

Triptans for Migraine Therapy

A Pharmacoepidemiologic Analysis

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Executive Summary

Overall Trends in Triptan Use

Triptan use in Canada has increased by 13% over the past 4 years. Over 3 million units were dispensed in Canada in the third quarter (Q3) of 2013. In Ontario, the overall rates of triptan use and costs were similar to other provinces (7,480 units and \$86,133 per 100,000 population in Ontario compared to an average of 7,678 units and \$86,588 per 100,000 population across Canada, Q3 2013). However, the Ontario Public Drug Program only paid for 2.8% of all triptan prescriptions dispensed in Ontario, with the majority of triptans being paid for by private drug plans (77.4%) and cash (19.3%). As a result, Ontario has among the lowest rates of publically-funded triptan use in Canada (931 units per 100,000 eligible population in Q3 2013 compared to national average, 5,358 units per 100,000 eligible Canadians), which is balanced by having among the highest rates of triptan use paid by other means (e.g. cash, private insurance; 7,271 units per 100,000 population in Ontario compared to a national average of 6,473 units per 100,000 population across Canada; Q3 2013).

Trends among Public Drug Plan Beneficiaries

Overall, triptan use among older (aged 65+) public drug plan beneficiaries is lower than that of younger (less than 65 years) beneficiaries. Rates of use among older beneficiaries have increased across all provinces studied, whereas rates among younger beneficiaries remained fairly constant over the past 13 years. Although Ontario's rate of publically-funded triptan use was the lowest of all provinces studied, the average quarterly costs per publically-funded triptan user were highest in Ontario (\$511 per user at end of 2012, compared to national average of \$207 per user across Canada) where preferential use of generic forms of brand name agents (where available) is not required by the public drug program.

Market Share of Triptans

The most commonly prescribed, and most costly triptans in Canada (Q3 2013) are rizatriptan (27.1%; \$9.8 million), sumatriptan (23.9%; \$9.1 million), and zolmitriptan (20.9%; \$6.1 million). Use of publically-funded sumatriptan and rizatriptan has increased markedly in Ontario since 2000, with these drugs being the most commonly used publically funded triptans in 2012. At the end of 2012, quarterly costs for these two triptans (sumatriptan and rizatriptan) were \$215,954 and \$135,668, respectively. In contrast to national trends (where zolmitriptan is the third most commonly dispensed triptan), additional requirements for public drug coverage of zolmitriptan has made it the least prevalent publically funded triptan in Ontario.

Triptan Quantities and Medication Overuse

The median number of triptan units dispensed per public drug plan beneficiary varies considerably between provinces, and aligns with differences in quantity limits. In Ontario, where no quantity limits are in place, the median quantity dispensed per person annually (median 60 units, interquartile range 24 to 126 units) was the highest in Canada (range 18 to 36 units across other provinces studied). Furthermore, almost one in five publically-funded triptan users in Ontario received more than 12 units per month, the highest quantity limit in place across the provinces. This surpassed utilization in all other provinces, including Alberta, which does not have quantity limits in place.

Patterns of Triptan Use and Discontinuation

There were 1,090 publically funded triptan users in Ontario in 2012, 281 (25.8%) of which were new users. Triptan users tended to be less than 65 years of age, female, and to live in urban areas. Among older triptan users, (aged 66 and over), the median time to discontinuation of triptans was less than 1

year (333 days), and approximately 1 in 5 individuals only filled 1 prescription. Over 50% of older triptan users were also treated with an opioid during their course of therapy, and approximately 40% were also treated with NSAIDs (although whether these therapies were indicated for migraines is unknown).

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Introduction

Triptans are a class of drugs used to manage episodic migraines in adults. Seven triptans are available in Canada (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan), and coverage of these drugs on public drug formularies differs substantially across provinces. In some provinces, triptans are available as a general benefit (Quebec and British Columbia), while in others access is restricted and quantity limits are in place (Appendix A). In Ontario, 5 triptans are available through the Ontario Public Drug Program (OPDP; almotriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) under the Exceptional Access Program (EAP) with no established quantity limits.

Given the high degree of variation in public drug coverage for triptans across Canada, it is likely that the rate of triptan use, costs and method of payment differ between provinces. The objectives of this report are to describe national and provincial trends in triptan use, along with characteristics and patterns of therapy among publically-funded triptan users in Ontario. Specifically, this report aims to:

1. Present national trends of triptan utilization in Canada, including cross-provincial comparisons of population-adjusted rates of triptan use.
2. Conduct cross-provincial comparisons of rates of publically-funded triptan use, costs and patient characteristics.
3. Compare rates of potential medication overuse between provinces in Canada.
4. Describe triptan use in the Ontario Public Drug Program, including use, costs, and rates of discontinuation.

