneficiaries .....	21
Exhibit 9: Population-Adjusted Rate of Provincially-funded OAB Medication Users in Canada overtime, by Province.....	21
Trends in Use of OAB Medications among Adults in Ontario .....	24
Exhibit 11: Total Number of Prescriptions and Cost for OAB Medications Dispensed in Ontario, by Payer and Quarter .....	24
Exhibit 12: Total Number of Prescriptions and Cost for OAB Medications Dispensed in Ontario by All Payers, by Drug and Quarter .....	25

Characteristics of Provincially-Funded OAB Medication Users in Ontario in Fiscal Year 2012-2013 .....	28
Exhibit 13a: Characteristics of Provincially-Funded OAB Medications Users in Ontario in Fiscal Year 2012-2013, by Drug .....	28
Exhibit 13b: Characteristics of Provincially-Funded OAB Medications Users in Ontario in Fiscal Year 2012 and 2013, by Drug (Continued) .....	29
Exhibit 14a: Characteristics of Newly Initiated Provincially-Funded OAB Medications Users in Ontario in Fiscal Years 2012-2013, by Drug Initiated.....	31
Exhibit 14b: Characteristics of Newly Initiated Provincially-Funded OAB Medications Users in Ontario in Fiscal Years 2012-2014, by Drug Initiated (Continued) .....	32
Patterns of OAB Medication Use among Adult New Users in Ontario.....	34
Exhibit 15: Patterns of Provincially-Funded OAB Medications Use among Adult Continuous Users Aged 66 and Older .....	34
Exhibit 17: Patterns of Provincially-Funded OAB Medications Use among Adult Continuous Users Aged 66 and Older from 2011 to 2013, by Drug Initiated .....	36
Health Equity .....	37
Limitations.....	37
Generalizability.....	37
Adherence.....	37
Overall Conclusion.....	38
Reference List.....	39
Review of the Observational Literature .....	40
Objectives .....	40
Methods .....	40
Search Strategy.....	40
Inclusion criteria: .....	40
Results .....	40
Conclusions.....	41
Literature Review References .....	42
Appendix A: Public Plan Listings for OAB Medications in Canada, by Province.....	43
Appendix B: Medline Search Strategy .....	44
Appendix C: Summary of Included Studies.....	45

## Executive Summary

### National and Provincial Trends in Overactive Bladder (OAB) Medication Use

Quarterly dispensing of prescriptions for overactive bladder (OAB) medications in Canada have 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. 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. 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 the total market share of OAB medications dispensed. This reduction is likely due to expanded reimbursement of other available agents (i.e. tolterodine and solifenacin) and the introduction of new treatments (i.e. darifenacin, fesoterodine, and mirabegron).

Ontario had the second highest rate of publicly-funded OAB medication prescriptions in Canada, which increased from 10 prescriptions per 1,000 population in Q4 2009 to 14 prescriptions per 1,000 population in Q4 2014. In contrast, Ontario was found to have the lowest rate of non-publicly funded prescriptions (5 prescriptions per 1,000 population in Q4 2014) in Canada. This dissimilarity between public and non-public use is likely due to the Ontario Public Drug Program (OPDP) having one of the most liberal listing for this drug class. Only in Ontario (62.5%) and Quebec (66.9%), which have the most liberal listing for OAB medications, are the majority of OAB medication covered by provincial drug plans. In comparison, in all other provinces, less than 50% of OAB medications are covered by public drug programs. In the majority of provinces, for both public and non-public payers, oxybutynin was the most commonly dispensed OAB medication in 2014. Ontario was the only province where oxybutynin (20.0%; N=147,589 prescriptions) use was surpassed by tolterodine prescribed (39.4%; N=290,763 prescriptions) in 2014. In contrast, in British Columbia, almost all prescriptions reimbursed by provincial payers were for oxybutynin (92.6%; N=57,113 prescriptions) due to the province's highly restrictive access to other OAB medications on the formulary and the implementation of step-based reimbursement requirements.

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), 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 but oxybutynin (974 users per 1,000 eligible). In contrast, Ontario had the second highest cost per user (\$400-450) among provinces examined.

## Use of OAB Medications 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.

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.

## Characteristics and Pattern of Use of Publicly-Funded OAB Medication Users within Ontario

In fiscal years 2012-2014, there were 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=23,675), darifenacin (4%; N=4,613), fesoterodine (2.7%; N=3,071), 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.

Approximately half of all users were new users of OAB medications over this time period (48%; N=54,739). In the year prior to treatment initiation, approximately one-fifth of users (18.9%; N=21,589) were hospitalized for any reason, 2.2% (N=2,459) were hospitalized for a fall or fracture, and 3.1% (N=3,545) were hospitalized for a urinary tract infection or vulvovaginitis. In the 3 months prior to OAB medication initiation 42.8% of users (N=48,732) also used a psychotropic drug, 13.1% (N=14,902) used alpha-blockers, and 6.0% (N=6,821) used 5-alpha reductase drugs. Approximately half of users that initiated darifenacin (49.1%; N=2,263), fesoterodine (64.1%; N=1,970), solifenacin (49.5%; N=11,729), trospium (63.5%; N=418), or dual therapy (46.2%; N=78) visited a urologist in the past 6 months compared to only 23.9% of tolterodine users (N= 11,841) and 14.0% of oxybutynin users (N=4,543). Only a small proportion of users (10.8% to 20.3%) in Q3-2015 had any previous oxybutynin use.

In fiscal years 2012-2014, we identified 43,183 users ages 66+ who newly initiated an OAB medication in Ontario. The average age at time of initiation was 77 years. Most new users 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). Less than half of patients (46.2%; N=19,963) received only one prescription in a 180 day period. A high proportion of new users of oxybutynin had only one prescription over the period of continuous use (59.6%, N=5,963).

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, 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).

### **Overall Conclusion**

Use of OAB medication continues to grow both nationally and in Ontario. Ontario was found to have some of the highest rates of publicly-funded OAB medication use in Canada, which is likely due to having the most open criteria for reimbursement for the drug class. With the introduction of newer brand name agents in the last few years we found a large shift in utilization trends away from oxybutynin and tolterodine and towards solifenacin and mirabegron. Early evidence suggests that the addition of mirabegron may further change current utilization trends; continued monitoring of utilization trends is needed. With a growing elderly population, extended life-expectancy, and the addition of newer brand-name medication we expect this trend to continue in the future and anticipate continued growth in cost and use of this drug class.

## Introduction

In Canada, there are currently seven medications (darifenacin, fesoterodine, mirabegron, solifenacin, oxybutynin, tolterodine, and trospium) that are used in the treatment overactive bladder (OAB). These medications are available in a variety of formulations (oral, transdermal, and gel). Four of these treatments (darifenacin, fesoterodine, mirabegron, solifenacin) were approved by Health Canada in the last 10 years. Additionally, these medications differ in their public plan listings on provincial formularies across Canada. Detailed information on public plan listings is provided in **Appendix A**.

The objectives of this report are to:

1. To present national and provincial utilization trends in use of treatments for OAB among adults in Canada, by drug dispensed and by payer (public drug programs, private insurers, cash payment and Non-Insured Health Benefits).
2. To present cross provincial comparisons of the trends in use of OAB medications among adults in public drug programs across Canada using population-adjusted rates of use.
3. To examine trends in use of medications used to treat OAB among adults funded through the OPDP.
4. To describe characteristics of adult patients prescribed provincially-funded medications for OAB in Ontario.
5. To describe the course and length of OAB medication therapy among newly initiated users in Ontario.
6. To summarize observational studies that investigated and evaluated adherence and safety of OAB medications.

### IMS Geographic Prescription Monitor (GPM<sup>12</sup>)

IMS Geographic Prescription Monitor (GPM<sup>12</sup>) is a premium source of sales intelligence on retail prescription activity in Canada. Data is obtained from a representative sample of 65% of all Canadian pharmacies and is projected monthly by province or customized geography. Projections incorporate the number of pharmacies in a given area, the distance between IMS-captured and uncaptured pharmacies, and the size of the pharmacies. Projections are representative of provincial and national sales volumes. Data available through IMS Geographic Prescription Monitor (GPM<sup>12</sup>) includes prescription volumes dispensed, and are stratified by payer type (e.g. public drug plan, private drug plan, cash, Non-Insured Health Benefits). Data from IMS Geographic Prescription Monitor (GPM<sup>12</sup>) is available from the fourth quarter of 2009 to the first quarter of 2015.

### Canadian Institute for Health Information NPDUIS

The National Prescription Drug Utilization Information System (NPDUIS) was developed by the Canadian Institute for Health Information (CIHI) to provide pan-Canadian information on

public drug programs. NPDUIS data can be used to obtain estimates of populations eligible for provincial drug coverage in Alberta, British Columbia (BC), Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Newfoundland and Labrador and Prince Edward Island (PEI). Data from NPDUIS is available from calendar year 2000 to 2014. Data is only available as of 2002 for Nova Scotia, 2005 for PEI, 2006 for BC and 2009 for Newfoundland and Labrador.

## Administrative Databases in Ontario

These datasets were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

### Ontario Drug Benefit Database

The Ontario Drug Benefit (ODB) database contains individual-level claims data for all prescription drugs dispensed to Ontario residents eligible for public drug funding. Eligibility criteria include unemployment, disability, high prescription drug costs relative to net household income, receipt of home care services, residence in a long-term care facility, or age 65 years or older. This database is of high quality, with an error rate of <1% and can be linked to other health administrative databases to obtain patient demographic information<sup>1</sup>. We analyzed data from the ODB between January 2000 and June 2015.

### Other Health Administrative Databases

We used data from the Ontario Registered Persons Database (RPDB), Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and National Ambulatory Care Reporting System (CIHI-NACRS), Ontario Health Insurance Plan (OHIP) and the ICES Physician Database (IPDB) to obtain patient vital statistics, describe health care use, and other patient comorbidities and characteristics.

## Methods

All analyses were approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

### National and Provincial Trends in OAB Medication Use

We used data from IMS Geographic Prescription Monitor (GPM<sup>12</sup>) to examine overall trends in the prescribing volumes of medications used to treat OAB among all individuals, at both national and provincial levels. We examined the number of prescriptions dispensed for OAB medications between October 1 2009 and December 31 2014. Analyses were stratified by drug and province, by coverage (private, public, cash, Non-Insured Health Benefits) and by OAB medication. Publicly funded prescriptions were those paid for through public drug programs; non-publicly funded prescriptions were those paid for through private insurance plans, cash payments, or Non-Insured Health Benefits. All cross-provincial analyses compared population-adjusted rates.

### Population Adjustment

Provincial population estimates were obtained from Statistics Canada for each quarter from

2009 to 2014 and used to standardize overall utilization rates (per 1,000 population) of OAB medications dispensed across the provinces. Because all individuals (both those eligible for public drug programs and non-beneficiaries) might pay for OAB medications out of pocket, measures of non-provincially funded use were adjusted using overall provincial population estimates from Statistics Canada.

## **Cross-Provincial Comparisons of Publicly-Funded OAB Medication Use**

We used claims data from NPDUIS and ODB to examine trends in the number and rate of provincially funded users of OAB medications at the provincial level between January 2000 and December 2014. We examined the number and rate of users in 2014. Analyses were stratified by province, drug, and age (<65 and 65+). Provincially funded prescriptions were those paid for through public drug programs. All cross-provincial analyses compared population-adjusted rates (per 1,000 active beneficiaries), using the number of active drug beneficiaries in each provincial drug program. Data was not available for Quebec or the territories.

## **Characteristics of Provincially-Funded OAB Medication Users in Ontario in Fiscal Years 2012-2013**

We used claims data from ODB to perform additional analyses of use of OAB medications among users in Ontario, stratifying by drug, between April 2012 and March 2014. These analyses examined demographic and clinical characteristics of users who were prescribed an OAB medication in Ontario.

