ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

FINAL REPORT

LAMA Products for the Treatment of COPD

Pharmacoepidemiology Unit: Censored Final Report

Tara Gomes, Andrea Gershon, Matthew Stanbrook, Ximena Camacho, Diana Martins, Samantha Singh, Zhan Yao, Michael Paterson, David Juurlink and Muhammad Mamdani

November 25th, 2014

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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Summary

National and Provincial Trends in LAMA Prescribing (all indications)

LAMA products are the fourth most commonly prescribed inhaled anti-inflammatory/bronchodilator therapies in Canada, with 536,148 prescriptions dispensed in the fourth quarter (Q4: October to December) of 2013. Nearly all (97.4%; 522,227 prescriptions; Q4 2013) prescriptions for LAMA products dispensed in Canada were for tiotropium. Total national expenditures on LAMA products in the last quarter of 2013 were $47.9 million, 18.4% of the overall national spending on anti-inflammatory/bronchodilator products ($247.2 million, Q4 2013). Ontario has the third-highest utilization rate of provincially-funded LAMA products with 4,874 prescriptions dispensed per 100,000 eligible population compared to the national average of 3,275 prescriptions per 100,000 eligible population in Q4 2013. Ontario also has the second highest costs of provincially-funded LAMA products ($557,308 per 100,000 eligible population vs. national average of $399,287 per 100,000 eligible population in Q4 2013) (data not shown).

Use of LAMA Products in Ontario (all indications)

The majority of LAMA products dispensed in Ontario are paid for through the Ontario Public Drug Program (OPDP). In Q4 2013, 83.1% of prescriptions (N= 148,224) were paid for through OPDP, 12.5% (N=22,263) through private health insurance, and the remainder (4.4%; N=7,861) through cash payments and Non-Insured Health Benefits (NIHB). LAMA products are most commonly prescribed to patients with COPD; in fiscal 2012, 87.8% of all patients prescribed LAMA products had a diagnosis of COPD (with or without a concurrent asthma diagnosis). Despite LAMA products being indicated for the treatment of COPD only, in Ontario 12.2% (N=16,636) of all users of LAMA products did not have any indication of such a diagnosis in administrative claims data (3.6% asthma diagnosis only [$2.1 million], 8.6% no evidence of asthma or COPD [$4.7 million]). Among the patients prescribed LAMA products with no diagnosis of COPD or asthma, 9.4% (N=1,101) had indication of prior respiratory disease (e.g. cystic fibrosis). Some of the individuals with no indication of COPD or asthma may in fact have minor disease that has not yet been identified in the administrative data.

Characteristics of LAMA users in Ontario

In 2012, 112,649 COPD patients received provincially-funded LAMA products in Ontario, almost one-quarter (27,131; 24.1%) of whom were new users. COPD patients prescribed LAMA products through the OPDP were typically over 65 years of age (N=93,218; 82.8%), had moderate COPD severity (N=67,779; 60.2%), and lived in urban locations (N=92,927; 82.5%). Almost half of all treated COPD patients had a concurrent diagnosis of asthma (42.7%), although this was higher among younger patients (51.4%) compared to older patients (40.8%).

LAMA Patterns of Use and Discontinuation in Ontario

More than half of COPD patients aged 66 and older who were new users of a LAMA, between April 2008 and March 2013, were treated with only a LAMA product; less than 10% were treated with concurrent single-agent ICS or LABA products ("dual therapy"); and slightly less than 40% were treated with a LAMA in addition to both ICS and LABA products (either as single-agents or ICS+LABA combination therapy; "triple therapy"). Among the new users with more than one LAMA prescription, adherence to triple therapy was higher compared to dual therapy and single therapy ($p<0.0001$). Along with higher adherence, triple therapy users also had more severe COPD compared to dual and single therapy users (20-30% vs. 20-30% vs. 10-20%, respectively). Single therapy users were less likely to have used other COPD therapies prior to initiation of LAMA therapy compared to dual and triple therapy users (50-60% vs. 10-20% vs. 10-20%, respectively).

Among dual therapy users, over one-third of patients were using ICS with LAMA dual therapy compared to using LABA with LAMA dual therapy. Patients treated with LABA+LAMA therapy were more adherent to therapy compared to those treated with ICS+LAMA therapy ($p=0.0002$).

Table of Contents

Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The work was supported by the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC, and by the Canadian Institute for Health Information (CIHI). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred. The statements, findings, conclusions, views, and opinions contained and expressed in the report are based in part on data obtained under license from IMS Health Canada Inc. concerning the following information service(s): Geographic Prescription Monitor (GPM12), data period October 1 2009 - March 31 2014. All Rights Reserved. The statements, findings, conclusions, views, and opinions expressed herein are not necessarily those of IMS Health Canada Inc. or any of its affiliated or subsidiary entities.

Introduction

Long-acting muscarinic antagonists (LAMA) products are drugs indicated for the treatment of chronic obstructive pulmonary disease (COPD). Three LAMA products are currently available in Canada: tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler) and aclidinium (Tudorza Genuair). Aclidinium is the newest of the LAMA products (available September 2013); it is not yet on the Ontario public drug formulary. The remaining two products (tiotropium and glycopyrronium bromide) are available in Ontario as general benefits on the Ontario Drug Benefit (ODB) formulary.

The objectives of this report are to describe national and provincial trends in the use of LAMA products and to identify patterns of therapy among COPD patients with provincial drug coverage. Specifically, this report aims to:

1. Present national utilization trends of LAMA products in Canada, including cross-provincial comparisons of population-adjusted rates of use
2. Examine trends in indication for treatment with LAMA products dispensed through the Ontario Drug Benefit program
3. Describe characteristics of COPD patients treated with provincially-funded LAMA products in Ontario
4. Describe the adherence to single, dual, and triple LAMA therapy for treatment of COPD in Ontario

Data Sources

IMS Geographic Prescription Monitor (GPM^{12})

IMS Geographic Prescription Monitor *(GPM^{12})* 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^{12})* includes prescription volumes and units (e.g. tablets, patches) 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^{12})* is available from the fourth quarter of 2009 to the first quarter of 2014.

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, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island. Data is available from NPDUIS from 2000 to 2012.

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, and age ≥ 65 years. 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.[1] We analyzed data from the ODB between January 2000 and March 2013.

Ontario Chronic Obstructive Pulmonary Disease Database

The Ontario Chronic Obstructive Pulmonary Disease (COPD) database contains prevalence data on all Ontario COPD patients identified since fiscal year 1991/92. The database was created using hospital discharge abstracts from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), same-day surgery records from the National Ambulatory Care Reporting System (NACRS), physician service claims from the Ontario Health Insurance Plan (OHIP) claims database, and demographic information on persons eligible for health care coverage in Ontario from the Registered Persons Database (RPDB). The case definition for COPD uses 1 or more ambulatory care claims and/or 1 or more hospitalizations for COPD to ascertain prevalence, and yielded a sensitivity of 85% (95% confidence interval [CI] 77-91%) and specificity of 78.4% (95% CI 73.6-82.7%) when compared to a clinical reference standard.[2]

Ontario Asthma Database

The Ontario Asthma database contains prevalence data on all Ontario asthma patients identified since fiscal year 1993/94. The database was created using hospital discharge abstracts from CIHI-DAD, same-day surgery records from NACRS, physician service claims from OHIP, and demographic information from RPDB. The case definition for asthma uses 1 or more hospitalizations and/or 2 or more ambulatory care visits for asthma within 2 years to ascertain prevalence, and yielded a sensitivity of 83.8% (95% CI 77.1-89.1%) and specificity of 76.5% (95% CI 71.8-80.8%) in a chart abstraction validation study.[3]

Methods

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

National Trends in Utilization of Testosterone Products

We used data from I MS Geographic Prescription Monitor (GPM[12]) to examine overall trends in the prescribing volumes of therapies used to treat COPD, including inhaled anti-inflammatory agents, bronchodilator agents, and combination products, at both national and provincial levels. We examined the number of prescriptions dispensed for inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), ICS+LABA combination products, short-acting beta-agonists (SABA), long-acting anti-muscarinic agents (LAMA), and short-acting anti-muscarinic agents (SAMA) dispensed between October 2009 and December 2013. Note that in these analyses, we were unable to restrict prescription volumes

specifically to those patients with COPD, and therefore these represent all use of these medications for any indication. Analyses were stratified by payer (provincially-funded vs. non-provincially-funded). Provincially-funded prescriptions were those paid for through public drug programs; non-provincially-funded prescriptions were those paid for through private insurance plans, cash payments, or Non-Insured Health Benefits (NIHB). All cross-provincial analyses compared population-adjusted rates.

Population Adjustment – Overall Utilization

Provincial population estimates were obtained from Statistics Canada for each year from 2009 to 2013 and used to adjust the overall utilization rates of LAMA products per 100,000 population across the different provinces.

Population Adjustment – Stratified by Payer

For measures examining provincially-funded utilization of LAMA products, we used the number of individuals eligible for provincial drug coverage in each year from 2009 to 2013 to standardize utilization rates. In the case of provinces where we had individual-level data available through NPDUIS and ODB (i.e. Alberta, Manitoba, Saskatchewan, Ontario, New Brunswick, Nova Scotia and Prince Edward Island), we defined the number of eligible beneficiaries in each year as any individual who had at least one publically funded drug claim over the time period. In the case of British Columbia, Quebec, and Newfoundland and Labrador, we obtained estimates of eligible populations from the annual reports of each public drug program. For all provinces, eligible population counts for the most recent years were estimated using linear extrapolation where data was not available.

Because all individuals (both those eligible for public drug programs and non-beneficiaries) might pay for LAMA products out of pocket, measures of non-provincially-funded utilization were adjusted using overall provincial population estimates from Statistics Canada.

Trends in Provincially-Funded LAMA Products in Ontario

We used claims data from ODB to perform additional analyses of utilization of LAMA products in Ontario. These analyses included estimating the market share and costs of LAMA products as well as the number of users of publically-funded LAMA products across all indications. We also looked at demographic characteristics of patients prescribed LAMA products for the treatment of COPD.

Adherence among New Users of LAMA Single, Dual or Triple Therapy

We established a cohort of COPD patients who were new users of a LAMA product between April 1, 2008 and March 31, 2012, to examine the duration of LAMA therapy in Ontario. Public drug coverage is universal for individuals aged over 65, and we do not have complete eligibility information for younger beneficiaries. Therefore, we restricted this analysis to individuals aged 66 and older in order to ensure complete medication records and accurate ascertainment of new use of LAMA therapy. We defined LAMA therapy as use of a LAMA alone (single therapy), as concurrent use of a LAMA with either ICS or LABA single agents (dual therapy), or as concurrent use of LAMA with either ICS+LABA combination product or with use of both ICS and LABA agents (either as two single agents, or a combination ICS/LABA

agent; triple therapy). We followed each individual forward from the time of their first prescription (if using LAMA alone) or from the time of the first concurrent prescription (if using ICS+LABA combination product or ICS and LABA single agents) until they discontinued therapy, died, had 2 years of follow-up or reached the end of the study period (March 31, 2013). Discontinuation for single therapy was defined on the basis of no subsequent prescription for a LAMA within 180 days of the previous prescription, which is consistent with previously published studies.[4;5] Discontinuation for dual and triple therapy was defined as the end of the period of continuous use, which is the date of reducing to single therapy or dual therapy, respectively.

Indications for LAMA products

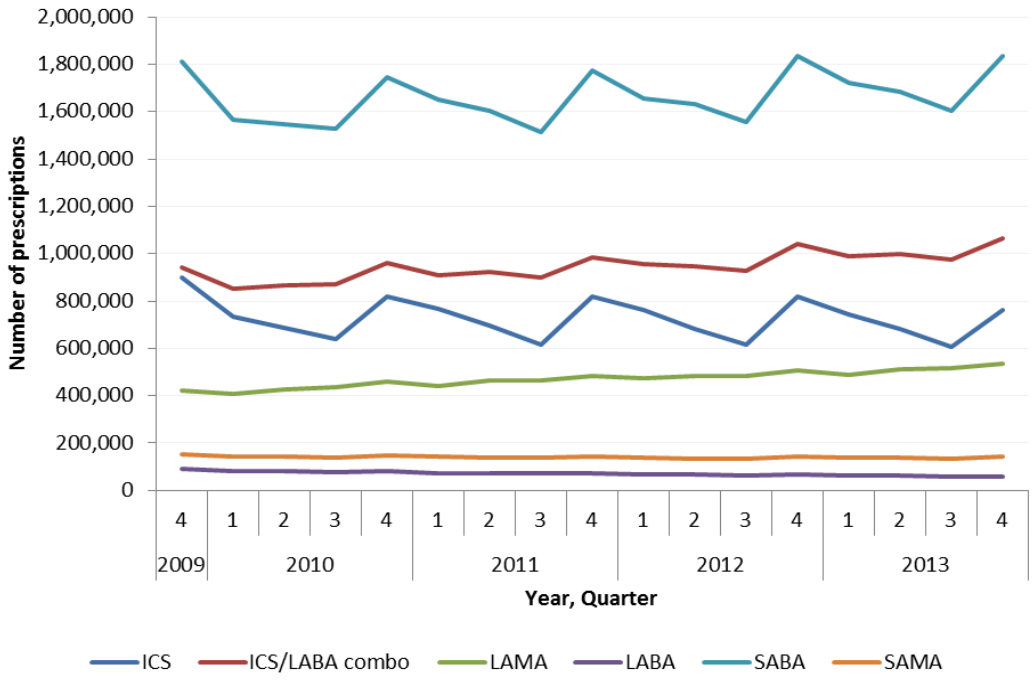
There are currently three LAMA products marketed in Canada:

LAMA Drug (Brand)	Indication in Canada	Availability in Canada	Formulation	Ontario Public Drug Formulary Listing
Tiotropium (Spiriva)	COPD	November 2002	Dry powder inhaler	General benefit
Glycopyrronium bromide (Seebri Breezhaler)	COPD	January 2013	DPI	General benefit
Aclidinium (Tudorza Genuair)	COPD	September 2013	DPI	Not listed

Exhibits and Findings

National Trends in Utilization of Inhaled Anti-Inflammatory and Bronchodilator Therapies

Exhibit 1: Total number of prescriptions for inhaled anti-inflammatory and bronchodilator agents dispensed in Canada, by quarter

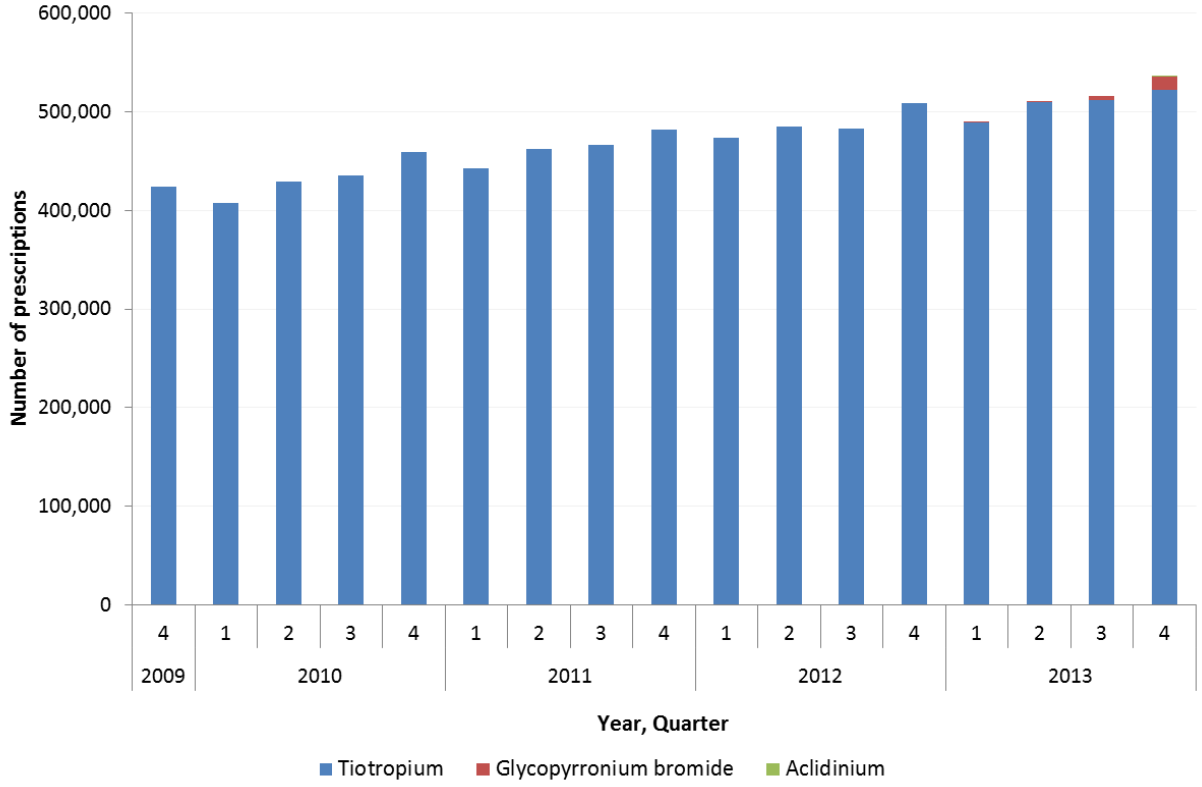


LAMA products are the fourth most commonly prescribed anti-inflammatory/ bronchodilator agents in Canada.

Summary of Findings for Exhibit 1

1. Short-acting beta-agonists (SABA) are the most commonly prescribed inhaled anti-inflammatory / bronchodilator agents in Canada.
2. The prescription market share in the fourth quarter (Q4) of 2013 was:
    a. SABA products: 41.7%; 1.8 million prescriptions
    b. Inhaled corticosteroid/long-acting beta-agonist (ICS+LABA) combination products: 24.2%; 1.1 million prescriptions
    c. Inhaled corticosteroids (ICS): 17.3%; 761,746 prescriptions
    d. Long-acting anti-muscarinic agents (LAMA): 12.2%; 536,148 prescriptions
    e. Short-acting anti-muscarinic agents (SAMA): 3.2%; 140,942 prescriptions
    f. Long-acting beta-agonists (LABA): 1.4%; 60,283 prescriptions

Exhibit 2: Total utilization of LAMA products in Canada, by product and quarter



Utilization of LAMA products has increased by 26.6% over the past 4 years. Tiotropium remains the most commonly prescribed LAMA product (97.4% of market share).

Summary of Findings for Exhibit 2

1. The use of tiotropium has increased approximately 23% over the past 4 years, from 423,631 prescriptions (Q4 2009) to 522,227 prescriptions (Q4 2013).
2. Among all LAMA prescriptions dispensed in Q4 2013 (536,148) nearly all (97.4%; 522,227 prescriptions) were for tiotropium, followed by glycopyrronium bromide (2.5%; 13,648 prescriptions) and aclidinium (0.1%; 273 prescriptions).
3. Since its introduction into the Canadian market in early 2013, the number of prescriptions for glycopyrronium bromide has increased from 29 prescriptions (Q1 2013) to 13,648 prescriptions (Q4 2013). Despite this increase, its overall market share remains considerably low compared to tiotropium (13,648 vs 522,227 prescriptions in Q4 2013).
4. There were only 273 prescriptions for aclidinium since its introduction (Q4, 2013).
5. Increased costs of LAMA products mirror the increased utilization in Canada. In the last quarter of 2013, a total of $47.9 million was spent on all LAMA products nationally, an increase of approximately 28% since Q4 2009 ($37.2 million) (data not shown).

Population-adjusted rates of LAMA utilization, by funding type

Methodological Note:

Non-provincially funded use represents use outside of provincial drug plans. This includes prescriptions paid by:

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

Public plan listings for LAMA products across the provinces are as follows:

- General benefits without restrictions (tiotropium, glycopyrronium bromide): Alberta, Ontario, Quebec
- Restricted (enforced) (tiotropium, glycopyrronium bromide): British Columbia, Manitoba, Saskatchewan, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland (NOTE: glycopyrronium bromide is not covered in PEI or Newfoundland)
- Aclidinium is currently only covered in Quebec (as a general benefit)

Exhibit 3: Population-adjusted utilization of provincially funded LAMA products in Canada, by province

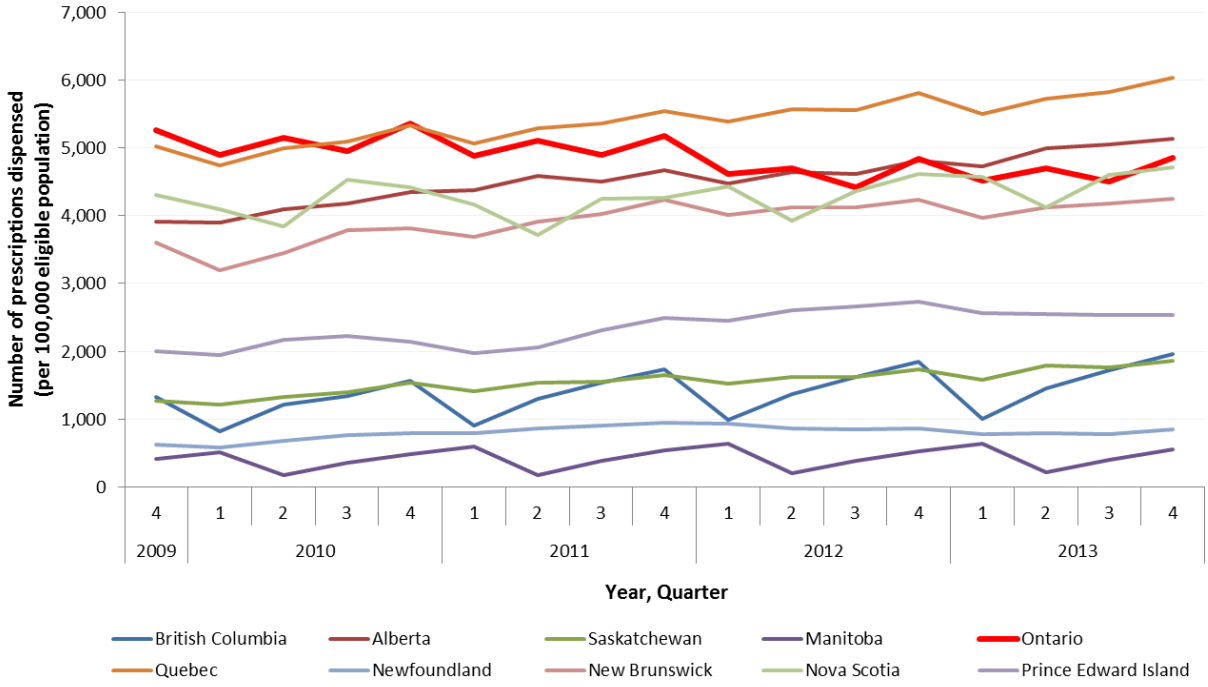
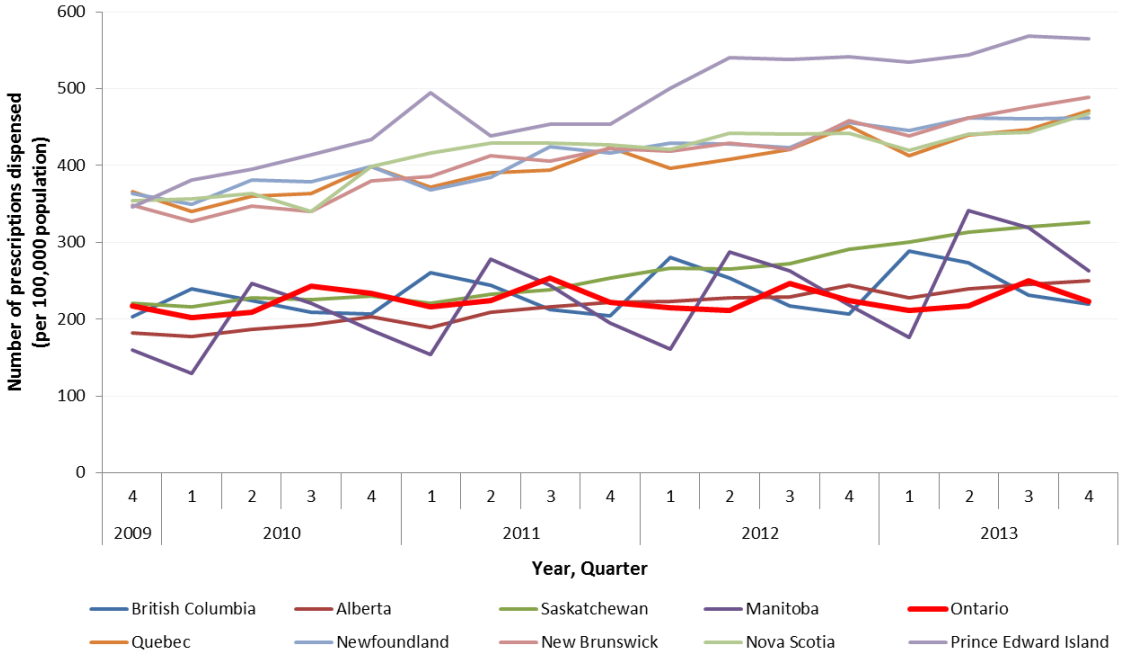