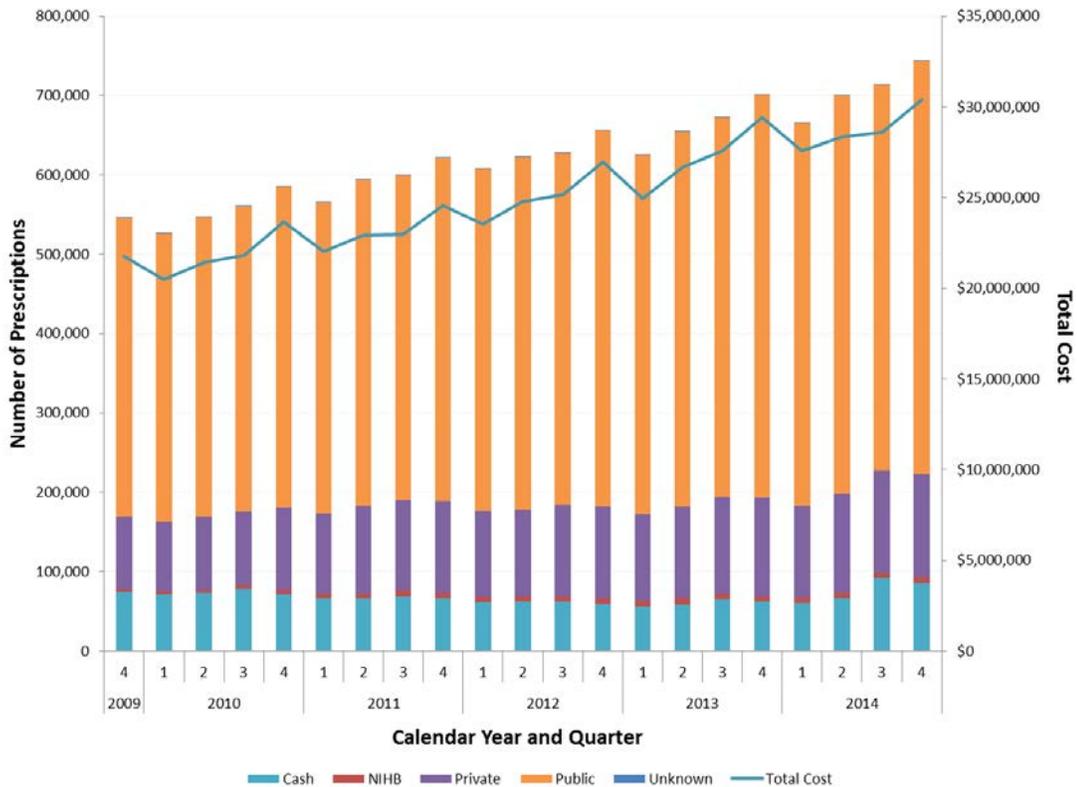
## **Patterns of OAB Medication Use among Adult New Users in Ontario**

We established a cohort of adults, aged 66 and older, who were new users of OAB medications between April 1, 2012 and March 31, 2014 to examine the duration of therapy OAB medication users in Ontario. A new user aged 66 and older was defined as having no prescription for an OAB medication in the past year (since all of these individuals are eligible for ODB). We followed each individual forward from the time of their first prescription until they discontinued any OAB medication, died, had 2 years of follow-up, or reached the end of the study period (March 31, 2015). Discontinuation was defined on the basis of no subsequent prescription for an OAB medication within 180 days of the previous prescription, which is consistent with previously published studies.<sup>2-4</sup> Discontinuation date was defined as date of last prescription plus the day supply of the last prescription. We determined discontinuation of any OAB drug for the cohort and we conducted an analysis of discontinuation of initial OAB drug stratified by the OAB drug initiated.

# Exhibits and Findings

## National Trends in Use of OAB Medications

**Exhibit 1: Total Number of Prescriptions for OAB Medications Dispensed to All Individuals in Canada, by Payer and Quarter**



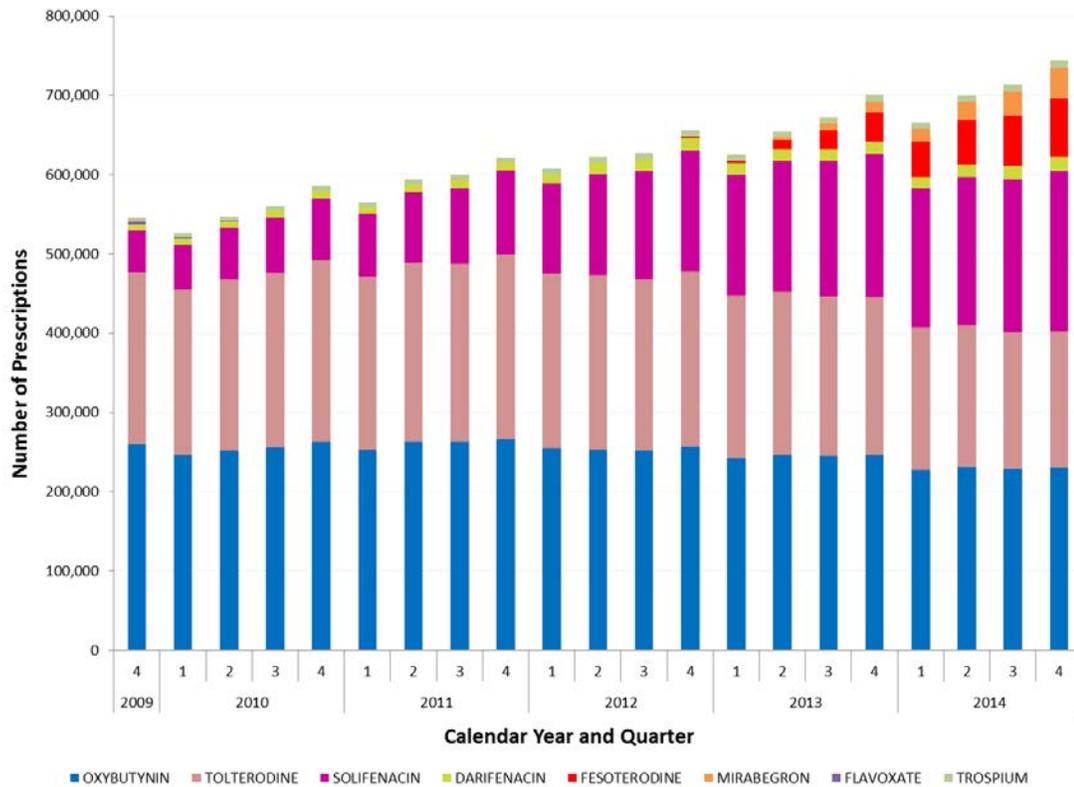
Data Source: IMS GPM<sup>12</sup>

The number of prescriptions dispensed for OAB medications in Canada increased by 36% over the study period. This rising use is associated with an increase of 40% in spending on these products nationally.

### Summary of Findings for Exhibit 1

1. The number of prescriptions dispensed for OAB medications in Canada has increased 36.2% over the past 5 years, from 545,985 prescriptions dispensed in Q4 2009 to 743,653 prescriptions dispensed in Q4 2014.
2. Costs for OAB medications have similarly increased 39.8% between Q4 2009 (\$21.4 million) and Q4 2014 (\$30.4 million).
3. Overall, public (not including NIHB) payers accounted for the majority of all OAB medication prescriptions in Canada (376,122 (68.9%) in Q4 2009 and 519,807 (69.9%) prescriptions in Q4 2014). Private payer and cash payments accounted for the majority of the remainder:
  - a. Private payer: 91,669 (16.8%) prescriptions in Q4 2009 and 130,578 (17.6%) prescriptions in Q4 2014
  - b. Cash: 74,314 prescriptions (13.6%) in Q4 2009 and 86,097 (11.6%) prescriptions in Q2

## Exhibit 2: Total Number of Prescriptions for OAB Medications Dispensed to All Individuals in Canada, by Drug and Quarter



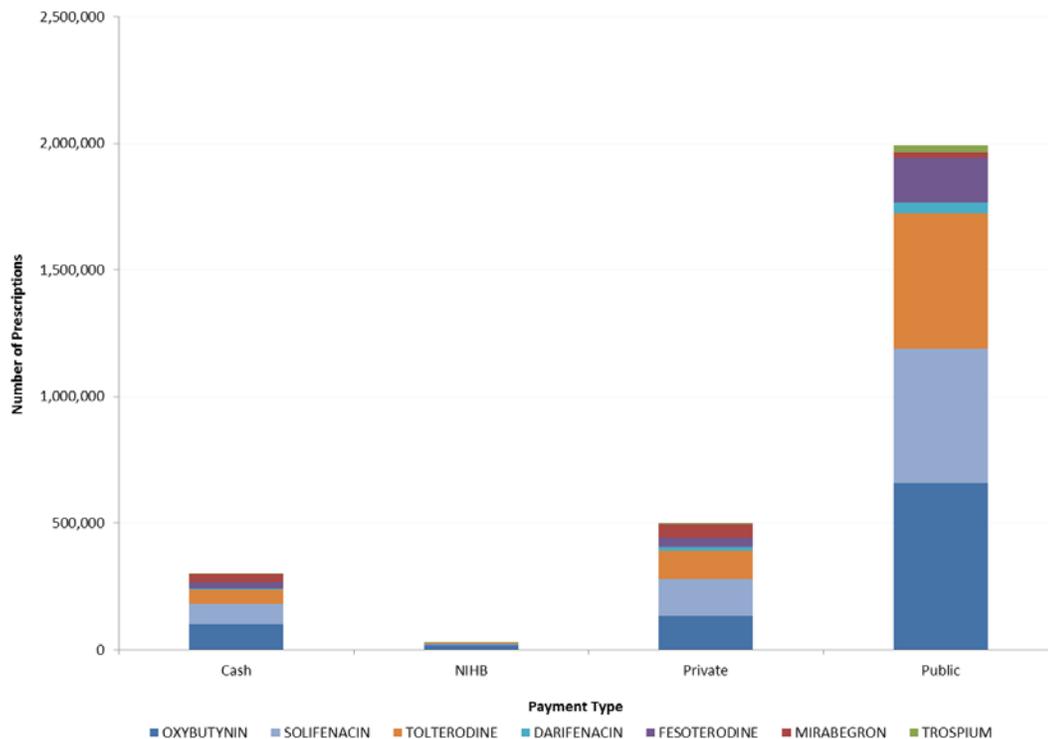
Data Source: IMS GPM<sup>12</sup>

Oxybutynin was the most commonly dispensed OAB medication in Canada; however its market share has dropped from 48% in Q4 2009 to 31% in Q4 2014.

### Summary of Findings for Exhibit 2

- Oxybutynin was the most commonly dispensed OAB medication from Q4 2009 (47.5%; N=260,091 prescriptions) to Q4 2014 (31.0%; N=230,340 prescriptions) in Canada despite a drop in its total market share over the study period.
- In Q4 2009 tolterodine (39.6%; N=216,401 prescriptions) was the second most commonly dispensed OAB medication but by Q4 2014 tolterodine (23.1%; N=171,697 prescriptions) dropped to the 3<sup>rd</sup> most commonly dispensed OAB medication.
- A rise in the use of newer OAB medications was found over the study period, including solifenacin (from 9.7%; N=53,066 prescriptions to 27.2 %; N=202,562 prescriptions), darifenacin (from 1.4%; N=7,700 prescriptions to 2.4%; N=17,943 prescriptions), and fesoterodine (from 0 prescriptions to 9.9%; N=73,298 prescriptions). Solifenacin was the 2<sup>nd</sup> most commonly dispensed OAB medication in Q4 2014 in Canada.
- Mirabegron, although only introduced to the Canadian market in Q2 2013, has seen a sharp rise in use in a short period of time (5.2%; N=230,340 prescriptions in Q4 2014).
- Trospium (0.9%; N=4,977 prescriptions to 1.2%; N=9,143 prescriptions) and flavoxate (0.7%; N=3,750 prescriptions to 0%; N=0 prescriptions) were found to have minimal use by the end of the observation period in Q4-2014.