Exhibit 4: Population-adjusted utilization of non-provincially funded LAMA products in Canada, by province



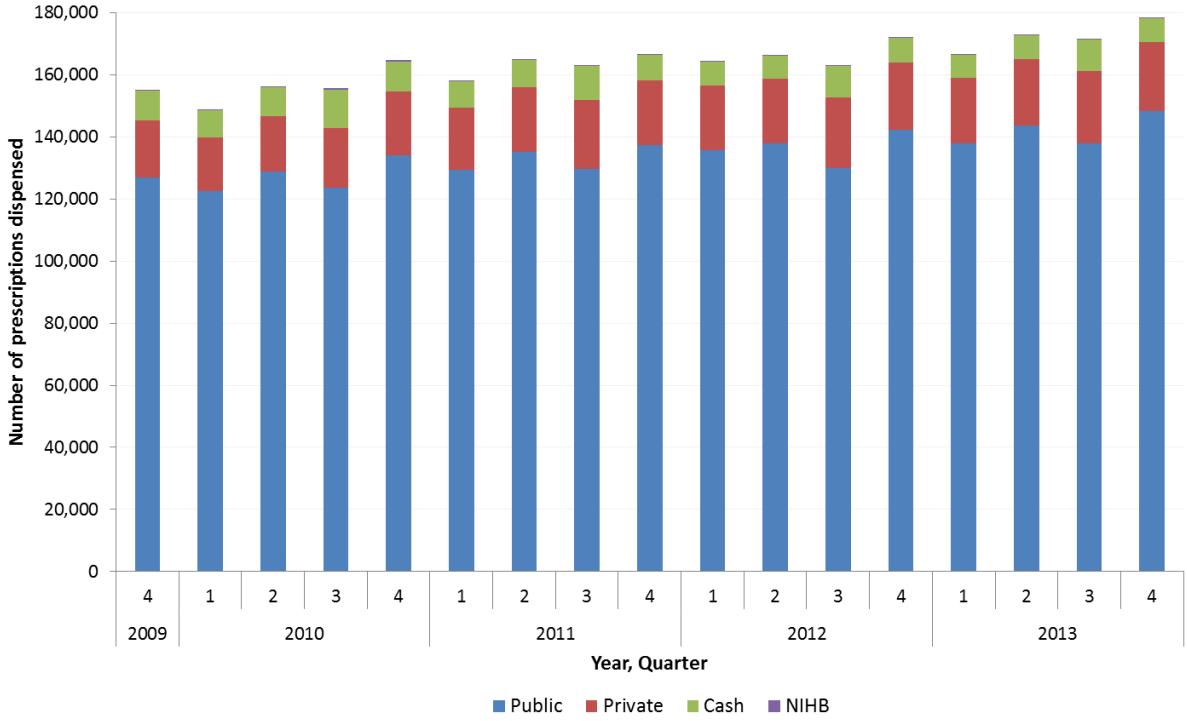
Ontario has the third highest utilization of provincially funded LAMA products in Canada and one of the lowest utilization rates of non-provincially funded LAMA products.

Summary of Findings for Exhibit 3 & Exhibit 4

1. There was wide variation in the number of provincially funded LAMA prescriptions dispensed between provinces (range in Q4 2013: 559 [Manitoba] to 6,030 [Quebec] prescriptions per 100,000 eligible population).
2. In Q4 2013, Ontario had the third highest rate of provincially funded LAMA use (4,874 prescriptions per 100,000 eligible population compared to the national average of 3,275 prescriptions per 100,000 eligible population). The high rate of use of LAMA products in Quebec, Alberta and Ontario may reflect unrestricted access to these medications through the public drug program (i.e. listing as general benefit on the provincial formularies).
3. In Q4 2013, Ontario had the second lowest rate of non-provincially funded LAMA use (222 prescriptions per 100,000 eligible population compared to the national average of 373 prescriptions per 100,000 eligible population).
4. Overall, a higher number of prescriptions for non-provincially funded LAMA products were noted among the Maritime provinces and Quebec. In Q4 2013, PEI had the highest rate of non-provincially funded LAMA products (564 prescriptions per eligible population), followed by New Brunswick, Quebec, Nova Scotia, and Newfoundland (488, 471, 467, 461 prescriptions per 100,000 eligible population, respectively). This could reflect restricted access to tiotropium (which is the most commonly prescribed provincially funded LAMA product in Canada) in New Brunswick, Nova Scotia, PEI and Newfoundland.

Trends in Provincially-Funded LAMA Products in Ontario

Exhibit 5: Total utilization of LAMA products in Ontario, by coverage

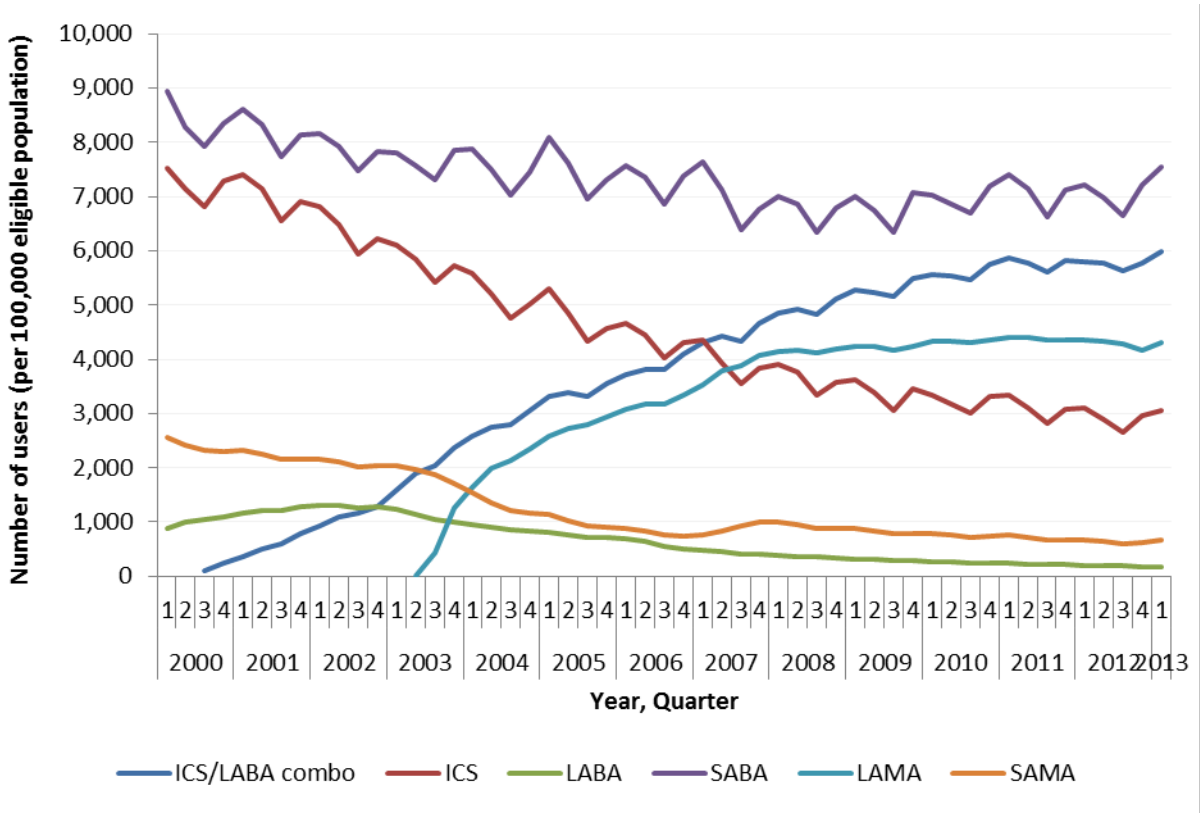


83% of LAMA prescriptions were paid for by the Ontario Public Drug Program in the last quarter of 2013. Only 4.3% of LAMA prescriptions were paid for with cash.

Summary of Findings for Exhibit 5

1. The number of prescriptions dispensed for LAMA products in Ontario has increased 14.9%, from 155,192 prescriptions at the end of 2009 to 178,348 prescriptions at the end of 2013.
2. The vast majority of prescriptions for LAMA products dispensed in Ontario are paid for by provincial drug coverage. This has increased 16.8% over the study period, from 126,958 prescriptions in Q4 2009 to 148,224 in Q4 2013.
3. By Q4 2013, the distribution of payers for LAMA products dispensed in Ontario was 83.1% public, 12.5% private insurance, 4.3% cash, and 0.1% NIHB.

Exhibit 6: Rate of use of inhaled respiratory medications among public drug plan beneficiaries in Ontario

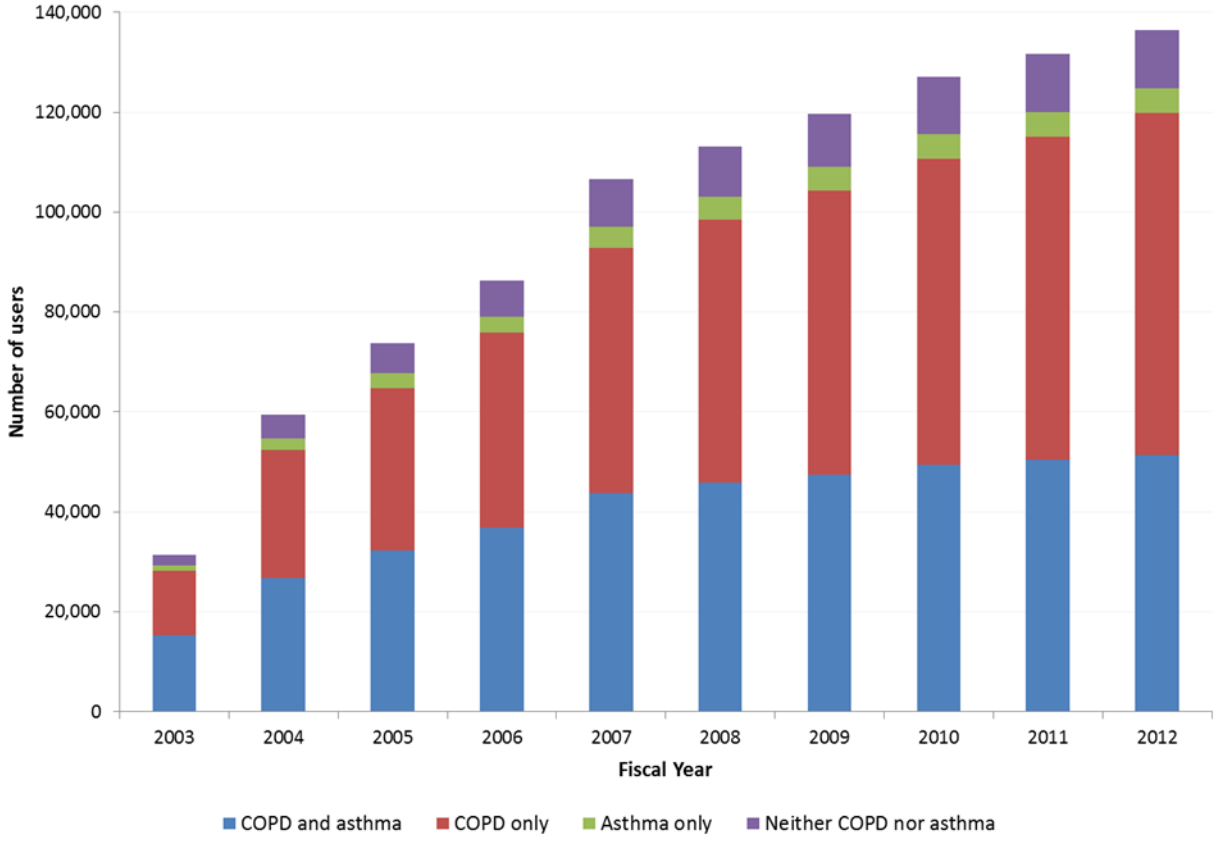


The rate of use of LAMAs and ICS+LABA combination products has increased over time, while use of all other inhaled respiratory medications has declined.