### Exhibit 3: Total Number of Prescriptions for OAB Medications Dispensed to All Individuals in Canada in 2014, by Drug and Payer



Data Source: IMS GPM<sup>12</sup>

In 2014, oxybutynin was the most dispensed OAB medication across all payers except private payers where solifenacin was the most dispensed OAB agent.

#### Summary of Findings for Exhibit 3

1. In 2014, oxybutynin was the most commonly dispensed OAB medication among individuals paying for medications with cash (33.6%; N=102,274 prescriptions), through NIHB (71.9%; N=20,431 prescriptions), or through public drug plans (33.1%; N=527,185 prescriptions). Among private insurers, the most commonly dispensed OAB agent was solifenacin (29.3%; N=146,010 prescriptions).
2. Mirabegron was most common among cash (11.4%; N=34,798 prescriptions) and private payers (10.9%; N=54,415 prescriptions) and lowest among public provincial payers (2.7%; N=19,884 prescriptions) in 2014 across Canada. NIHB did not reimburse any mirabegron prescriptions in 2014.

## Cross Provincial Trends in Use of OAB Medications among Adults

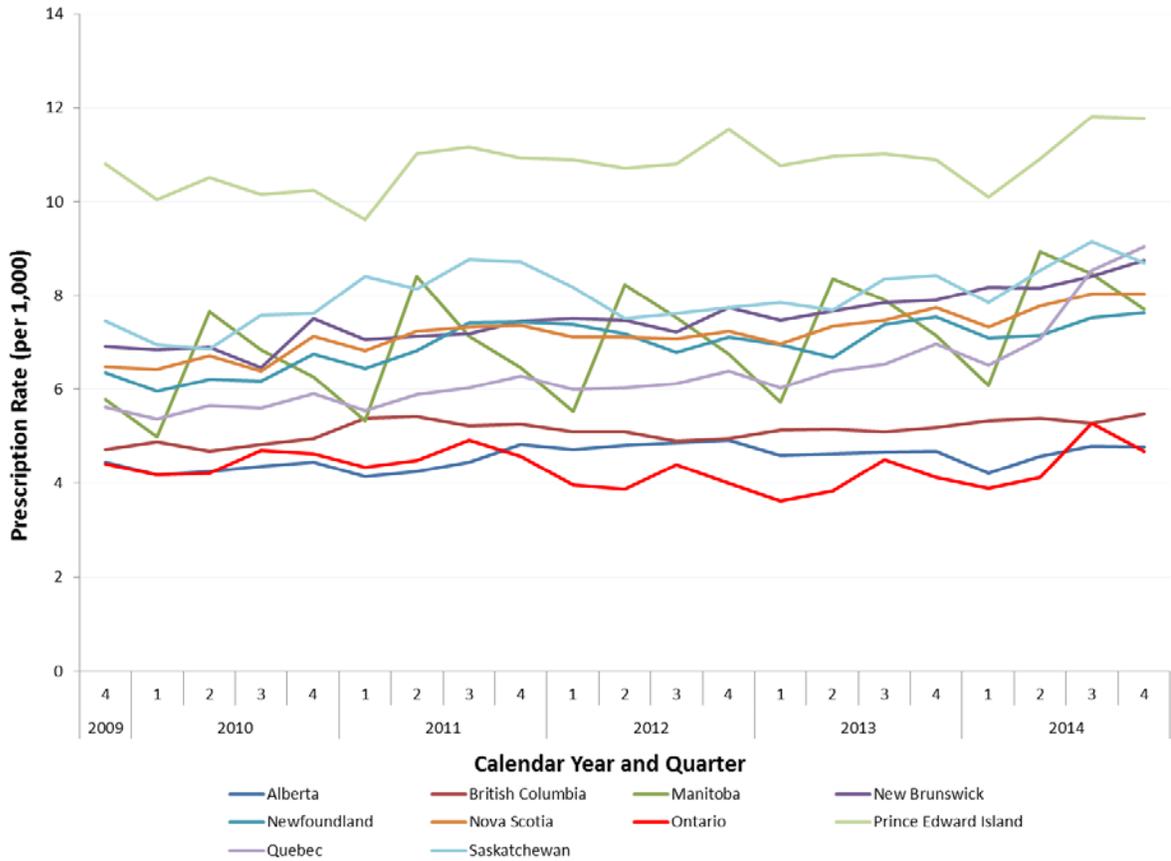
**Methodological Note:**

Non-publicly funded use represents use outside of provincial drug plans and are referred to as non-public. This includes prescriptions paid by:

- Private drug insurance
- Cash
- Non-Insured Health Benefits

Provincial plan listings for OAB medications vary across provinces by drug. More detailed information on provincial plan listings is provided in Appendix A.

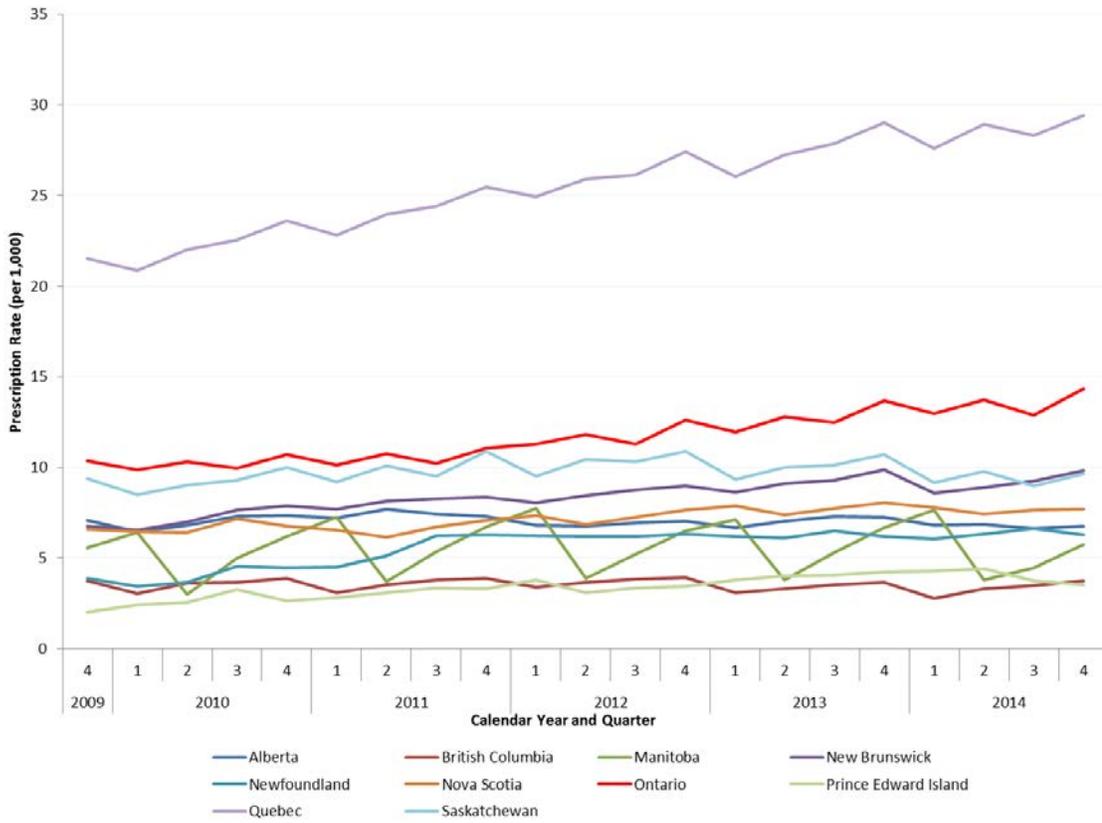
**Exhibit 4: Population-Adjusted Rate of Non-Publicly-Funded Prescriptions for OAB Medications Dispensed in Canada, by Province and Quarter**



Data Source: IMS GPM<sup>12</sup>

Ontario had the lowest rate of non-publicly funded OAB medication prescribing in Canada, with rates similar to Alberta and British Columbia

**Exhibit 5: Population-Adjusted Rate of Publicly Funded Prescriptions for OAB Medications Dispensed in Canada, by Province and Quarter**



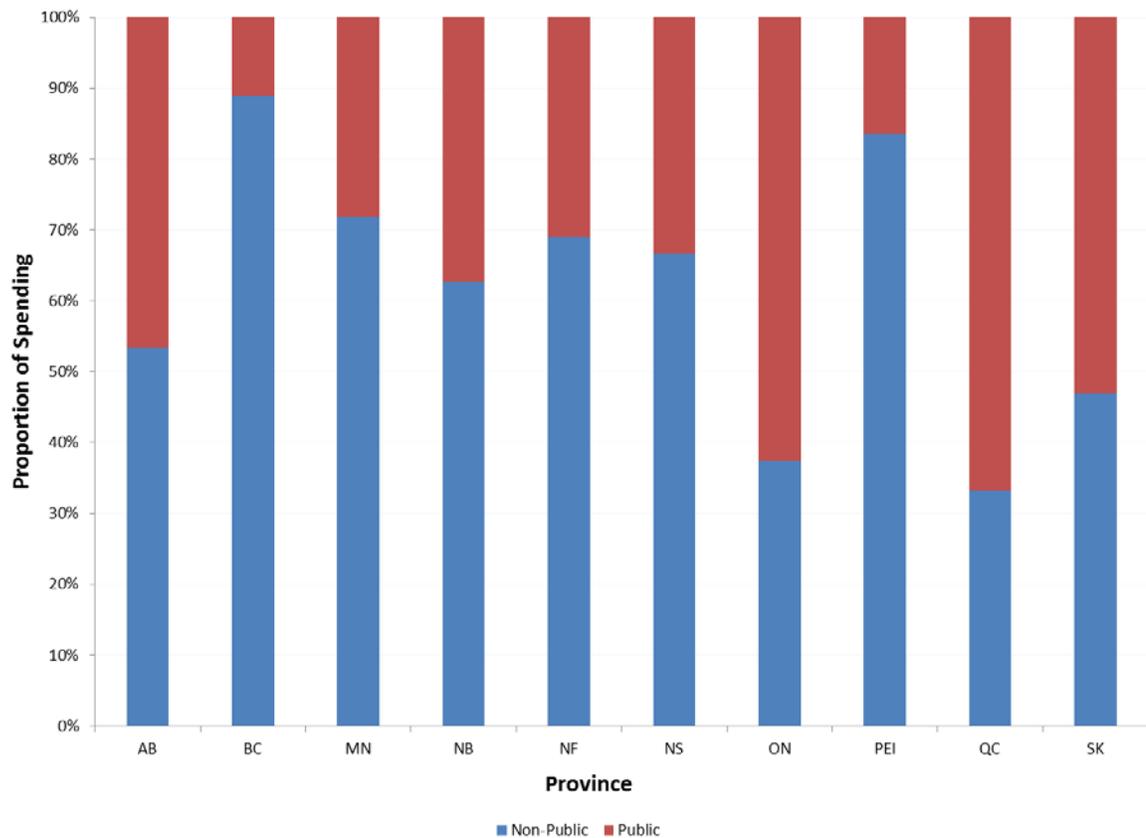
Data Source: IMS GPM<sup>12</sup>

Ontario had the second highest rate of publicly funded OAB medication prescribing in Canada behind Quebec.