Summary of Findings for Exhibit 6

1. Use of LAMAs increased markedly following their listing on the Ontario public drug formulary in 2003, reaching 4,303 per 100,000 beneficiaries in Q1 2013. Despite the steep uptake, LAMA use has plateaued in Ontario since the last quarter of 2007.
2. There was a corresponding decrease in short-acting anti-muscarinic agents (SAMAs) following the introduction of LAMAs. SAMA use dropped 64.7% between the third quarter of 2003 (189 per 100,000 beneficiaries) and the first quarter of 2013 (663 per 100,000 beneficiaries).
3. The rate of use of ICS+LABA combination products in Ontario also increased over the study period, from 111 per 100,000 beneficiaries in Q3 2000 to 5,993 per 100,000 beneficiaries in Q1 2013.

Exhibit 7: Number of users of provincially-funded LAMA products in Ontario, by patient diagnosis



87.5% of LAMA products are used by individuals with COPD, the majority of whom (57.2%) do not have a co-diagnosis of asthma.

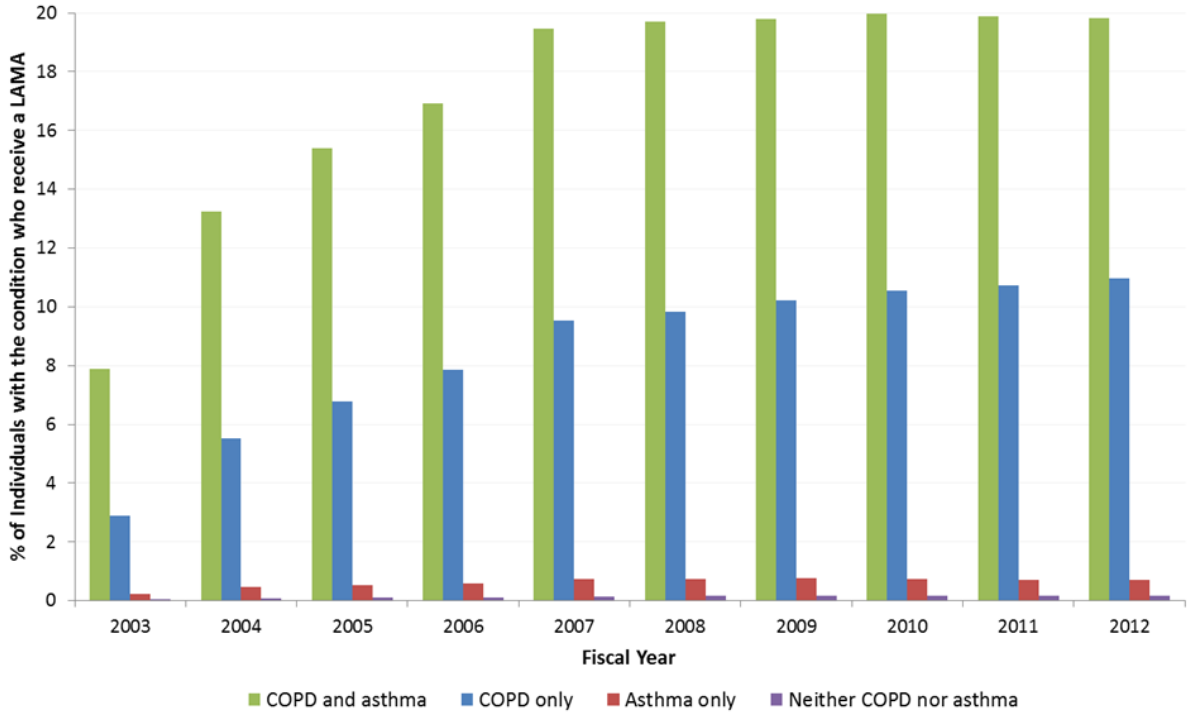
Summary of Findings for Exhibit 7

1. Use of LAMA products among patients with only COPD (i.e. without a concurrent diagnosis of asthma) has increased 5-fold since tiotropium became available in 2003, from 12,927 users in 2003 to 68,615 users in 2012.
2. In fiscal year 2012, 51,255 (37.5%) of LAMA users had both COPD and asthma, 68,615 (50.3%) of LAMA users had only COPD, 4,871 (3.6%) of LAMA users had only asthma, and 11,765 (8.6%) of LAMA users had no indication of COPD or asthma.
3. Among the 11,765 patients treated with LAMAs with no indication of COPD or asthma, 9.4% (N=1,101) had a prior diagnosis of another respiratory disease (e.g. cystic fibrosis).

Methodological Note

Data for glycopyrronium bromide and aclidinium were not captured during this time period.

Exhibit 8: Prevalence of provincially-funded LAMA use among public drug plan beneficiaries in Ontario, by patient diagnosis



Utilization rates of LAMA products are markedly higher among public drug plan beneficiaries with both COPD and asthma than those with other indications. Use of LAMAs is very low among those without COPD diagnoses.

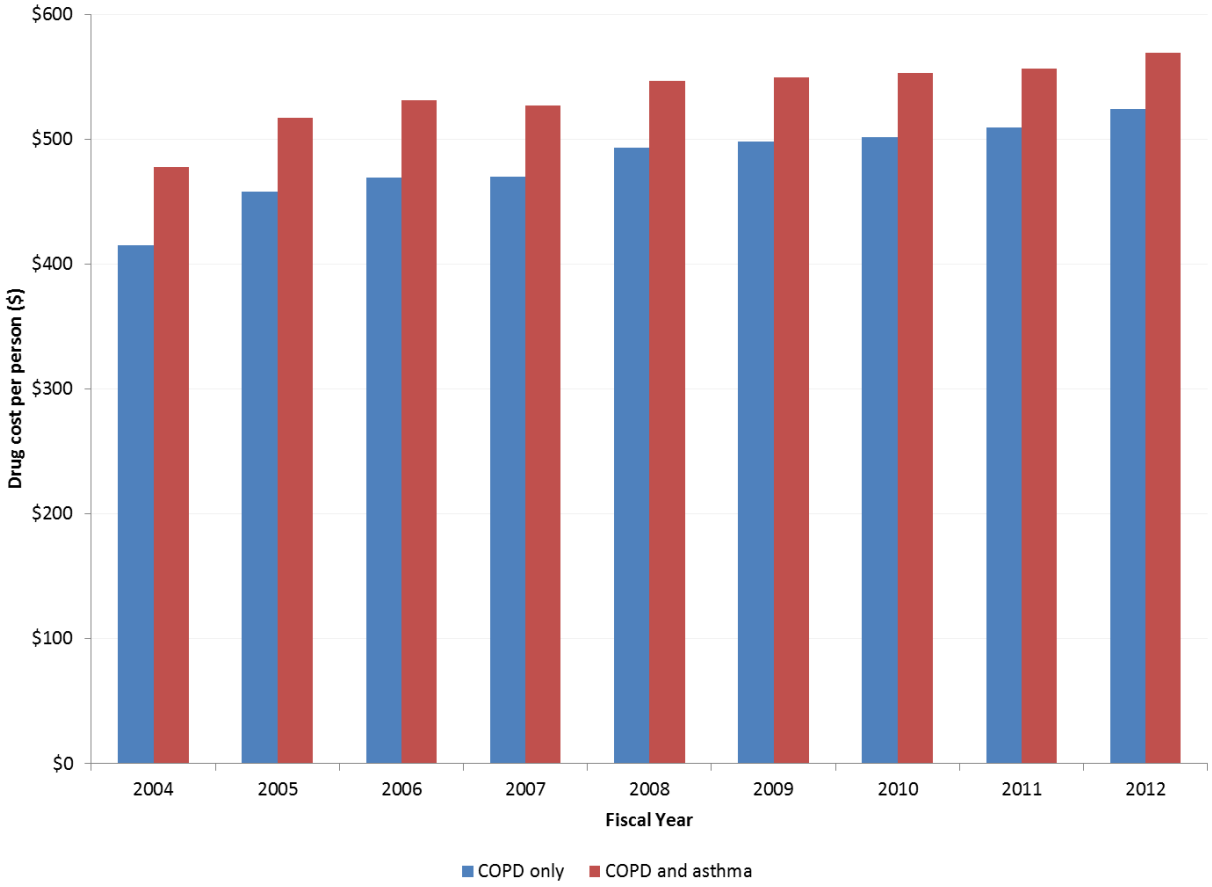
Summary of Findings for Exhibit 8

1. Utilization of LAMA products is highest among patients with both COPD and asthma. The prevalence of LAMA use increased 147% between 2003 and 2007 (from 7.9% to 19.4%) before plateauing at approximately 20% from 2007 to 2012.
2. As expected, prevalence rates of LAMA products are second-highest among patients with COPD only (i.e. among COPD patients without a concurrent diagnosis of asthma). Prevalence of LAMA use among this group has increased nearly 4-fold, from 2.9% in 2003 to 11.0% in 2012.
3. Prevalence of LAMA use is very low among individuals with no history of COPD diagnoses. In 2012, only 0.7% of patients with asthma used a LAMA, and 0.2% of those with no indication of asthma or COPD.

Methodological Note

2003 was the first full year in which tiotropium was available.
Data for glycopyrronium bromide and aclidinium were not captured during this time period.

Exhibit 9: Annual per-person cost of provincially-funded LAMA products among public drug plan beneficiaries with COPD in Ontario, by patient diagnosis



The average annual cost per-person for LAMA therapy is higher among COPD patients with a concurrent diagnosis of asthma compared to patients with COPD only.

Summary of Findings for Exhibit 9

1. In fiscal 2012, the average annual cost per-person of LAMA therapy among patients with COPD was $524 for users with no concurrent asthma diagnosis and $570 for users with COPD and asthma.
2. The average cost of LAMA therapy among patients with COPD has stayed relatively stable since fiscal year 2004, from $415 per person in 2004 to $524 per person in 2012 among patients with COPD only and from $478 per person in 2004 to $570 per person in 2012 among patients with COPD and asthma.

Methodological Note

Data for glycopyrronium bromide and aclidinium were not captured during this time period.