**Summary of Findings for Exhibit 4 and Exhibit 5**

1. Ontario rates of non-publicly funded OAB medication use have remained relatively stable over time (4 prescriptions per 1,000 population in Q4 2009 to 5 prescriptions per 1,000 population in Q4 2014).
2. Ontario had the lowest rate of non-publicly funded OAB medication use (5 prescriptions per 1,000 population, national average of 7 prescriptions per 1,000 population in Q4 2014) in Canada. Both British Columbia (5 prescriptions per 1,000 population in Q4 2014) and Alberta (5 prescriptions per 1,000 population in Q4 2014) had similarly low rates of non-publicly funded OAB use over the study period.
3. Ontario rates of publicly-funded OAB medication use have increased over time (10 prescriptions per 1,000 population in Q4 2009 to 14 prescriptions per 1,000 population in Q4 2014).
4. In Q4 2014, Ontario had the second highest rate of publicly-funded OAB medication use (14 prescriptions per 1,000 population, national average of 10 prescriptions per 1,000 population) relative to other provinces. Quebec had the highest rates of use (29 prescriptions per 1,000 population in Q4 2014). The remaining provinces exhibited lower rates of use (range in Q4 2014: 4 [British Columbia and Prince Edward Island (PEI)] to 10 [New Brunswick] prescriptions per 1,000 population).

### Exhibit 6: Proportion of Spending for OAB Medications Dispensed in Canada, by Province and Payer in 2014



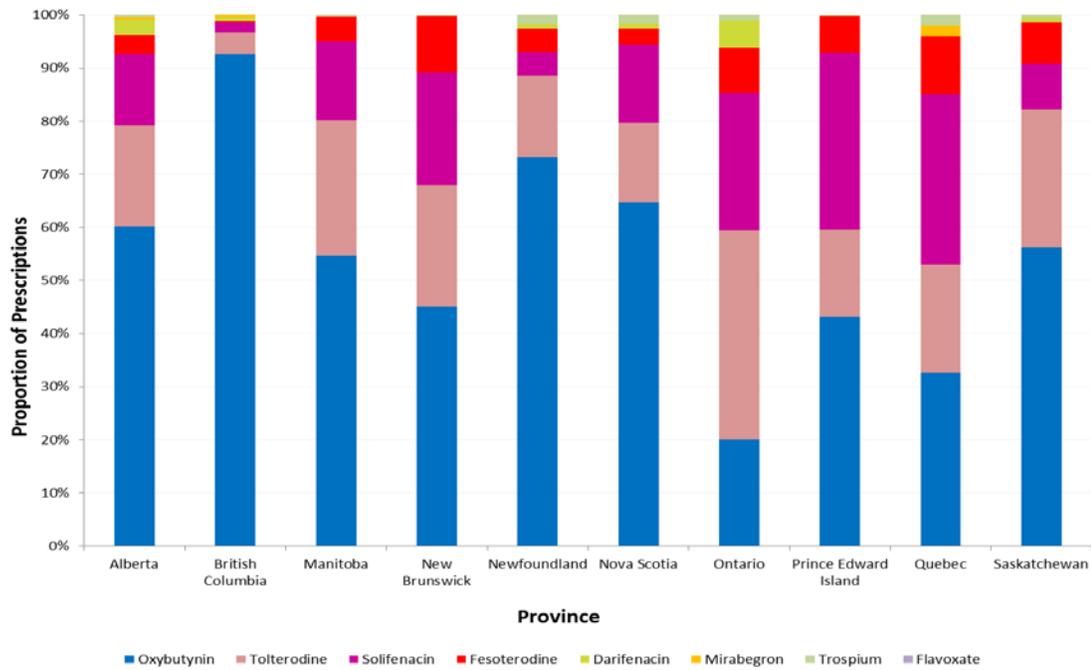
Data Source: IMS GPM<sup>12</sup>

The majority of OAB medication costs in Canada (55%) are paid for by provincial drug plans, however this differs considerably by province.

#### Summary of Findings for Exhibit 6

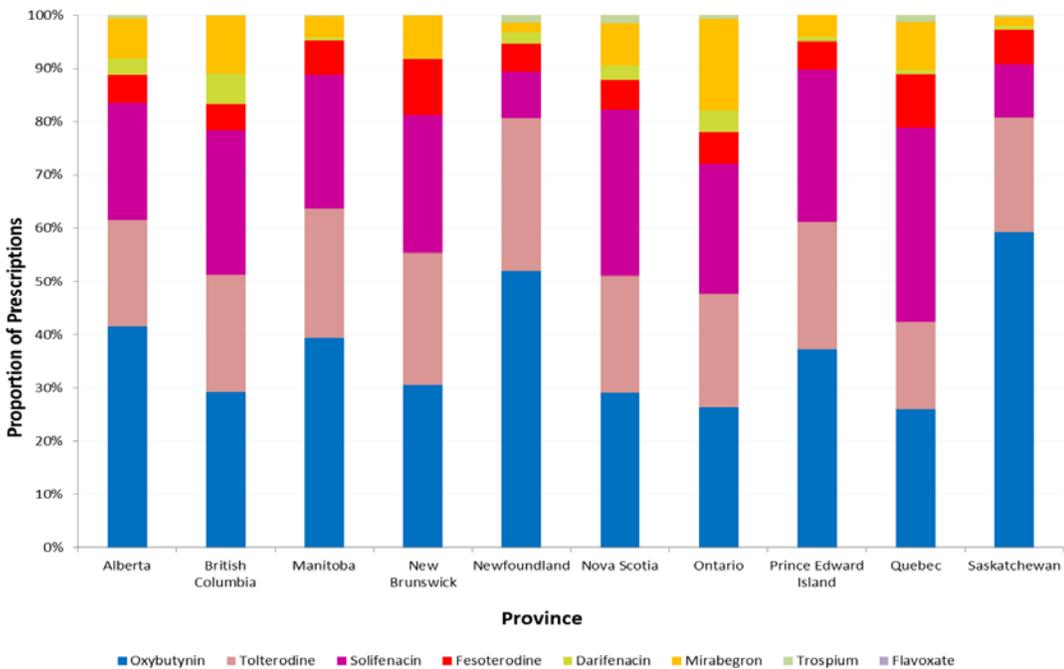
1. In 2014, a total of \$115 million was spent nationally on all OAB medications. Close to half of these costs (55.2%; \$63.5 million) are paid for by public drug coverage (data not shown).
2. In Ontario, a total of \$50.7 million was spent on all OAB medications. The majority of these costs (62.5%; \$31.7 million) were paid by the public drug plan, which may reflect the unrestricted listing of these medications on the formulary.
3. Only in Ontario (62.5%) and Quebec (66.9%), where access to OAB medications is more liberal, were the majority of OAB medication costs paid for by public drug plans.
4. Conversely, provinces such as British Columbia (88.8%; \$7.0 million) and PEI (83.6%; \$0.5 million) that have more restrictive access to these medications on public formularies have a larger proportion of costs paid through non-publicly funded payers.

**Exhibit 7: Prescriptions for Publicly Funded OAB Medications Dispensed in Canada, by Province and Drug in 2014**



Data Source: IMS GPM<sup>12</sup>

**Exhibit 8: Prescriptions for Non-publicly Funded OAB Medications Dispensed in Canada, by Province and Drug in 2014**



Data Source: IMS GPM<sup>12</sup>

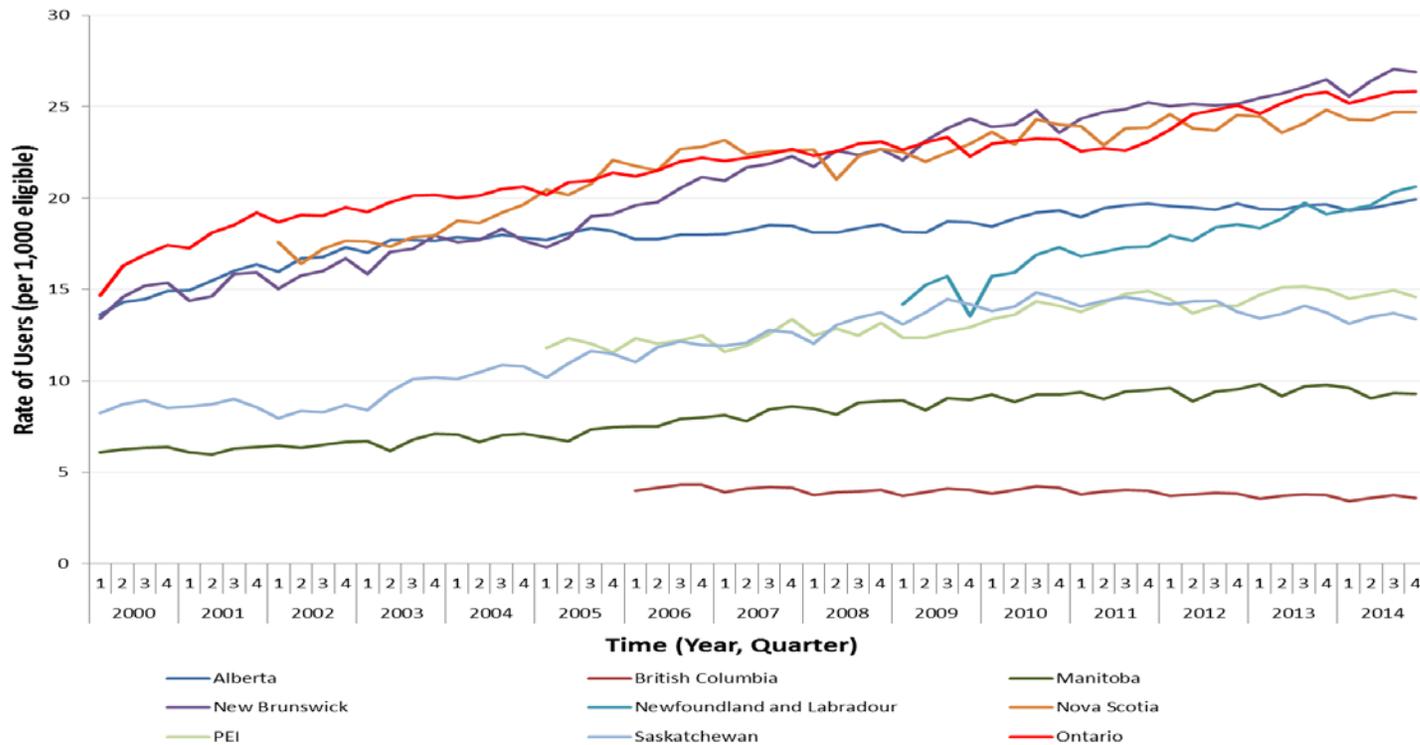
In the majority of provinces, regardless of payer, oxybutynin was the most commonly dispensed OAB medication. Ontario was an exception as tolterodine was the most commonly dispensed OAB medication prescription for public payers.

#### **Summary of Findings for Exhibit 7 and Exhibit 8**

1. In the majority of provinces, for both public and non-public payers, oxybutynin was the most commonly dispensed OAB medication in 2014. Ontario was the only province where oxybutynin (20.0%; 147,589 prescriptions) was not the most commonly dispensed OAB medication by public payers. Instead, in Ontario, tolterodine (39.4%; 290,763 prescriptions) was the most common publicly funded OAB medication.
2. British Columbia had the highest rate of oxybutynin (92.6%; 57,113 prescriptions) prescriptions by public payers due to its highly restrictive access to other OAB medications and the implementation of a step-based reimbursement structure.
3. Tolterodine (4 provinces) and Solifenacin (3 provinces) were most often the second most commonly dispensed agents across provinces for public payers. For non-provincial payers solifenacin was the second most commonly dispensed agent in 6 provinces.