Characteristics of users of provincially-funded LAMA products in Ontario

Exhibit 10: Baseline characteristics of COPD patients treated with provincially-funded LAMA products in Ontario, by age, Fiscal Year 2012/13

	OVERALL	AGE < 65	AGE 65+
Number of COPD patients treated with LAMA products	112,649	19,431	93,218
Number of new LAMA users	27,131 (24.1%)	5,628 (29.0%)	21,503 (23.1%)
Age (Median, IQR)	74.9 (68.2-81.7)	57.3 (52.2-61.4)	77.2 (71.7-83.0)
Males	56,047 (49.8%)	9,174 (47.2%)	46,873 (50.3%)
LTC resident	7,126 (6.3%)	449 (2.3%)	6,677 (7.2%)
Urban residence	92,927 (82.5%)	16,177 (83.3%)	76,750 (82.3%)
Socioeconomic status			
Missing	464 (0.4%)	107 (0.6%)	357 (0.4%)
Q1 (lowest)	30,654 (27.2%)	8,590 (44.2%)	22,064 (23.7%)
Q2	25,004 (22.2%)	4,369 (22.5%)	20,635 (22.1%)
Q3	21,348 (19.0%)	2,844 (14.6%)	18,504 (19.9%)
Q4	19,014 (16.9%)	2,130 (11.0%)	16,884 (18.1%)
Q5 (highest)	16,165 (14.3%)	1,391 (7.2%)	14,774 (15.8%)
History of asthma	48,045 (42.7%)	9,979 (51.4%)	38,066 (40.8%)
COPD severity			
Moderate	67,779 (60.2%)	11,861 (61.0%)	55,918 (60.0%)
Severe	19,607 (17.4%)	4,098 (21.1%)	15,509 (16.6%)
Very severe	25,263 (22.4%)	3,472 (17.9%)	21,791 (23.4%)
COPD maintenance therapy (previous 1 year)	89,949 (79.8%)	16,090 (82.8%)	73,859 (79.2%)
ICS	17,621 (15.6%)	3,812 (19.6%)	13,809 (14.8%)
LABA	2,729 (2.4%)	342 (1.8%)	2,387 (2.6%)
ICS/LABA combo	62,855 (55.8%)	10,526 (54.2%)	52,329 (56.1%)
SABA	7,594 (6.7%)	1,518 (7.8%)	6,076 (6.5%)
SAMA	67,988 (60.4%)	13,847 (71.3%)	54,141 (58.1%)
Theophylline	3,157 (2.8%)	497 (2.6%)	2,660 (2.9%)
Treatment for COPD exacerbations (previous 1 year)[1]	54,524 (48.4%)	9,374 (48.2%)	45,150 (48.4%)
Cost of LAMA prescriptions, per user (Mean, SD)[2]	550.6 ± 299.2	507.2 ± 316.9	559.7 ± 294.5

[1] Defined as any prescription for an oral, short-duration antibiotic or oral steroid [2] Over fiscal year 2012/13

There were 112,649 COPD patients who were treated with provincially-funded LAMA products in Ontario in fiscal 2012, almost one-quarter (24.1%) of whom were new users. These patients tended to be older, have moderate COPD severity, and live in urban areas.

Summary of Findings for Exhibit 10

1. There were 112,649 COPD patients treated with provincially-funded LAMA products in fiscal 2012, 27,131 (24.1%) of whom were new LAMA users.
2. The majority of treated COPD patients were over 65 years of age (N=93,218, 82.8%), had moderate COPD severity (N=67,779, 60.2%), lived in urban areas (N=92,927, 82.5%), were not living in long term care facilities (N=105,523, 93.7%) and had lower socioeconomic status.
3. Older users had more advanced disease (23.4% of those aged 65 and over had very severe COPD, compared to 17.9% among users aged under 65), but were less likely to have been prescribed other COPD therapy prior to initiating LAMA therapy (79.2% vs. 82.8%, older vs. younger users).
4. The majority of LAMA product use was among individuals with moderate COPD severity (60.2%). Less than a quarter of users of these products had very severe COPD (N=25,263; 22.4%).
5. About half of all COPD patients using LAMA products were treated for a COPD exacerbation in the previous year (N=54,527, 48.4%).
6. Concurrent diagnosis with asthma was more common among those aged under 65 (51.4%; N=9,979) compared to those aged 65 and older (40.8%; N=38,066).

Patterns of COPD therapy use and discontinuation

Exhibit 11: Time to discontinuation of provincially-funded LAMA products in Ontario, among individuals aged 66 and older, by therapy type, April 2008 – March 2013

ICS+LABA	Received Only 1 Prescription %	Median time to discontinuation*
Single Therapy	40-50%	3-6 months
Dual Therapy	0%**	6-9 months
ICS + LAMA	0%**	6-9 months
LABA+LAMA	0%**	6-9 months
Triple Therapy	0%**	9-12 months

*Among those prescribed >1 prescription

**Note: >1 prescription required as definition of continuous use in definition for dual and triple therapy

In general, individuals treated with LAMA triple therapy products adhere to therapy for longer than those treated with LAMA dual and single therapy.

Summary of Findings for Exhibit 11:

1. Just over half of COPD patients who were new users of a LAMA, between April 2008 and March 2013, were treated with only a LAMA product; less than 10% were treated with concurrent single-agent ICS or LABA products ("dual therapy"); and slightly less than 40% were treated with a LAMA in addition to both ICS and LABA products (either as single-agents or ICS+LABA combination therapy; "triple therapy").
2. Over one-third of COPD patients treated with dual therapy were using ICS with LAMA products compared to LABA with LAMA products.
3. Almost half of COPD patients initiating single LAMA therapy received only one prescription before discontinuing therapy.
4. Among patients with more than one LAMA prescription, adherence to triple therapy was higher compared to dual therapy and single therapy ($p<0.0001$). Among the dual therapy users, patients were more adherent to LABA+LAMA therapy compared to ICS+LAMA therapy ($p=0.0002$).
5. Along with higher adherence, triple therapy users had more severe disease compared to dual and single therapy users (20-30%. 20-30% and 10-20% with very severe COPD, respectively).
6. Concomitant use of COPD drugs over the course of therapy was lowest among single therapy users (50-60%) compared to dual and triple LAMA therapy users (70-80% and 70-80% respectively). Use of concomitant COPD therapy was higher among ICS+LAMA dual therapy users (80-90%) compared to those treated with LABA+LAMA dual therapy (60-70%). The most common concomitant therapy was short-acting beta agonists.
7. Just over half of patients initiating single therapy had no prior COPD therapy in the past 1 year. This was lower among those initiating dual therapy and triple therapy.

Key Findings

National and Provincial Trends in LAMA Prescribing

Long-acting muscarinic antagonist (LAMA) products are the fourth most commonly prescribed inhaled respiratory medications in Canada (following SABA, ICS/LABA combination and ICS products), with 536,148 prescriptions dispensed in the fourth quarter of 2013. The use of LAMAs has increased in Canada by 26.5% from Q4 2009 to Q4 2013, amounting to a total cost of $47.9 million in the last quarter of 2013. Nearly all of the prescriptions for LAMA products dispensed in Canada were for tiotropium (97.4% in Q4 2013). Glycopyrronium bromide was added to the Canadian market in January 2013 and comprised only 2.5% of the market share at the end of 2013. Aclidinium was only added to the Canadian market in September 2013 and comprised only 0.1% of the market share at the end of 2013. All the LAMA products captured are only indicated for the treatment of COPD.

Ontario has the third-highest utilization rate of provincially funded LAMA products (4,874 prescriptions dispensed per 100,000 eligible population vs. national average of 3,275 prescriptions per 100,000 eligible population in Q4 2013). In contrast, use of LAMA products paid for by non-provincial means (i.e. private insurance, cash payments, Non-Insured Health Benefits) was below the national average (222 prescriptions per 100,000 eligible population in Ontario; national average of 373 prescriptions per 100,000 eligible population, Q4 2013). This likely reflects the broad coverage of these products on the Ontario provincial drug formulary (i.e. listing as general benefit for tiotropium and glycopyrronium bromide), which suggests that there are no considerable access issues.

Use of LAMA Products in Ontario

The majority of LAMA products dispensed in Ontario are paid for through the Ontario Public Drug Program (OPDP). In the last quarter of 2013, 83.1% of prescriptions were paid for through provincial drug coverage, 12.5% through private health insurance, 4.3% cash payments, and <1% through Non-Insured Health Benefits.

The majority of LAMA users in Ontario had COPD; in fiscal 2012, 50.3% of LAMA users had only COPD (without a concurrent diagnosis of asthma) and 37.5% had both COPD and asthma. Despite the fact that LAMA products are indicated for the treatment of COPD only, 3.6% of patients who received a LAMA product had a diagnosis of asthma only (with no co-diagnosis of COPD) and almost 10% of patients did not appear to have a diagnosis for asthma or COPD. Among the patients prescribed LAMA products with no diagnosis of COPD or asthma, 9.4% (N=1,101) had indication of prior respiratory disease (e.g. cystic fibrosis). Diagnoses of COPD and asthma relied on validated administrative databases, with high sensitivity and specificity. However, misclassification is possible and some of the individuals with no indication of COPD or asthma may in fact have minor disease that has not yet been identified in the administrative data.

Characteristics of LAMA users in Ontario

In fiscal year 2012, there were 136,506 users of provincially-funded LAMA products. Of these, the majority (112,649; 82.5%) had a diagnosis of COPD, and almost one-quarter (27,131; 24.1%) were new users of LAMA products. In general, COPD patients receiving provincially-funded LAMA products tended to be over 65 years of age, have moderate COPD severity, and live in urban locations. Older users tended to have more advanced disease (23.4% of those aged 65 and over had very severe COPD, compared to 17.9% among users aged under 65), but were less likely to have been prescribed other COPD therapy prior to initiating LAMA therapy (79.2% vs. 82.8% among younger users). Prevalence of concurrent asthma diagnosis was higher among younger patients (51.4% younger than 64) compared to older patients (40.8% aged 65 and older).

LAMA Patterns of Use and Discontinuation, for COPD, in Ontario

Among the new users of provincially-funded LAMA products aged 66 and older in Ontario, between April 2008 and March 2013, the majority were treated with single therapy followed by triple therapy and dual therapy. Almost half of COPD patients initiating single therapy received only one prescription for a LAMA before discontinuing therapy. Among the patients who had more than one prescription for LAMA, adherence to therapy was highest among those prescribed triple therapy compared to dual therapy and single therapy ($p<0.0001$). Along with being more adherent to LAMA therapy, triple therapy users also had more severe disease compared to dual and single therapy users. Single therapy users were less likely to have used other COPD therapies prior to starting LAMA therapy and less likely to have concomitant COPD therapy during their course of LAMA treatment compared to dual and triple therapy users.

Among dual therapy users, over one-third of COPD patients were using ICS with LAMA dual therapy compared to LABA with LAMA dual therapy. Dual therapy users receiving LABA with LAMA therapy were more adherent to therapy compared to ICS with LAMA users ($p=0.0002$) and were less likely to be using concomitant COPD therapy. While COPD severity was the same between dual therapy groups, ICS+LAMA dual therapy users were more likely to have a history of asthma compared to LABA+LAMA dual therapy users. This is expected since ICS is used in the treatment of asthma.

Cyclic Trends

We observed seasonality for SABA and ICS products across Canada, with the total number of prescriptions being lowest in the third quarter of the year and highest in the fourth quarter of the year. We observed a major cyclic trend in rates of provincially-funded use of LAMA products in British Columbia, with rates being lowest in the first quarter of the year and highest at the end of the year. A similar trend exists in Manitoba, with rates being highest in the first quarter of the year. British Columbia and Manitoba have more expanded public drug coverage among the younger population through their PharmaCare programs, and therefore it is likely that this phenomenon is being driven by patterns of deductible payments and associated stockpiling of drugs near the end of the coverage period (calendar year [January – December] in British Columbia, and fiscal year [April – March] in Manitoba). Smaller cyclic trends were observed in other provinces, which may reflect seasonal influences on COPD management.

Health Equity

Stratified analyses suggest that there isn't a major equity issue in access to these medications by age. Overall, LAMA utilization was higher among older patients, which aligns with the higher prevalence of COPD among seniors. Given the broad listing of these agents on the Ontario public drug formulary, rates of use of LAMAs in the Ontario population eligible for drug coverage are among the highest in Canada suggesting no considerably access issues.

Limitations

Data Availability

Several limitations to 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[12]) 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. Data on the number of individuals eligible for public drug coverage was estimated based on prescription trends (where available) and public annual reports. 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.
4. Diagnoses of COPD and asthma rely on administrative databases. Although these databases have been validated, and have high sensitivity and specificity, some misclassification of diagnoses is possible. In particular, some of the individuals treated with LAMA products with no indication of COPD or asthma may in fact have minor disease that has not yet been picked up in

the administrative data.