## Cross Provincial OAB Medication Use among Public Drug Plan Beneficiaries

Exhibit 9: Population-Adjusted Rate of Provincially-funded OAB Medication Users in Canada overtime, by Province



Data Source: CIHI NPDUIS and ICES

All provinces studied, with the exception of British Columbia, have seen an increase in the rate of use of publicly-funded OAB medications between 2000 and 2014.

**Exhibit 10: Population-Adjusted Rate of Provincially-funded OAB Medication Users in Canada in 2014, by Province and by Drug**

Province	Total Number of Users	Total Number of Users <65	Total Number of users 65+	Rate of Users by Drug†					
				Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium
<b>Alberta</b>	13,604	1,657	11,947	43	79	518	235	234	9
<b>British Columbia</b>	11,185	4,777	6,408	3	2	974	14	14	*
<b>Manitoba</b>	7,657	3,355	4,302	1	62	617	194	190	3
<b>Saskatchewan</b>	9,374	3,841	5,533	9	87	744	83	178	7
<b>New Brunswick</b>	3,691	1,002	2,689	*	128	514	226	236	3
<b>Newfoundland and Labrador</b>	2,642	1,053	1,589	10	49	815	60	157	13
<b>Nova Scotia</b>	4,490	459	4,031	12	41	695	173	146	15
<b>PEI</b>	601	95	506	0	52	789	136	67	*
<b>Ontario</b>	90,942	17,650	73,292	61	119	244	301	366	10

†per 1,000 eligible

\*In accordance with the CIHI privacy policy, cases where the number of active beneficiaries (\*) is less than 5 (but greater than 0) have been suppressed to ensure confidentiality. Note: These results exclude Quebec and the territories . Data Source: CIHI NPDUIS and ICES

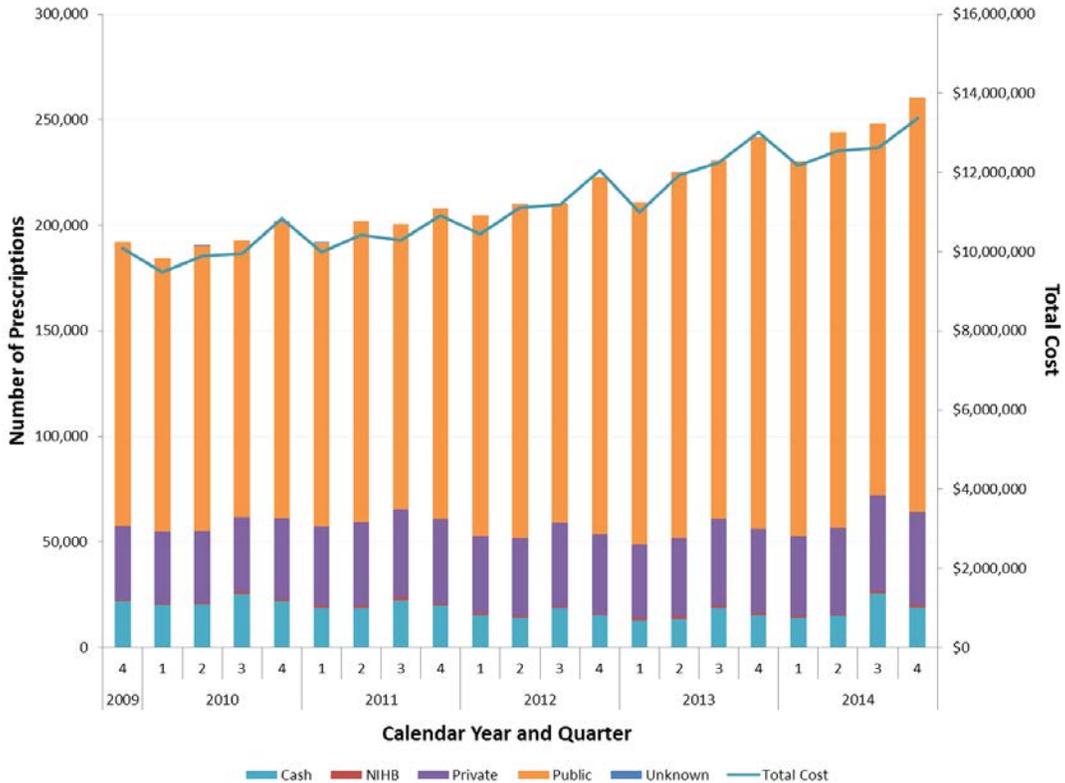
Ontario had the highest number of OAB users and overall costs for OAB medications compared to other studied provinces.

**Summary of Findings for Exhibit 9 and Exhibit 10**

1. The rate of OAB medication use 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).
2. New Brunswick (NB) and Ontario exhibited the highest rates of OAB medication use, with the rates increasing 93% (from 14 to 27 users per 1,000 beneficiaries) and 76% (from 15 to 26 users per 1,000 beneficiaries) over the 14 year period for New Brunswick and Ontario, respectively.
3. The rate of publicly-funded use is lowest in British Columbia, where a majority of OAB medications are unavailable on the provincial drug plan.
4. Oxybutynin was the most commonly used publicly-funded OAB medication among all studied provinces (with the exception of Ontario), which may be due to the general listing status of the generic formulation in all provinces.
5. The majority (80.1%) of publicly-funded OAB medication users in Ontario were 65 years of age and older.
6. In Ontario, tolterodine had the highest rate of provincially-funded use (366 users per 1,000 eligible), followed by solifenacin (301 users per 1,000 eligible), oxybutynin (244 users per 1,000 eligible) fesoterodine (119 users per 1,000 eligible), darifenacin (61 users per 1,000 eligible) and trospium (10 users per 1,000 eligible).
7. British Columbia had the lowest average provincially funded cost per user (\$100-150) due to its strict listing (Data not shown). Listing in British Columbia highly restricts access to all agents but oxybutynin (974 users per 1,000 eligible). In contrast, Ontario had the second highest cost per user (\$400-450) among provinces examined.

## Trends in Use of OAB Medications among Adults in Ontario

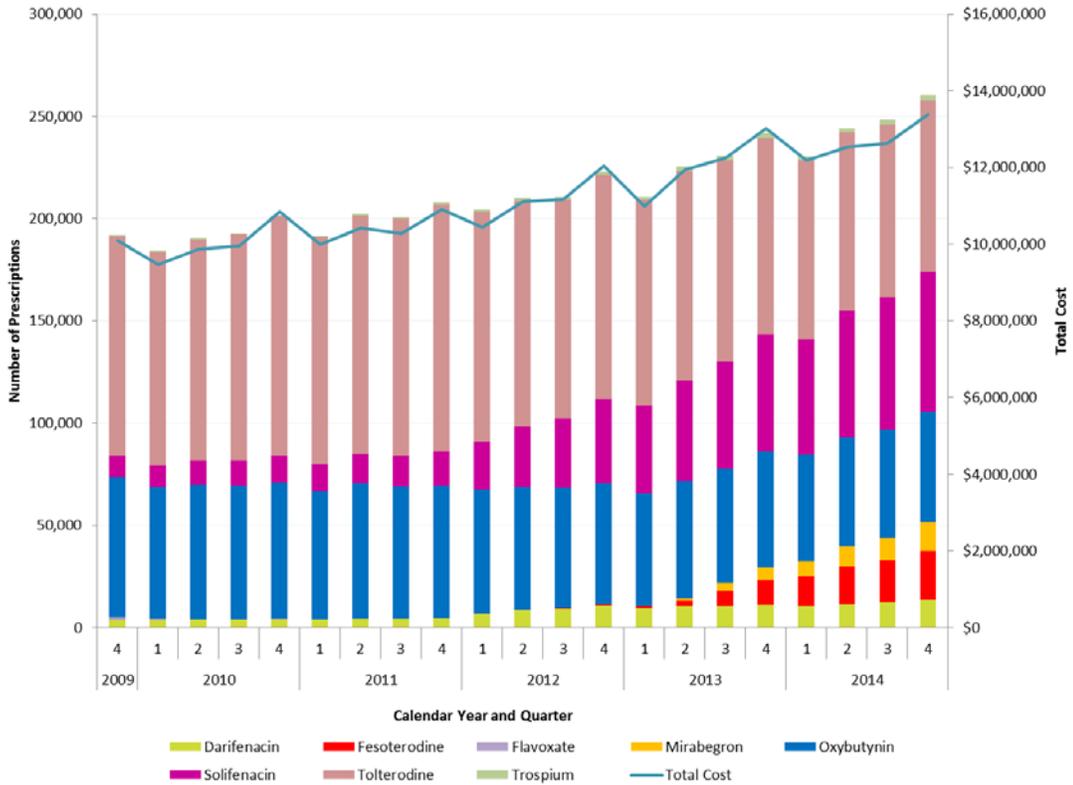
**Exhibit 11: Total Number of Prescriptions and Cost for OAB Medications Dispensed in Ontario, by Payer and Quarter**



Data Source: IMS GPM<sup>12</sup>

Prescriptions and costs of OAB medications in Ontario have increased by 35.6% and 32.6% over the study period, respectively. In Q4 2014, 75.3% of OAB medications dispensed in Ontario were paid for by the provincial drug program.

**Exhibit 12: Total Number of Prescriptions and Cost for OAB Medications Dispensed in Ontario by All Payers, by Drug and Quarter**



Data Source: IMS GPM<sup>12</sup>

In Q4 2009, the majority of prescribing in Ontario was for oxybutynin and tolterodine. By Q4 2014, following expanded listing on the public drug formulary, solifenacin use was similar to that of both oxybutynin and tolterodine.

**Summary of Findings for Exhibit 11 and Exhibit 12**

1. Similar to national trends, the number of prescriptions dispensed for OAB medications has increased 35.6% in Ontario, from 192,030 prescriptions dispensed in Q4 2009 to 260,446 prescriptions dispensed in Q4 2014. Costs of OAB medication have similarly increased by 32.6% over the study period in Ontario, from \$10.1 million in Q4 2009 to \$13.4 million in Q4 2014.
2. In Q4 2014, three quarters (75.3%; 196,113 prescriptions) of OAB medications dispensed in Ontario were paid for by public payers, followed by private insurance (17%; 44,236 prescriptions), cash payments (7.3%; 18,921 prescriptions) and NIHB (<1%).
3. At the beginning of the study period, tolterodine accounted for over half (56%; 107,691 prescriptions) of all OAB medication prescriptions dispensed in Ontario (N=192,030 prescriptions) followed by oxybutynin (35.7%; 68,553 prescriptions), solifenacin (5.3% 10,213 prescriptions), darifenacin (1.9%; 3,743 prescriptions), and trospium (0.3%; 556 prescriptions).
4. The number of prescriptions dispensed for solifenacin has increased 4-fold following the change of listing status (i.e. Limited Use code) in late 2011, from 16,870 prescriptions (Q4 2011) to 68,497 prescriptions (Q4 2014). Significant increases following the change of listing status were also noted for darifenacin (from 4,724 prescriptions (Q4 2011) to 13,546 prescriptions (Q4 2014)) and fesoterodine (from 2,726 prescriptions (Q2 2013) to 23,833 prescriptions (Q4 2014)).
5. By the end of the study period, the number of prescriptions dispensed for both tolterodine and oxybutynin decreased approximately 22% (from 107,691 (Q4 2009) to 83,837 (Q4 2014) prescriptions dispensed and 53,762 (Q4 2009) to 68,553 (Q4 2014) prescriptions dispensed, respectively). This decrease is likely due to the addition of several agents onto the formulary in 2011 and 2013 (with Limited Use criteria) as well as the introduction of mirabegron in 2012.
6. In Q4 2014, tolterodine had the largest market share of OAB medications in Ontario (32.2%; 83,837 prescriptions), followed by solifenacin (26.3%; 68,497 prescriptions), oxybutynin (20.6%; 53,762 prescriptions), fesoterodine (9.1%; 28,833), mirabegron (5.5%; 14,344 prescriptions), darifenacin (5.2%; 13,546 prescriptions), and trospium (1.0%; 2,627 prescriptions).