5. Our definition of COPD severity is limited to the information available through administrative data holdings, which does not include clinical measures such as forced expiratory volume (FEV). However, the definition was developed based on consultation with clinical experts to attempt to approximate the severity measures reported in the GOLD guidelines. It incorporates a variety of measures such as exacerbations, emergency department visits, hospitalizations, oxygen therapy and lung reduction procedures in an attempt to obtain as close an approximation to true severity as possible with the data available.

Generalizability

1. All analyses using IMS Geographic Prescription Monitor (GPM[12]) data reflect medication use among the entire population, however we are unable to stratify these analyses by indication for therapy.
2. Analyses of prescribing trends conducted among public drug beneficiaries were restricted to those aged 35 and older, and therefore are only generalizable to this adult population.
3. Due to incomplete data on public drug plan eligibility in Ontario among those aged less than 65 years, we restricted our analysis of drug adherence among new users of LAMA products to patients aged 66 and older. Therefore, these findings may not be generalizable to the younger population of LAMA users.

Adherence

All data used in these analyses are based on dispensing patterns, and therefore we do not know whether people took the medications. This is particularly questionable among the population of individuals who only received one prescription for a LAMA product. It is possible that they never tried the medication, or tried it and did not finish their initial course of therapy.

Review of the Observational Literature (LAMAs)

The safety and efficacy of LAMA combination products 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 LAMAs and other COPD therapies. A review of the observational literature comparing LAMAs to other available therapies will help provide real-world estimates of safety and effectiveness of these products.

Objectives

We conducted a rapid review of the observational literature to investigate the comparative safety and effectiveness of LAMA products compared to other COPD drug therapies. Because tiotropium was the only LAMA available until 2013, all studies focused on comparisons between tiotropium and other drug therapies.

Methods

Search Strategy

We performed a Medline search for all literature published between 1996 and January 2014. Search terms included are listed in Appendix B. Overall, 526 abstracts were reviewed, and potentially relevant articles were obtained in full text. Two additional studies submitted through Evidence Submission Packages were also considered for inclusion in the review.

Inclusion Criteria:

- English Language
- Published between 1996 and January 2014
- COPD patient population
- Safety or Effectiveness outcome reported
- Comparison between LAMA and other COPD drug therapy

Overall 13 studies were included in the final review. See Appendix A for a summary of all included studies.

Results

Tiotropium vs. Short-Acting Anticholinergics

We identified three observational studies that compared the effectiveness or safety between tiotropium and short-acting anticholinergics.[6-8] Outcomes investigated in these studies included COPD exacerbation/hospitalization and acute urinary retention.

COPD Exacerbations/Hospitalizations

Two propensity-matched cohort studies compared rates of COPD exacerbations/hospitalizations

between tiotropium and ipratropium.[6;7] The first was a propensity-matched cohort study funded by Boehringer Ingelheim and conducted in the United Kingdom, which included 633 patients treated with combined ipratropium/salbutamol and 1,222 matched patients treated with tiotropium.[6] All patients were followed forward up to 12 months to compare rates of COPD exacerbations (defined as addition of oral steroids or short-term antibiotics to the patient's study medication for either a lower respiratory tract infection or COPD) and COPD-related referrals/hospitalizations. On average, included patients were 69 years old, 57% were male, and 88% had a concurrent diagnosis of asthma. Following propensity score matching, patients in both groups were similar on a variety of characteristics including age, gender, smoking status, and BMI. This study found significantly reduced incidence of exacerbations among users of tiotropium (13.2%) vs. ipratropium/salbutamol (17.9%; relative risk [RR], 95% confidence interval [CI] 0.74, 0.64 to 0.85). Similarly, users of tiotropium had lower risk of COPD-related referrals/ hospitalizations (RR, 95% CI 0.57, 0.46 to 0.70). Two key limitations of this analysis are the requirement for patients to be adherent on therapy for the entire 12 month follow-up and the high degree of asthma co-diagnosis which may limit the generalizability of these findings. The second study compared patients initiating tiotropium and ipratropium in a high-dimensional propensity matched cohort study in British Columbia, Canada.[7] The authors identified all individuals initiating one of these products within 30 days of a COPD-related hospitalization, and followed them forward for 6 months to assess risk of COPD-related hospital readmission. A total of 992 tiotropium users and 2731 ipratropium were identified. On average, patients were 73 years old and 49% were men. Among 750 tiotropium users who were matched to an equal number of ipratropium users, the authors found no significant difference in the risk of hospital readmission (HR, 95% CI 0.98, 0.72-1.34).

Acute Urinary Retention

One nested case-control study investigated the risk of acute urinary retention among new users of inhaled anticholinergic medications (overall, and stratified by tiotropium, short-acting anticholinergics (SAACs), or combination tiotropium/SAAC).[8] Among a large population of patients with COPD in Ontario, Canada, the authors identified 11,238 cases of acute urinary retention and 55,885 matched controls with COPD. In the primary analysis, the authors found that men recently initiating an inhaled anticholinergic had a 42% increased risk of acute urinary retention compared to non-users (odds ratio [OR], 95% CI 1.42, 1.20 to 1.68). No significant association was observed among women. In a secondary analysis, the authors conducted a case-control study among men newly treated with tiotropium, SAACs, or both in the past 30 days. This analysis found no significant difference in the risk of acute urinary retention between men initiating tiotropium vs. SAACs (odds ratio [OR], 95% CI 0.89, 0.63 to 1.27). However, men initiating a combination of tiotropium and SAACs had a slightly increased risk of developing this outcome compared to those initiating SAACs alone (OR, 95% CI 1.84, 1.25 to 2.71). The authors suggest that the observed association among users of combination products may suggest a dose-response relationship; however this is not explored further in this study.

Key Findings

The evidence from 3 observational studies comparing tiotropium to short-acting anticholinergics suggest that tiotropium use may be associated with decreased risk of COPD exacerbations and related hospitalizations compared to combination ipratropium/salbutamol users, however there does not appear to be a reduction in hospital readmissions associated with tiotropium use following a hospitalization (compared to ipratropium). Although an association between inhaled anticholinergic use and acute urinary retention was observed in men, this risk did not appear to differ between long-acting and short-acting formulations of these products.

Tiotropium vs. Long-Acting Beta Agonists (LABAs)

We identified 4 observational studies that compared the risks of all-cause mortality, cardiovascular events, and COPD exacerbations/hospitalizations between users of tiotropium and long-acting beta-agonists (LABAs).[9-12]

All-Cause Mortality

Three cohort studies compared survival between tiotropium and LABAs. The first, a cohort study conducted by Gershon et al. in Ontario, Canada, included 3,018 individuals newly treated with tiotropium and 4,200 newly treated with a LABA following a COPD-related hospitalization.[10] The study found that patients treated with tiotropium were less likely to die over a 180 day follow-up period compared to LABA users (HR, 95% CI 0.80, 0.70 to 0.93). This was consistent in an analysis of those treated with tiotropium and inhaled corticosteroids (ICS) compared to those treated with LABA and ICS (HR, 95% CI 0.75, 0.63 to 0.90). A key limitation of this study is that patients differed at baseline for a variety of potentially important confounders (Charlson comorbidity score, socioeconomic status, previous lung volume reduction surgery). Although the authors adjusted for these variables in regression analyses, this lack of balance suggests that there could be residual, unmeasured confounding that could influence the findings. A second study by Gershon et al. attempted to address this limitation by conducting a propensity-matched cohort study among patients initiating tiotropium or LABA in Ontario, Canada.[9] In this study, 15,532 new users of tiotropium were matched to an equal number of new LABA users, and were followed over a 5.5 year follow-up period. In general, both exposure groups were well matched on a variety of measured confounders following propensity score matching. On average, included patients were 77 years old, and 51% were men. The findings of this study suggest that new tiotropium users have a slightly increased risk of death compared to those initiating LABAs (HR, 95% CI 1.14, 1.09 to 1.19). Although ongoing drug use was not required over follow-up in this study, a sensitivity analysis of on-treatment effects had similar results (HR, 95% CI 1.10, 1.04 to 1.17). Finally, a propensity-score adjusted cohort study conducted by Jara et al. in the United Kingdom and funded by Boehringer Ingelheim compared the risk of all-cause mortality among 1,061 new users of tiotropium and 1801 new users of LABAs.[12] Overall, 75% of tiotropium users and 68% of LAMA users had a COPD diagnosis. After adjusting for a propensity score, there was no difference in risk of death among users of tiotropium and LABAs. However, follow-up was short in this study (combined 1216 person-years of follow-up) and only 88 deaths were recorded. Therefore, this study may have been underpowered to

establish a significant finding and is unable to provide evidence of differential risk of death among long-term users of these products.

Key Findings

Although three studies have compared the risk of death between users of tiotropium and LABAs, they have reported inconsistent findings. This is likely due to a variety of factors, including relatively small sample sizes and short duration of follow-up.

COPD Exacerbations/hospitalizations

Two cohort studies compared the risks of COPD exacerbations or hospital visits between tiotropium and LABAs. In the large cohort study by Gershon et al. described earlier[9], the authors compare the risks of hospitalizations and emergency department (ED) visits for COPD. In their primary analysis, this study found that there was a small elevated risk of both COPD-related hospitalizations (HR, 95% CI 1.13, 1.05 to 1.16) and ED visits (HR, 95% CI 1.09, 1.00 to 1.17) among new users of tiotropium compared to LABAs. However, in a sensitivity analysis investigating on-treatment effects, the results were attenuated. A composite of death, hospitalization or ED visit for COPD was only marginally associated with tiotropium use (HR, 95% CI 1.05, 1.01 to 1.10). In contrast, the study by Jara et al.[12] described earlier investigated the outcome of COPD exacerbation and found no significant difference in risk between users of tiotropium and LABAs (HR, 95% CI 1.15, 0.79 to 1.67).

Key Findings

One large cohort study suggests a small elevated risk of COPD-related hospital visits among new users of tiotropium compared to LABAs. A second study also finds a similar risk estimate; however it does not reach statistical significance, which may be due to its small sample size.

Cardiovascular Events

Two studies investigated the risk of cardiovascular events among new users of tiotropium and LABAs. In the study by Jara et al. (described previously)[12], the authors investigated the risk of several cardiac events including angina, atrial fibrillation and flutter, heart failure, myocardial infarction and tachycardia. The authors found no significant difference in risk of any of these outcomes between the two drug therapy groups. In a large nested case-control study conducted by Gershon et al.[11] in Ontario, Canada, the authors identified hospitalizations for acute coronary syndrome, heart failure, ischemic stroke or cardiac arrhythmia among a nest of patients aged 66 years and older with a diagnosis of COPD. In all, 26,628 cases were matched to a control on a variety of factors (including age, sex, duration of COPD, and history of cardiovascular disease). On average, cases and matched controls were 79 years of age and 52% were male. This study found that new users of both tiotropium (OR, 95% CI 1.14, 1.01 to 1.28) and LABAs (OR, 95% CI 1.31, 1.12 to 1.52) were at an increased risk of cardiovascular events compared to patients with COPD treated with neither of these products. However, there was no difference in risk of cardiovascular events between new users of LABAs compared to tiotropium (OR, 95% CI 1.15, 0.95 to 1.38).

Key Findings

Two studies comparing the risk of cardiovascular events found no significantly increased risk of event between users of tiotropium and LABAs.

Tiotropium HandiHaler vs. Respimat Soft Mist Inhaler

We identified only one observational study that compared the use of two formulations of tiotropium: Respimat Soft Mist Inhaler and HandiHaler.[13] The objective of this study was to compare the risks of mortality between these two products. In this cohort study, the authors identified 11,287 patients with COPD who provided 24,522 episodes of tiotropium use. On average, patients included in the study were 68 years of age and 52% were male. The authors found that use of Respimat was associated with an increased risk of death compared to HandiHaler. However, at baseline, individuals treated with Respimat had higher COPD severity which could have influenced these findings, particularly since they are based on a small number of events (496 deaths in 11,973 treatment years).