*Some details are censored in this report so as not to preclude publication.*

### **Censored Figure Overview:**

**Figure** - Total Number of Provincially-Funded OAB Drug Users by Drug and by Quarter in Ontario

### **Major Findings:**

Overall, the number of provincially-funded users of oxybutynin and flavoxate decreased while the number of users of solifenacin, darifenacin, fesoterodine, trospium, and mirabegron have increased. Tolterodine use increased until the introduction of newer agents in 2012 led to a decline in its use.

1. The number of provincially-funded oxybutynin users in Ontario decreased by close to 25% over a 15 year period from 2000 to 2015
2. Although the number of provincially-funded tolterodine users increased 10-fold to approximately 35,000 users in Q4-2011 the number of users has been declining since Q4 2011 when newer agents were introduced to the formulary, dropping to approximately 20,000 users in Q3 2015.
3. The largest increase in use was in solifenacin users which quickly became the second most commonly dispensed OAB agent after its introduction in Q4 2011, with approximately 16,000 users in Q3 2015.
4. Although mirabegron was only recently listed (Q2 2015), there were over 11,000 mirabegron users in Q3 2015, and it was the 4<sup>th</sup> most utilized OAB medication in that quarter.

## Characteristics of Provincially-Funded OAB Medication Users in Ontario in Fiscal Year 2012-2013

### Exhibit 13a: Characteristics of Provincially-Funded OAB Medications Users in Ontario in Fiscal Year 2012-2013, by Drug

Characteristic	Overall	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium	Dual Therapy
<b>Number of Users</b>	<b>N=113,980</b>	<b>N=4,613</b>	<b>N=3,071</b>	<b>N=32,347</b>	<b>N=23,675</b>	<b>N=49,447</b>	<b>N=658</b>	<b>N=169</b>
<b>Number of New Users</b>	54,739	2,975 (64.5%)	2,887 (94.0%)	15,280	16,963	16,181	432 (65.7%)	21 (12.4%)
<b>Age (Median (IQR))</b>	73 (65-81)	76 (68-82)	74 (67-81)	70 (55-80)	73 (66-80)	75 (67-82)	78 (70-84)	71 (61-80)
<b>Sex - Male (N, %)</b>	36,682	1,639 (35.5%)	1,389 (45.2%)	8,965 (27.7%)	8,706 (36.8%)	15,654	269 (40.9%)	60 (35.5%)
<b>Long Term Care (N, %)</b>	4,663 (4.1%)	161 (3.5%)	112 (3.6%)	1,246 (3.9%)	546 (2.3%)	2,551 (5.2%)	37 (5.6%)	10 (5.9%)
<b>Income Quintile</b>								
1	26,983	892 (19.3%)	666 (21.7%)	8,855 (27.4%)	5,092 (21.5%)	11,287	145 (22.0%)	46 (27.2%)
2	23,803	983 (21.3%)	640 (20.8%)	7,017 (21.7%)	4,778 (20.2%)	10,227	117 (17.8%)	41 (24.3%)
3	21,625	851 (18.4%)	552 (18.0%)	5,971 (18.5%)	4,578 (19.3%)	9,532 (19.3%)	118 (17.9%)	23 (13.6%)
4	21,067	921 (20.0%)	629 (20.5%)	5,501 (17.0%)	4,557 (19.2%)	9,309 (18.8%)	119 (18.1%)	31 (18.3%)
5	20,028	951 (20.6%)	569 (18.5%)	4,844 (15.0%)	4,587 (19.4%)	8,893 (18.0%)	157 (23.9%)	27 (16.0%)
<b>OAB Diagnosis (N, %)</b>	76,196	3,732 (80.9%)	2,405 (78.3%)	17,776	18,442	33,132	565 (85.9%)	144 (85.2%)
<b>Hospitalizations within the last year</b>								
1 or more Hospitalizations	21,589	938 (20.3%)	639 (20.8%)	5,893 (18.2%)	4,619 (19.5%)	9,284 (18.8%)	176 (26.7%)	40 (23.7%)
Falls/Fracture	2,459 (2.2%)	108 (2.3%)	61 (2.0%)	670 (2.1%)	444 (1.9%)	1,151 (2.3%)	22 (3.3%)	<=5
UTI/Vulvovaginitis	3,545 (3.1%)	140 (3.0%)	96 (3.1%)	1,024 (3.2%)	706 (3.0%)	1,535 (3.1%)	37 (5.6%)	7 (4.1%)
<b>Physician office visits within the last year Median (IQR)</b>	11 (6-17)	13 (8-19)	12 (7-19)	10 (5-18)	12 (7-18)	10 (6-16)	13 (8-19)	11 (7-19)
<b>Charlson Morbidity Index</b>								
No hospitalization	71,889	2,773 (60.1%)	1,909 (62.2%)	20,952	14,783	31,042	345 (52.4%)	85 (50.3%)
0	18,747	866 (18.8%)	496 (16.2%)	5,459 (16.9%)	4,038 (17.1%)	7,744 (15.7%)	108 (16.4%)	36 (21.3%)
1	8,869 (7.8%)	387 (8.4%)	235 (7.7%)	2,287 (7.1%)	1,828 (7.7%)	4,043 (8.2%)	69 (10.5%)	20 (11.8%)
2+	14,475	587 (12.7%)	431 (14.0%)	3,649 (11.3%)	3,026 (12.8%)	6,618 (13.4%)	136 (20.7%)	28 (16.6%)

**Exhibit 13b: Characteristics of Provincially-Funded OAB Medications Users in Ontario in Fiscal Year 2012 and 2013, by Drug (Continued)**

Characteristic	Overall	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium	Dual Therapy
<b>Number of Users</b>	<b>N=113,980</b>	<b>N=4,613</b>	<b>N=3,071</b>	<b>N=32,347</b>	<b>N=23,675</b>	<b>N=49,447</b>	<b>N=658</b>	<b>N=169</b>
<b>Number of unique medications (DINS) in last year (Median (IQR))</b>	12 (7-18)	13 (8-19)	12 (7-18)	12 (7-18)	12 (7-18)	13 (8-19)	13 (9-20)	18 (12-26)
<b>Concomitant medication use in previous 3 months (N, %)</b>								
Psychotropics	48,732	1,952 (42.3%)	1,190 (38.7%)	14,732	9,360 (39.5%)	21,116	289 (43.9%)	93 (55.0%)
Alpha-blockers	14,902	727 (15.8%)	700 (22.8%)	2,338 (7.2%)	3,991 (16.9%)	7,004 (14.2%)	117 (17.8%)	25 (14.8%)
5-alpha reductase	6,821 (6.0%)	431 (9.3%)	330 (10.7%)	847 (2.6%)	1,940 (8.2%)	3,188 (6.4%)	70 (10.6%)	15 (8.9%)
<b>Specialist visits within 6 months (N, %)</b>								
Urology	32,842	2,263 (49.1%)	1,970 (64.1%)	4,543 (14.0%)	11,729	11,841	418 (63.5%)	78 (46.2%)
Gynecology	9,838 (8.6%)	818 (17.7%)	316 (10.3%)	2,324 (7.2%)	2,819 (11.9%)	3,470 (7.0%)	79 (12.0%)	12 (7.1%)

<sup>†</sup> dual therapy defined as two different OAB drugs (based on drug name) prescribed at index. Data Source: ICES

Oxybutynin users were younger and had fewer hospitalizations in the last year. Solifenacin and tolterodine were the most commonly prescribed medications by urologists.

### Exhibit 13C: Previous Oxybutynin use among Provincially-Funded OAB Medications Users in Ontario in Q3-2015, by Drug

Drug	Darifenacin	Fesoterodine	Mirabegron	Solifenacin	Tolterodine	Trospium
Total Number of Users	<b>3,269</b>	<b>8,343</b>	<b>11,346</b>	<b>16,965</b>	<b>19,720</b>	<b>439</b>
Any previous oxybutynin use in past 5 years	<b>529</b> <b>(16.2%)</b>	<b>1,340</b> <b>(16.1%)</b>	<b>1,609</b> <b>(14.2%)</b>	<b>2,809</b> <b>(16.6%)</b>	<b>2,123</b> <b>(10.8%)</b>	<b>89</b> <b>(20.3%)</b>

Data Source: ICES

Only a small proportion (10.8% to 20.3%) of OAB medication users had any previous oxybutynin use in the past 5 years.

#### Summary of Findings for Exhibit 13a, 13b and 13c

- Overall, there were 113,980 users of provincially-funded OAB medications in Ontario in FY 2012 and 2013. The majority of users were prescribed tolterodine (43.3%; N=49,447), followed by oxybutynin (28.3%; N=32,347), solifenacin (20.8%; N=23,675), darifenacin (4%; N=4,613), fesoterodine (2.7%; N=3,071) and trospium (0.6%; N=658). Less than 1% were dual therapy users (0.1%; N=169).
- The median age of users was 73 years (IQR 65-81 years), approximately one-third were males (32.2%; N=36,682), and 4.1% (N=4,663) were long-term care residents.
- Overall, 66.9% of users (N=76,196) had an OAB diagnosis in the past 5 years. This differed by medication prescribed, with over 80% of users using darifenacin, trospium, and dual therapy having an OAB diagnosis compared to 55% of oxybutynin users.
- Approximately one-fifth of users (18.9%; N=21,589) had a hospitalization in the past year, 2.2% (N=2,459) were hospitalized for a fall or fracture, and 3.1% (N=3,545) were hospitalized for a urinary tract infection or vulvovaginitis. OAB medication users had a median of 11 (IQR 6-17) physician office visits in the past year.
- Of the 113,980 OAB medication users 42.8% of OAB medication users (N=48,732) had used a psychotropic drug in the past 3 months, 13.1% (N=14,902) used alpha-blockers, and 6.0% (N=6,821) used 5-alpha reductase drugs.
- Overall, 28.8% of users (N=32,842) had visited an urologist in the past 6 months, though this differed by drug. Approximately half or more of users that were treated with darifenacin (49.1%; N=2,263), fesoterodine (64.1%; N=1,970), solifenacin (49.5%; N=11,729), trospium (63.5%; N=418), or dual therapy (46.2%; N=78) visited an urologist in the past 6 months compared only 23.9% of tolterodine users (N=11,841) and 14.0% of oxybutynin users (N=4,543).
- Overall, 8.6% of users (N=9,838) visited a gynecologist in the last 6 months. This differed by medication, for example, 17.7% of darifenacin users (N=818) visiting a gynecologist compared to approximately 7% of oxybutynin, tolterodine, and dual therapy users.
- A small proportion of users (10.8% to 20.3%) in Q3-2015 had any previous oxybutynin use in the past 5 years despite the current Limited Use criteria, which limits the use of these medications to users who have failed or could not tolerate oxybutynin.