Key Findings

Although one cohort study reports differences in risk of death between two tiotropium products, the findings may be biased by different population characteristics at baseline. Indeed, a subsequent RCT that investigated this question found no difference in risk of mortality between these products.[14]

Tiotropium vs. ICS/LABA Combination Products

Two cohort studies conducted in the United States, by the same group of authors, compared outcomes between new users of tiotropium and fluticasone-propionate/salmeterol (FSC) combination products.[15;16] Both studies were funded by GlaxoSmithKline.

In the first study, Dalal et al. report the findings of a large cohort study of patients aged 40 and older with COPD initiating FSC or tiotropium.[15] In all, 16,684 new users of FSC and 12,659 new users of tiotropium were included in this study and were followed forward for 3 to 12 months to assess outcomes. On average, new users of FSC were 63 years of age and 45% were male. In comparison, tiotropium users were on average 65 years of age and 54% were male. Furthermore, at baseline the two exposure groups differed for a variety of other factors including prevalence of asthma, past cardiovascular disease, and past healthcare utilization. An adjusted time-to-event analysis found that new users of tiotropium had an elevated risk of ED visits (HR, 95% CI 1.33, 1.17 to 1.51), hospitalizations or ED visits (HR, 95% CI 1.29, 1.17 to 1.41), outpatient visits with oral corticosteroids (HR, 95% CI 1.49, 1.26 to 1.76), and outpatient visits with antibiotics (HR, 95% CI 1.33, 1.17 to 1.51) compared to FSC users. Despite the consistency of findings, this should be interpreted with caution since tiotropium users had higher prevalence of cardiovascular comorbidities and more COPD-related healthcare utilization prior to their index date. Therefore, although the multivariate analysis adjusts for these factors, it is possible that there remains a degree of confounding that may be influencing these results. In a second study conducted in the same population, the authors leverage a propensity-score matched design to attempt to adjust for these differences in patient characteristics at baseline.[16] In this study, 8,135 tiotropium users with at least 12 months of follow-up were matched on propensity score to an

equal number of FSC users with at least 12 months of follow-up for the same outcomes described above. After matching, the groups were similar for a variety of baseline characteristics with the exception of prior COPD-related outpatient visits (p=0.001). In general, the findings of this study were consistent with those of Dalal et al., with tiotropium users having an elevated risk of hospitalizations or ED visits, outpatient visits, outpatient visits with oral corticosteroids and ED visits compared to FSC (exact OR not reported). However, in this analysis, there were no longer significant differences in risks of hospitalization (OR, 95% CI 1.10, 0.94 to 1.28) or outpatient visits with antibiotic (OR, 95% CI 1.14, 0.98 to 1.32).

Key Findings

Two large studies in a US population with COPD suggest that there may be increased risk of healthcare utilization among new users of tiotropium compared to FSC. Although the study by Roberts et al. employs a propensity score methodology that provides more comparable groups, the patient groups remained imbalanced with respect to past COPD-related outpatient visits which could imply differences in COPD severity between groups.[16] No other data relating to COPD severity (e.g. duration of COPD, other COPD therapies used) are reported, and therefore we were unable to determine the extent to which unmeasured confounding may still be influencing these findings.

Tiotropium as Part of Triple Therapy (Tiotropium + ICS + LABA)

Two cohort studies compared the use of tiotropium in combination with ICS and LABAs to either tiotropium alone[17] or to ICS+LABA alone[18]. The outcomes investigated include COPD exacerbation/ hospitalization and all-cause mortality.

Exacerbations/Hospitalizations

Chatterjee et al. conducted a cohort study in the United States, funded by GlaxoSmithKline.[17] In this study, users of tiotropium aged 40 or older who had a COPD diagnosis, history of exacerbations and at least 1 prescription for a SAAC were stratified according to whether they were co-prescribed FSC. In all, 2,481 individuals were categorized as tiotropium-only users and 852 were users of triple therapy (tiotropium + FSC). Patients were followed forward one year to identify COPD exacerbation events, stratified into moderate and severe exacerbations. On average, patients were 66 years of age and 47% were men. In a time-to-event analysis, the authors found that patients treated with triple therapy had a lower risk of exacerbation compared to those treated with tiotropium alone (HR, 95% CI 0.77, 0.64 to 0.93). When stratified by severity of exacerbation, results remained statistically significant for moderate exacerbations only (HR, 95% CI 0.76, 0.65 to 0.95). One limitation discussed by the authors is that they aimed to evaluate sequential COPD management according to GOLD guidelines.[17] Therefore, they excluded individuals with past ICS+LABA combination use. However, over 20,000 patients were excluded with these criteria, suggesting that a large proportion of COPD patients are treated with ICS+LABA prior to ever receiving tiotropium. As a result, the generalizability of these findings to general practice may be limited. Furthermore, the two treatment groups (tiotropium vs. triple therapy) differed among many baseline covariates including age, Charlson comorbidity index, diagnosis of asthma and

measures of COPD severity. Although these variables were adjusted for in a multivariate regression analysis, unmeasured confounding may also be influencing these findings. In a second study by Lee et al, the authors report the findings of a propensity-score adjusted cohort study in a Veteran's Affairs database in the United States.[18] This study compared new users of tiotropium in combination with other medications (ICS + LABA) to patients in a historic cohort prior to the introduction of tiotropium who were newly switched to ICS+LABA. Outcomes measured included COPD exacerbations and COPD hospitalizations with a follow-up of up to 547 days. In all, 3,240 patients initiated a regimen that included tiotropium and 38,850 initiated ICS+LABA alone. The mean age of study patients was 70 years, and almost all (98%) were male. Those initiating tiotropium regimens were more likely to have had COPD exacerbations at baseline and had a higher likelihood of having 2 or more outpatient visits in the past year compared to those initiating ICS+LABA. Overall, patients initiating triple therapy (ICS+LABA+tiotropium) had a significantly lower risk of COPD exacerbations (HR, 95% CI 0.84, 0.73 to 0.97) and hospitalizations (HR, 95% CI 0.78, 0.62 to 0.98) compared to those initiating ICS+LABA. However, when adding ipratropium to triple therapy (i.e. ICS+LABA+tiotropium+ipratropium), there was no longer a difference for either outcome.

Key Findings

In two large cohort studies, patients initiating triple therapy with tiotropium, ICS and LABA had a significantly lower risk of COPD exacerbations compared with those treated with tiotropium alone or ICS+LABA alone despite generally having more cormorbidities at baseline.

All-Cause Mortality

The study conducted by Lee et al. (described above) also investigated the risk of mortality among new users of triple therapy compared with ICS+LABA.[18] This study found that users of triple therapy (ICS+LABA+tiotropium) had a lower risk of mortality (HR, 95% CI 0.60, 0.45 to 0.79) compared to ICS+LABA.

Key Findings

Evidence from one cohort study suggests that users of tiotropium in combination with ICS and LABA may be at lower risk of death compared with those treated with ICS and LABA alone, although this finding needs to be confirmed in additional studies.

Tiotropium Adherence

We identified one cohort study funded by GlaxoSmithKline and conducted in Quebec, Canada, that investigated adherence to tiotropium therapy (either alone or in combination with FSC) and assessed whether higher adherence was associated with reduced COPD exacerbations over a median 22 month follow-up.[19] In all, 23,707 patients with COPD were included in the study, who contributed 35,385 periods of observation: 24,237 for tiotropium monotherapy and 11,148 for triple therapy (TIO + FSC). Included patients were on average 73 years old, and 47% were male. Adherence to therapy was measured in two ways. First, compliance was assessed using a medication possession ratio (MPR). A patient was defined to be compliant if they had an MPR ≥ 80%. Second, persistent patients were

defined as those with no gap exceeding 30 days between consecutive prescriptions over follow-up. Overall, among new users of tiotropium, compliance and persistence to therapy were 61.1% and 47.6%, respectively. Similarly, compliance and persistence to triple therapy (tiotropium + FSC) was 62.9% and 45.3%. Among those treated with tiotropium alone, compliance to therapy was associated with reduced risks of moderate (OR, 95% CI 0.57, 0.53 to 0.61) and severe (OR, 95% CI 0.77, 0.72 to 0.83) exacerbations. Results were consistent among users of triple therapy and when stratifying patients based on persistence on therapy.

Key Findings

Overall, adherence to tiotropium (both when used alone and in combination with FSC) is moderate, with approximately two-thirds of patients being compliant to therapy over a mean 22 months follow-up. Furthermore, this study suggests that adherence to tiotropium therapy is associated with reduced risks of COPD exacerbations.

Conclusions

Although several observational studies have assessed the benefits and risks of tiotropium (either alone or in combination with ICS+LABA), the results are inconsistent for many outcomes. This may be influenced by difficulties in balancing baseline characteristics between patient groups in observational studies, particularly as it relates to COPD severity.

COPD Exacerbations

Overall, limited evidence suggests that tiotropium use may be associated with decreased risk of COPD exacerbations compared to users of combination ipratropium+salbutamol. Similarly, a small number of studies suggest that triple therapy (tiotropium + ICS + LABA) is associated with decreased exacerbations compared with ICS+LABA alone or tiotropium alone. However, studies comparing tiotropium to LABAs and FSC suggest that there may be a small but significantly increased risk of COPD exacerbations among tiotropium users. This evidence is not consistent and many of the studies suffer from the potential to have unmeasured confounders influence the findings.

Mortality

Studies investigating the risks of mortality among tiotropium users are largely inconsistent. Among three studies comparing tiotropium to LABAs, results differed in each of the studies, however the largest study with the longest follow-up suggested that there may be a small elevated risk of mortality among tiotropium users compared to LABA users. Further, a study comparing two different tiotropium devices concluded that Respimat may have an elevated risk of death compared to Handihaler, however these findings have been questioned in a recent RCT which found no significant difference for mortality outcomes between these devices.[14] Finally, results from one, large study among users of triple therapy suggests that triple therapy may be associated with reduced risks of mortality compared to users of ICS+LABA.

Safety Outcomes

There does not appear to be any evidence that use of tiotropium leads to increased risks of cardiovascular disease compared with LABA users. Although use of both SAACs and tiotropium may lead to increased risk of acute urinary retention in men, there does not appear to be an increased risk of this outcome among tiotropium users compared to SAAC users.

Adherence

Results from one study suggest that adherence to tiotropium therapy over almost 2 years is moderate (approximately 60%), and that improved adherence to therapy is associated with reduced risks of moderate and severe COPD exacerbations.

Appendix A: Summary of Included Studies

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Tiotropium vs. Short-Acting Anticholinergics						
Griffin et al.[6]	Propensity matched cohort study	United Kingdom 1,222 TIO 633 iptratropium/ salbutamol (I/S)	TIO vs I/S	COPD exacerbation COPD hospital referral	• Tiotropium use associated with reduced risk of COPD exacerbations and COPD-related referrals/hospitalizations compared to users of ipratropium/salbutamol.	• Industry funded • Patients required to be compliant on therapy for 12 month follow-up. Therefore, generalizability to individuals with less use unknown • High degree of co-diagnosis of asthma (>85%) • No COPD severity/lung function data
Kawasumi et al.[7]	High dimensional propensity score matched cohort study	Canada 750 TIO 750 Ipratropium	TIO vs. Ipratropium within 30 days of a hospitalization for COPD	COPD hospital readmission	• No significant difference in risk of hospital readmission between treatment groups was observed over a 6 month follow-up period.	• No COPD severity/lung function

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Stephenson et al.[8]	Nested case-control study	Canada 347 cases 936 controls Men only	TIO vs. short-acting anticholinergics (SAAC) vs. combination (TIO + SAAC)	Acute urinary retention	• No significant difference in risk of acute urinary retention between men newly starting tiotropium vs. SAAC • Men starting combination tiotropium + SAAC had increased risk of acute urinary retention vs. those initiating SAAC alone.	• Combination users likely to have higher overall dose of drug suggesting this could be influenced by dose-response relationship • No lung function or smoking status

Tiotropium vs. LABA						
Gershon et al.[9]	Propensity matched cohort study	Canada 15,532 TIO 15,532 LABA	TIO vs LABA (note – continuous use not required)	All-cause mortality Hospitalizations and ED visits for COPD	• Patients initiated on tiotropium were more likely to die over the 5.5 year follow-up period compared to those initiated on LABA • Rates of hospitalizations and ED visits were also higher among those treated with tiotropium vs. LABA • In sensitivity analysis of on-treatment effects, tiotropium users still at increased risk of death and hospitalization for COPD compared to LABA, however no difference in other outcomes	• No lung function or COPD severity data available • Primary analysis intention-to-treat – therefore may not be persistent on therapy. Findings could be influenced if people with more severe COPD are initiated on TIO vs LABA.