**Exhibit 14a: Characteristics of Newly Initiated Provincially-Funded OAB Medications Users in Ontario in Fiscal Years 2012-2013, by Drug Initiated**

Characteristic	Overall	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium
<b>Number of New Users</b>	<b>N=43,184</b>	<b>N=2,621</b>	<b>N=2,475</b>	<b>N=10,007</b>	<b>N=14,213</b>	<b>N=13,474</b>	<b>N=394</b>
<b>Number of New Users with only 1 Prescription</b>	19,963 (46.2%)	1,018 (38.8%)*	991 (40.0%)*	5,963 (59.6%)	5,704 (40.1%)*	6,109 (45.3%)*	178 (45.2%)*
<b>Among New Users with &gt; 1 Rx</b>	<b>N=23,221</b>	<b>N=1,603</b>	<b>N=1,484</b>	<b>N=4,044</b>	<b>N=8,509</b>	<b>N=7,365</b>	<b>N=216</b>
<b>Sex - Male (%)</b>	9,009 (38.8%)	610 (38.1%)*	738 (49.7%)*	1,108 (27.4%)	3,551 (41.7%)*	2,902 (39.4%)*	100 (46.3%)*
<b>Age Median (IQR)</b>	77 (71-83)	78 (72-83)	77 (71-83)	77 (71-84)	76 (71-82)*	77 (71-84)	80 (74-85)*
<b>OAB diagnosis (N, %)</b>	16,151 (69.6%)	1,227 (76.5%)*	1,142 (77.0%)*	2,364 (58.5%)	6,354 (74.7%)*	4,887 (66.4%)*	177 (81.9%)*
<b>Physician office visits within the last year (Median (IQR))</b>	11 (6-17)	12 (8-18)*	11 (7-18)*	10 (5-16)	11 (7-17)*	11 (6-17)*	13 (8-19)*
<b>Hospitalizations within the last year (N, %)</b>							
1 or more hospitalizations	5,614 (24.2%)	360 (22.5%)	350 (23.6%)	1,090 (27.0%)	1,855 (21.8%)*	1,886 (25.6%)	73 (33.8%)*
Falls/Fracture	826 (3.6%)	60 (3.7%)	38 (2.6%)*	199 (4.9%)	220 (2.6%)*	295 (4.0%)	14 (6.5%)
UTI/Vulvovaginitis	1,041 (4.5%)	64 (4.0%)	58 (3.9%)	224 (5.5%)	301 (3.5%)	377 (5.1%)	17 (7.9%)
<b>Charlson Morbidity Index</b>							
No hospitalization	13,346 (57.5%)	947 (59.1%)	862 (58.1%)	2,251 (55.7%)	5,029 (59.1%)	4,151 (56.4%)	106 (49.1%)*
0	3,952 (17.0%)	302 (18.8%)	254 (17.1%)	684 (16.9%)	1,452 (17.1%)	1,233 (16.7%)	27 (12.5%)*
1	2,198 (9.5%)	143 (8.9%)	120 (8.1%)	419 (10.4%)	775 (9.1%)	716 (9.7%)	25 (11.6%)
2+	3,725 (16.0%)	211 (13.2%)*	248 (16.7%)	690 (17.1%)	1,253 (14.7%)	1,265 (17.2%)	58 (26.9%)*

\* Denotes standardized difference > 0.1 compared to oxybutynin. Data Source: ICES

### Exhibit 14b: Characteristics of Newly Initiated Provincially-Funded OAB Medications Users in Ontario in Fiscal Years 2012-2014, by Drug Initiated (Continued)

Characteristic	Overall	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium
<b>Among new users with &gt; 1 Rx</b>	<b>N=23,221</b>	<b>N=1,603</b>	<b>N=1,484</b>	<b>N=4,044</b>	<b>N=8,509</b>	<b>N=7,365</b>	<b>N=216</b>
<b>Number of unique medications in last year Median (IQR)</b>	13 (8-19)	13 (8-18)	13 (8-19)	13 (8-20)	12 (8-18)	13 (8-19)	14 (10-22)*
<b>Concomitant medication use in previous 3 months (N, %)</b>							
Psychotropics	9,298 (40.0%)	677 (42.2%)	569 (38.3%)	1,760 (43.5%)	3,307 (38.9%)	2,887 (39.2%)	98 (45.4%)
Alpha-blockers	4,656 (20.1%)	295 (18.4%)*	399 (26.9%)*	465 (11.5%)	1,855 (21.8%)*	1,592 (21.6%)*	50 (23.1%)*
5-alpha reductase	2,253 (9.7%)	187 (11.7%)*	204 (13.7%)*	168 (4.2%)	948 (11.1%)*	717 (9.7%)*	29 (13.4%)*
<b>Prescriber of initial prescriptions</b>							
Urology	7,582 (32.7%)	602 (37.6%)*	817 (55.1%)*	358 (8.9%)	3,617 (42.5%)*	2,078 (28.2%)*	110 (50.9%)*
Gynecology	1,334 (5.7%)	205 (12.8%)*	83 (5.6%)	207 (5.1%)	489 (5.7%)	334 (4.5%)	16 (7.4%)
General Practitioner	12,013 (51.7%)	627 (39.1%)*	503 (33.9%)*	3,003 (74.3%)	3,678 (43.2%)*	4,133 (56.1%)*	69 (31.9%)*
Other/Missing	2,292 (9.9%)	169 (10.5%)	81 (5.5%)	476 (11.8%)	725 (8.5%)	820 (11.2%)	21 (9.7%)
<b>Specialist visits within 6 months (n,%)</b>							
Urology	9,439 (40.6%)	742 (46.3%)*	934 (62.9%)*	633 (15.7%)	4,283 (50.3%)*	2,708 (36.8%)*	139 (64.4%)*
Gynecology	2,232 (9.6%)	270 (16.8%)*	134 (9.0%)	358 (8.9%)	843 (9.9%)	604 (8.2%)	23 (10.6%)

\* Denotes standardized difference > 0.1 compared to oxybutynin. Data Source: ICES

Overall, there were 43,184 new users of OAB medications in fiscal years 2012-2013, of which only half (53.8%) had more than one prescription over the period of continuous use. At initiation, oxybutynin users are on more concomitant psychotropics and very few patients were initiated (15.7%) by a urologist.

**Summary of Findings for Exhibit 14a and Exhibit 14b**

1. Among new OAB medication users with more than one prescription in their period of continuous use, solifenacin was most commonly initiated (36.6%; N=8509), followed by tolterodine (31.7%; N=7365), oxybutynin (17.4%; N=4,044), darifenacin (6.9%; N=1,603), fesoterodine (6.4%; N=1,484), and trospium (0.9%; N=216).
2. A high proportion of new users of oxybutynin received only one prescription (59.6%, N=5,963).
3. Overall, new users of OAB agents who received 2 or more prescriptions were a median of 77 years old (IQR 71-83).
4. While 69.6% of new users (N=16,151) had an OAB diagnosis in the 5 years prior to initiation, the proportion of oxybutynin users with an OAB diagnosis was relatively smaller (58.5%, N=2,364).
5. 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 an urologist. In contrast, 74.3% of oxybutynin users (N=3,678) and 56.1% of tolterodine users (N=4,133) obtained their initial prescription from a general practitioner.
6. A smaller proportion of oxybutynin initiators (15.7%, N=633) visited an urologist in the 6 months prior to initiation compared to all users (40.6%, N=9,439). Approximately one in ten users overall visited a gynecologist within the 6 months prior to initiation (9.6%, N=2,232).
7. Approximately one quarter of new OAB medication users (24.2%, N=5,614) had at least 1 hospitalization in the year prior to treatment initiation. Only a small proportion of users were hospitalized for a fall or fracture (3.6%, N=826) or urinary tract infection or vulvovaginitis (4.5%, N=1,041) in the prior year.
8. Overall, 40.0% of new users (N=4,656) had a previous prescription for psychotropic drugs in the past 3 months.

## Patterns of OAB Medication Use among Adult New Users in Ontario

### Methodological Note:

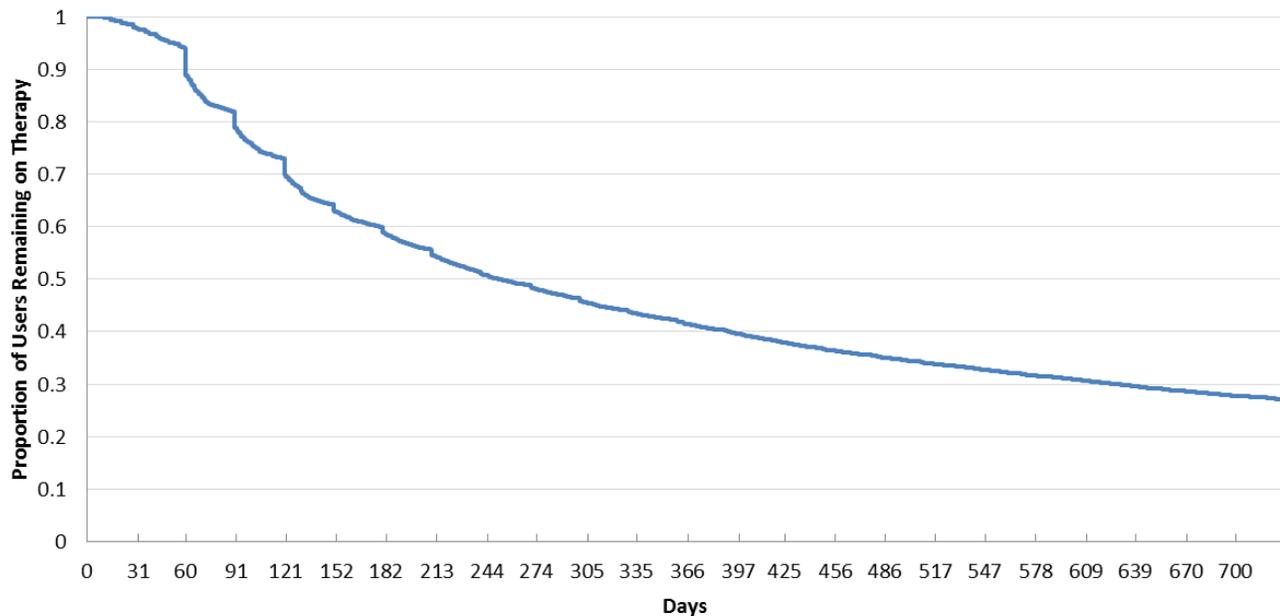
This analysis is limited to new users who had more than one prescription. We excluded new users who were prescribed two different drugs at treatment initiation.

### Exhibit 15: Patterns of Provincially-Funded OAB Medications Use among Adult Continuous Users Aged 66 and Older

Outcomes	Overall
<b>Number of New Users with &gt;1 Prescription</b>	<b>N=23,221</b>
<b>Number of Different OAB Agents over Follow-up</b>	
1	19,399 (83.5%)
2	3,314 (14.3%)
3+	508 (2.2%)
<b>Persistence to OAB Agents (N, %)†</b>	
6 months	13,439 (57.9%)
1 year	9,276 (39.9%)
<b>Number of Deaths over Follow-up (N, %)</b>	798 (3.4%)
<b>Median Time to Therapy Discontinuation (days)‡</b>	251

† Discontinuation of any OAB agent. Data Source: ICES

### Exhibit 16: Time to Discontinuation of Any Provincially-Funded OAB Medication among Adult Continuous Users Aged 66 and Older



Data Source: ICES

Of the 23,221 new users with more than one OAB agent prescription within the period of continuous use, the median time to discontinuation of any OAB drug was 251 days.

#### Summary of Findings for Exhibits 15 and 16

1. Overall there were 23,221 new users of OAB medications aged 66 and older who had more than one OAB medication prescription during their period of continuous use from 2011 to 2013.
2. Most users were prescribed only one type of OAB medication throughout their period of continuous use (83.5%, N=19,399).
3. 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. New users remained on therapy for a median of 251 days.
4. Overall, 3.4% of new OAB users (N=798) died during the period of continuous use.

**Exhibit 17: Patterns of Provincially-Funded OAB Medications Use among Adult Continuous Users Aged 66 and Older from 2011 to 2013, by Drug Initiated**

Outcomes	Darifenacin N=1,600- 1,650	Fesoterodine N=1,450- 1,500	Oxybutynin N=4,000- 4,050	Solifenacin N=8,500- 8,550	Tolterodine N=7,350- 7,400	Trospium N=200-250
<b>Number of Different OAB Agents over Follow-up</b>						
<b>1</b>	85-87%	90-92%	70-72%	88-90%	80-82%	88-90%
<b>2</b>	12-14%	8-10%	24-26%	8-10%	16-18%	8-10%
<b>3+</b>	2-4%	2-4%	2-4%	0-2%	2-4%	2-4%
<b>Switch from Initial OAB Agent (N, %)</b>						
<b>6 months</b>	10-12%	6-8%	24-26%	6-8%	12-14%	8-10%
<b>1 year</b>	12-14%	8-10%	26-28%	8-10%	14-16%	10-12%
<b>Median Time to Discontinuation<sup>†</sup> (days)</b>	200-210	210-220	110-120	240-250	180-190	180-190

<sup>†</sup> Discontinuation of initial OAB agent. Data Source; ICES

**Summary of Findings for Exhibit 17**

1. Oxybutynin users discontinued use or switched to a different OAB agent within 6 months after initiation (24-26%) compared to less than 14% among those who initiated other OAB medications.
2. The median time to discontinuation of a user's initial drug significantly different by drug initiated. The median time to discontinuation was lowest for oxybutynin (110-120 days) users and highest for solifenacin users (240-250 days).
3. These results are consistent with previously conducted persistence studies in both Ontario and other jurisdictions, which found low rates of persistence to this class of medications and greater rates of discontinuations with oxybutynin.<sup>4-6</sup>

## Health Equity

Stratified analyses suggest that there is not a major equity issue in access to OAB medications by sex. Given the passive nature of the restricted listing of these products on the Ontario public drug formulary, rates of use among those eligible for drug coverage in Ontario are among the highest in Canada. This suggests that there are no considerable barriers to access of these products.

## Limitations

Several limitations to the availability of data warrant discussion:

1. No data is available for the territories, and therefore all analyses are restricted to inter-provincial comparisons.
2. IMS Geographic Prescription Monitor (GPM<sup>12</sup>) does not collect patient-level data, and therefore information on privately funded prescriptions is only available at the prescription and unit (e.g. tablet) level.
3. There is no data available for publicly paid prescriptions in Quebec from CIHI NPDUIS. Therefore, we were unable to make comparisons between Ontario rates and rates of use in this province.
4. Data on the number of active beneficiaries eligible for public drug coverage was estimated based on active prescriptions in each quarter and annually. Therefore, these may slightly underestimate the true size of the public beneficiary population; however, this does reflect the number of active beneficiaries (e.g. those filling at least one prescription over a given year) each year.
5. All data presented are based on prescriptions filled. We are unable to confirm whether a patient actually took the medication.
6. Codes used to flag OAB diagnosis have not been validated and are likely underestimating diagnosis rates.

## Generalizability

Some analyses were restricted to elderly aged 66 and older. Therefore these findings are not necessarily generalizable to a younger population.

## Adherence

All data used in these analyses are based on dispensing patterns, and we do not know whether subjects actually took the medications. This is particularly questionable among the population of individuals who received only one prescription for an OAB medication. It is possible that they never tried the medication, or tried it and did not finish their initial course of therapy. For this reason, we looked at adherence measures among OAB medication users who were dispensed more than one prescription.

## Overall Conclusion

Use of OAB medication continues to grow both nationally and in Ontario. Ontario was found to have some of the highest rates of publicly-funded OAB medication use in Canada, which is likely due to having the most open criteria for reimbursement for the drug class on the public drug formulary. With the introduction of newer brand name agents in the last few years we found a large shift in market share of the various OAB agents. Early evidence suggests that the addition of mirabegron may further change current trends due to its quick uptake in early 2015. With a growing elderly population, extended life-expectancy, and the addition of newer brand-name medication we do not expect this trend to change in the future and anticipate continued growth in use of this drug class and related costs.

## Reference List

1. Levy A, O'Brien B, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Canadian Journal of Clinical Pharmacology* 2003; 10:67-71.
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3. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *Bmj* 2013; 346:f2610.
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5. Sicras-Mainar A, Rejas J, Navarro-Artieda R, et al. Antimuscarinic persistence patterns in newly treated patients with overactive bladder: a retrospective comparative analysis. *International Urogynecology Journal*. 2014;25(4):485-492.
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# Review of the Observational Literature

## Objectives

The comparative safety of OAB medications as established in randomized controlled trials is summarized in the report by the Systematic Review Team. However, these trials typically have strict inclusion criteria, and do not generally conduct head-to-head comparisons between OAB medications. A review of the observational literature comparing OAB medications will help provide real-world estimates of comparative safety of these products.

## Methods

### Search Strategy

We conducted a rapid review of the observational literature to investigate and understand the comparative safety, specifically falls and cognitive effects, of OAB medications. The exact search strategy performed can be found in **Appendix B**. The inclusion criteria for text screening are below:

### Inclusion criteria:

- English language
- Adult population
- Observational studies
- Comparing two or more OAB medications
- Falls or cognitive impairment reported
- Published between January 2005-November 2015

## Results

Overall, 518 abstracts were reviewed, and 10 potentially relevant articles were obtained in full text. We also reviewed 30 literature reviews located to ensure completeness of this rapid review. Only two studies were identified for the final review by meeting our inclusion criteria. Many studies have explored the class effect of anticholinergic, specifically oxybutynin, and their safety but few have conducted comparative studies within this class of medications.<sup>1 2</sup>

The two observational comparative safety studies identified in the review both employed a new-user design to compare the frequency of adverse events. The first study conducted by Gomes et al.<sup>3</sup> leveraged administrative claims data in Ontario for patients 66 years of age and older and matched oxybutynin and tolterodine users using a high-dimensional propensity score. Gomes et al. (n=111,522) found that there were no significant differences between oxybutynin and tolterodine for fractures (HR= 0.96 (0.82-1.13 95% CI)), falls (HR= 1.04 (0.95-1.14 95% CI)), or delirium (HR= 0.90 (0.66-1.23 95% CI)), within 90 days of OAB treatment initiations. An exploratory analysis of mortality (HR= 1.20 (1.07-1.35 95% CI)) found a higher risk with oxybutynin users that the authors suggest should be further explored.

The second study conducted by Jumadilova et al.<sup>4</sup> explored the relative risk, resource

utilization, and costs related to new-users of OAB treatment in the US claims data, this study looked at a younger population (mean age = 54). They matched new-users of tolterodine to new-users of oxybutynin Immediate Release (IR) and Oxybutynin Extended Release (ER) using propensity score methods. Jumadilova et al. found that tolterodine users had fewer UTIs and new comorbidities, which were outcomes of the study, when compared to both formulations of Oxybutynin. They found no difference in the rates of fracture between tolterodine and oxybutynin ER ( $P= 0.1140$ ) and oxybutynin IR ( $p=0.1356$ ). Oxybutynin IR users were found to have higher risk of depression ( $P=0.0133$ ) than tolterodine, while no difference was found with Oxybutynin ER ( $p=0.4137$ )

## Conclusions

Only two comparative observational studies of the safety of OAB medications were found. The evidence available on comparisons is minimal but may support that no differences in the rate of fractures exhibits between oxybutynin and tolterodine. No studies were found studying newer agents. Overall, due to the lack of evidence available, no conclusive statements can be made regarding differences in safety or between OAB medications. There is a large dearth of information on the real-world comparative safety of this class of medications.

## Literature Review References

1. Hunter KF, Wagg A, Kerridge T, et al. Falls risk reduction and treatment of overactive bladder symptoms with antimuscarinic agents: a scoping review. *Neurourology & Urodynamics* 2011;**30**(4):490-4.
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3. Gomes T, Juurlink DN, Ho JM, et al. Risk of serious falls associated with oxybutynin and tolterodine: a population based study. *Journal of Urology* 2011;**186**(4):1340-4.
4. Jumadilova Z, Varadharajan S, Girase P, et al. Retrospective evaluation of outcomes in patients with overactive bladder receiving tolterodine versus oxybutynin. *American Journal of Health-System Pharmacy* 2006;**63**(23):2357-64.

## Appendix A: Public Plan Listings for OAB Medications in Canada, by Province

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

No=not listed

Pas=restricted listing – passive (e.g., Limited Use in Ontario)

Res=restricted listing – enforced

FB=full benefit

Current as of October 26, 2015

## Appendix B: Medline Search Strategy

1. Darifenacin.mp (275)
2. Fesoterodine.mp (142)
3. Flavoxate.mp or exp flavoxate (170)
4. Mirabegron.mp (127)
5. Oxybutynin.mp (1247)
6. Solifenacin.mp (357)
7. Tolterodine.mp (793)
8. Trospium.mp (222)
9. Cholinergic.mp. or exp Cholinergic Agents/ (235,171)
10. Muscarinic Antagonists.mp. or exp Muscarinic Antagonists/ (50,381)
11. exp Adrenergic beta-3 Receptor Agonists/ (419)
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (236,554)
13. Urinary Incontinence.mp. or exp Urinary Incontinence/ (31,542)
14. overactive bladder.mp. or exp Urinary Bladder, Overactive/ (4,376)
15. exp Urinary Incontinence, Urge/ or exp Urinary Incontinence, Stress/ or exp Urinary Incontinence/ or incontinence.mp. (45,324)
16. 13 OR 14 OR 15 (47,474)
17. 12 AND 16 (3,082)
18. exp Safety/ or exp Patient Safety/ or safety.mp. (334,893)
19. exp "Drug-Related Side Effects and Adverse Reactions"/ or drug safety.mp. or exp Product Surveillance, Postmarketing/ (105,584)
20. exp Accidental Falls/ or Falls.mp. (37,784)
21. Somnolence.mp. (6,603)
22. exp Delirium/ or Delerium.mp. (6,493)
23. exp Fractures, Bone/ or exp Hip Fractures/ or Fractures.mp. or exp Osteoporotic Fractures/ (177,359)
24. 18 or 19 or 20 or 21 or 22 or 23 (643,449)
25. 17 AND 24 (518)

## Appendix C: Summary of Included Studies

Author	Study Design	Study period	Population (Sample Size)	New User Design (Y/N)	Country	Drugs Included	Age in years (mean (SD))	Duration of Follow-up	Outcomes	Key Findings
Gomes et al. <sup>3</sup>	Matched Cohort	2002-2008	Elderly (66+) new-users N = 111,522	Y	Canada	Oxybutynin, tolterodine	66+	3 months	<ul style="list-style-type: none"> <li>- Serious falls (ED or Hospital Visit)</li> <li>- Fractures</li> <li>- Delirium</li> </ul>	<ul style="list-style-type: none"> <li>• No difference between oxybutynin and tolterodine in short-term risk of falls, fractures or delirium 90-days after initiation</li> </ul>
Jumadilova et al. <sup>4</sup>	Matched Cohort	2001-2002	Patients with diagnosis for OAB and 1 Rx	Y	US	Tolterodine ER, Oxybutynin ER, Oxybutynin IR	54 +/- 14	12 months	<ul style="list-style-type: none"> <li>- Urinary Tract Infections (UTI)</li> <li>- Fractures</li> <li>- Depression</li> <li>- Any comorbidities</li> </ul>	<ul style="list-style-type: none"> <li>• Tolterodine ER use was associated with lower risk of UTI, depression, and other comorbidities than both formulations of oxybutynin.</li> <li>• No difference in the rate of fractures was found.</li> </ul>