Gershon et al.[10]	Cohort study	Canada 3,018 TIO 4,200 LABA	TIO vs LABA within 90 days of hospital discharge related to COPD	All-cause mortality	• Patients treated with tiotropium were less likely to die over a 180 day follow-up compared to LABA users. • Patients treated with tiotropium + inhaled corticosteroid (ICS) were less likely to die compared to LABA + ICS users. • Results consistent in analysis with 1 year follow-up	• Patients differ at baseline for a variety of confounders • These are adjusted for in regression analysis, but unmeasured confounding may bias findings.
Gershon et al.[11]	Nested Case-Control study	Canada 26,628 cases 26,628 controls	TIO vs LABA vs. unexposed	Hospitalizations and ED visits for cardiovascular events	• Newly prescribed tiotropium and LABAs were associated with increased risk of cardiovascular events compared with COPD patients using neither of these products • No significant differences in risks of events were found between tiotropium and LABA users.	• Large, population-based study • Death as a competing risk could impact findings, however death rare in both groups.

Jara et al.[12]	Propensity score controlled cohort study	United Kingdom 1,061 TIO 1,801 LABA	TIO vs. LABA	All-cause mortality COPD exacerbations Cardiovascular events	• No significant differences were observed for any outcome between groups. • The one exception is a decreased risk of asthma exacerbation among tiotropium users.	• Industry funded • Small study • Patients were not required to have COPD • No COPD severity/lung function
Tiotropium Respimat vs. Handihaler						
Verhamme et al.[13]	Cohort study	Netherlands 9,226 TIO Handihaler 2,827 TIO Respimat	Handihaler vs. Respimat	All-cause mortality	• Use of tiotropium Respimat was associated with an increased risk of death compared to Handihaler use, over a mean 155 days treatment duration	• Death rate low overall (496 deaths in 11,973 treatment years) • COPD severity higher at baseline – if Respimat dispensed to those with greater COPD severity, could bias findings

Tiotropium vs. FSC						
Dalal et al.[15]	Cohort study	United States 12,659 TIO 16,684 FSC**	TIO vs. FSC	COPD-related hospitalization and emergency department visits	• New tiotropium users had a higher risk of COPD-related hospital/ED visits compared to new FSC users over 1 year follow-up	• Industry funded • Substantial differences exist between TIO and FSC users at baseline (prevalence of asthma, past cardiovascular disease, past healthcare utilization). This could bias the findings if unmeasured confounding substantial.

Roberts et al.[16]	Cohort study – propensity score matched	United States 8,135 TIO 8,135 FSC	TIO vs. FSC	COPD-related outpatient visits, outpatient visits with antibiotic prescription, outpatient visits with oral corticosteroid (OCS) prescription, hospitalizations and ED visits	• Patients newly treated with tiotropium had a significantly higher risk of COPD-related hospitalization or ED visits, ED visits, outpatient visits with OCS, and overall outpatient visits over 12 months of follow-up	• Industry funded • Uses same cohort as Dalal et al, however employs propensity score methods to adjust for confounders • Imbalance in past outpatient visits remains after propensity matching, and details on COPD severity are limited. Therefore, findings may still be influenced by unmeasured confounding.

Tiotropium vs. Triple Therapy						
Chatterjee et al.[17]	Cohort study	United States 2,481 TIO 852 Triple Therapy*	TIO vs. Triple therapy (TIO + ICS + LABA)	COPD Exacerbation	• Patients initiating triple therapy had a significantly reduced risk of COPD exacerbations compared to those treated with tiotropium-only over 1 year follow-up.	• Industry funded • Study excludes all individuals with past use of ICS+LABA combination products (20,510 patients). Therefore, generalizability of triple therapy findings is questionable.
Lee et al.[18]	Propensity-score adjusted cohort study	United States 3,240 TIO 38,850 ICS+LABA	Triple therapy (TIO + ICS + LABA) vs. ICS+LABA alone	All-cause mortality COPD Exacerbations COPD-related Hospitalization	• Triple therapy (TIO + ICS + LABA) associated with significantly reduced risk of all outcomes compared to ICS+LABA alone • TIO used in combination with 1 or 2 other medications (not including ICS or LABA) associated with increased risk of most outcomes compared to ICS+LABA alone	• Tiotropium availability and restrictions for use in this population differed over time. The authors addressed this methodologically (historic controls), but could still lead to differences in COPD severity between groups and bias due to secular trends.

Therapy Compliance						
Ismaila et al.[19]	Cohort Study	Canada 24,237 TIO 11,148 Triple Therapy*	Compliant vs. Non-Compliant to therapy	Moderate and Severe COPD Exacerbations	• Compliance to therapy similar between TIO and Triple Therapy group (61.6% vs. 62.9%) over median 22 month follow-up. • Compliant (>80% Medication Possession Ratio) TIO and triple therapy users had a significantly lower risk of both moderate and severe COPD exacerbations compared to those who were non-compliant	• Industry funded • Large study • Compliance and persistence definitions rely on assumption that patient took prescriptions • Data may be incomplete due to inability to capture private insurance.

Triple therapy defined as tiotropium + fluticasone propionate + salmeterol

****FSC: fluticasone propionate + salmeterol; TIO: Tiotropium***

Appendix B: Medline Search Strategy

1. exp Pulmonary Disease, Chronic Obstructive/ (25060)
2. tiotropium.mp. (875)
3. aclidinium.mp. (62)
4. Long-acting Muscarinic Antagonists.mp. (19)
5. glycopyrronium.mp. (51)
6. scopolamine derivatives.mp. (809)
7. cholinergic antagonists.mp. (3245)
8. 1 and (2 or 3 or 4 or 5 or 6 or 7) (917)
9. limit 8 to (english and humans) (751)
10. limit 9 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial) (225)
11. 9 not 10 (526)
12. from 11 keep 3,6,33,38,45,47,55,68-69,74-75,90,102,104,107,109-112,117,130-131,140,142,171,173,184,187,219,236,244-245,249,255,266,276,315,338,351,366,386,417 (42)
13. From 12 keep 3, 5, 15, 16, 17, 22, 25, 27, 30, 35, 38, 39, 40
14. From 13 add 2 articles from stakeholder evidence submission

Appendix C: Public Plan Listings for LAMA Products in Canada, by Province

	Tiotropium	Glycopyrronium Bromide	Aclidinium
BC	Res	Res	No
Alberta	Ben	Ben	No
Saskatchewan	Res	Res	No
Manitoba	Res	Res	No
Ontario	Ben	Ben	No
Quebec	Ben	Ben	Ben
New Brunswick	Res	Res	No
Nova Scotia	Res	Res	No
PEI	Res	No	No
Newfoundland	Res	No	No
Yukon	Res	Res	No
NIHB/NT/NU	Res	Res	No

No=not listed

Res=restricted listing - enforced

Pas= restricting listing – passive

Ben=unrestricted listing

BC = British Columbia; NIHB = Non-Insured Health Benefits; NT = Northwest Territories; NU = Nunavut

Appendix D: Definition of COPD Severity

COPD severity was assigned hierarchically as follows:

(1) Very severe – if individual meets criteria for very severe COPD
(2) Severe – if individual meets criteria for severe COPD and is not very severe
(3) Moderate – if individual is not very severe or severe

Very Severe COPD

Patients were classified as having very severe COPD if they met any of the following criteria:

- 1 or more hospitalizations in the previous 2 years with a most responsible diagnosis of a COPD-related respiratory disease; OR
- Use of oral corticosteroids for longer than 180 days in the previous 2 years; OR
- Lung reduction procedure in the previous 5 years; OR
- Currently on oxygen therapy

Severe COPD

Patients were classified as having severe COPD if they met any of the following criteria:

- 2 or more exacerbations in the previous 2 years; OR
- At least 1 unscheduled emergency department visit in the previous 2 years with a most responsible diagnosis of a COPD-related respiratory disease

Moderate COPD

Patients were classified as having severe COPD if they met the following criteria:

- 0-1 exacerbations in the previous 2 years

COPD Exacerbations

Exacerbations were defined as receipt of a prescription for an oral corticosteroid or respiratory antibiotic within 7 days of a physician visit for bronchitis, pneumonia, influenza, emphysema, asthma, or other chronic obstructive pulmonary disease.

References

1. Levy A, O'Brien B, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol* 2003;10:67-71.

2. Gershon A, Wang C, Guan J, Vasilevsk-Ristovsk J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD* 2009;6:388-394.

3. Gershon A, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physican-diagnosed asthma in health administrative databases. *Can Respir J* 2009;16:183-188.

4. Dhalla I, Gomes T, Yao Z et al. Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a population-based cohort study. *Ann Intern Med* 2013;158:447-455.

5. Gomes T, Mamdani M, Holbrook A, Paterson J, Hellings C, Juurlink D. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ* 2013;185:E121-E127.

6. Griffin J, Lee S, Caiado M, Kesten S, Price D. Comparison of tiotropium bromide and combined ipratropium/salbutamol for the treatment of COPD: a UK General Practice Research Database 12-month follow-up study. *Prim Care Respir J* 2008;17:104-110.

7. Kawasumi Y, Paterson MJ, Morrow RL et al. Comparative effectiveness of tiotropium and ipratropium in prevention of hospital readmission for COPD: a population-based cohort study. *Clin Ther* 2013;35:523-531.

8. Stephenson A, Seitz D, Bell CM et al. Inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease: a population-based study. *Arch Intern Med* 2011;171:914-920.

9. Gershon A, Croxford R, To T et al. Comparison of inhaled long-acting beta-agonist and anticholinergic effectiveness in older patients with chronic obstructive pulmonary disease: a cohort study. *Ann Intern Med* 2011;154:583-592.

10. Gershon AS, Wang L, To T, Luo J, Upshur RE. Survival with tiotropium compared to long-acting Beta-2-agonists in Chronic Obstructive Pulmonary Disease. *COPD* 2008;5:229-234.

11. Gershon A, Croxford R, Calzavara A et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. *JAMA Intern Med* 2013;173:1175-1185.

12. Jara M, Lanes SF, Wentworth C, III, May C, Kesten S. Comparative safety of long-acting inhaled

bronchodilators: a cohort study using the UK THIN primary care database. *Drug Saf* 2007;30:1151-1160.

13. Verhamme KM, Afonso A, Romio S, Stricker BC, Brusselle GG, Sturkenboom MC. Use of tiotropium Respimat Soft Mist Inhaler versus HandiHaler and mortality in patients with COPD. *Eur Respir J* 2013;42:606-615.

14. Wise RA, Anzueto A, Cotton D et al. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013;369:1491-1501.

15. Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2011;6:13-22.

16. Roberts MH, Dalal AA. Clinical and economic outcomes in an observational study of COPD maintenance therapies: multivariable regression versus propensity score matching. *Int J Chron Obstruct Pulmon Dis* 2012;7:221-233.

17. Chatterjee A, Shah M, D'Souza AO, Bechtel B, Crater G, Dalal AA. Observational study on the impact of initiating tiotropium alone versus tiotropium with fluticasone propionate/salmeterol combination therapy on outcomes and costs in chronic obstructive pulmonary disease. *Respir Res* 2012;13:15.

18. (18) Lee TA, Wilke C, Joo M et al. Outcomes associated with tiotropium use in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2009;169:1403-1410.

19. Ismaila A, Corriveau D, Vaillancourt J et al. Impact of adherence to treatment with tiotropium and fluticasone propionate/salmeterol in chronic obstructive pulmonary diseases patients. *Curr Med Res Opin* 2014.