Data Sources

IMS Compuscript

IMS Compuscript provides sales data for outpatient prescriptions dispensed at retail pharmacies across Canada. Data is obtained from a representative sample of 65% of all Canadian pharmacies and is projected monthly by province. Projections incorporate the number of pharmacies in a given area, the distance between IMS-captured and uncaptured pharmacies, and the size of the uncaptured pharmacy. Projections are representative of provincial and national sales volumes. Data available through IMS Compuscript 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 Compuscript is available from the fourth quarter of 2009 to the third quarter of 2013.

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 generate estimates of prescription and unit volumes, as well as patient-level data (e.g. prevalence of drug use, demographic characteristics) for all provincially-funded prescriptions dispensed in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island.

Data is available from NPDUIS from 2000 to 2012.

Ontario Drug Benefit

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 demographics.¹ We analyzed data from the ODB between January 2000 and August 2013.

Methods

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

National Trends in Triptan Utilization

We used data from IMS Compuscript to examine overall trends in the volume of triptan prescribing at both national and provincial levels. We examined the total number of triptan units dispensed between October 2009 and September 2013, along with their corresponding costs. 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 of prescribing triptan.

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 rates of triptan utilization across the different provinces.

Population Adjustment – Stratified by Payer

For measures examining provincially-funded triptan utilization, 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 individuals (both public drug beneficiaries and non-beneficiaries) may pay for triptans out of pocket, measures of non-provincially-funded triptan utilization were adjusted using overall provincial

population estimates from Statistics Canada.

Cross-Provincial Analyses among Public Drug Plan Beneficiaries

We used data from NPDUIS and ODB to compare trends in triptan prescribing across provinces among individuals eligible for public drug coverage aged 18 and older. We defined the eligible population as those individuals aged 18 or older who were dispensed at least one provincially-funded prescription for any drug in each time period of interest (i.e. quarter or year). We examined the number and rate of public drug plan beneficiaries dispensed triptans in each quarter from January 2000 to December 2012, along with the average triptan costs per user.

We also looked at a cohort of individuals who were eligible for provincial drug coverage in 2012, and examined the prevalence of use of acute migraine therapies (i.e., butorphanol, butalbital-containing analgesics, ergot alkaloids and triptans) over the one-year period. We then performed a subgroup analysis on those individuals who had been prescribed triptans in 2012 where we examined demographic characteristics (age and gender) and prevalence of medication overuse.

One of the major safety considerations with triptans is medication overuse headache. As this measure was unavailable through our data holdings, we developed an approximation based on the quantity of drug dispensed using two methods, namely defined daily doses and quantity limits.

Defined Daily Doses

In the first method, we used defined daily doses (DDD) to calculate the amount of drug being dispensed to each triptan user over the course of the year, as done previously.² The DDD use for each triptan can be found in Appendix B. The International Headache Society defines triptan overuse as 10 or more days of therapy per month³, and the Canadian Headache Society limits triptans to 9 days of therapy per month.⁴ We translated this into annual quantities in order to account for fluctuations in triptan use. We therefore defined overuse as more than 120 DDD per year (International Headache Society guidelines) and more than 108 DDD per year (Canadian Headache Society guidelines). Finally, we used a more relaxed definition of overuse based on a study by Limmroth et al. that identified a critical upper limit of 18 DDD per month (216 DDD per year) before manifestation of medication overuse.⁵ We calculated the proportion of triptan users who exceeded these limits based on their prescribing history in 2012, overall, and stratified by patient age (<65 and 65+).

Quantity Limits

In the second method, we estimated the proportion of triptan users who exceeded a set of pre-defined quantity limits. Because triptans are typically packaged in quantities of 6, we modeled quantity limits of 6, 12 and 18 units per month (or 72, 144, and 216 units, annually). We categorized those patients who exceeded these quantity limits based on their prescribing history in 2012, and estimated the total number of excess triptan units that were dispensed in Ontario that year.

Triptan Use Among Public Drug Plan Beneficiaries in Ontario

We used claims data from ODB to perform additional analyses of triptan users in Ontario. These analyses included estimating the market share and costs of triptans, as well as the number of users of publically funded triptans, and their demographic characteristics.

We established a cohort of new users of triptans between January 2008 and August 2013 to examine the duration of triptan 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 triptan use. We followed each individual forward from the time of their first triptan prescription until they discontinued therapy, died, or reached the end of the study period (August 31, 2013). Triptan discontinuation was defined on the basis of refills for triptans within 180 days of the previous prescription. Users were allowed to switch between triptans in the primary analysis of all triptans; however, in subgroup analyses stratified by triptan type (rizatriptan, sumatriptan, and all others), we censored individuals if they switched between triptan drugs. We generated a Kaplan-Meier curve to determine the median time to discontinuation, and used the log-rank test to test whether adherence to therapy differed between triptans.

Drug Coverage by Province

All provinces provide prescription drug coverage for seniors aged 65 and older. With the exception of Saskatchewan, which provides universal drug coverage, most provinces only provide coverage for special populations under 65. These include, but are not limited to, residents of long-term care facilities, individuals on social assistance, and those with high medication costs relative to household income. A detailed breakdown of prescription drug coverage provided by each province can be found in Appendix C.

Timeline for Generic Triptans

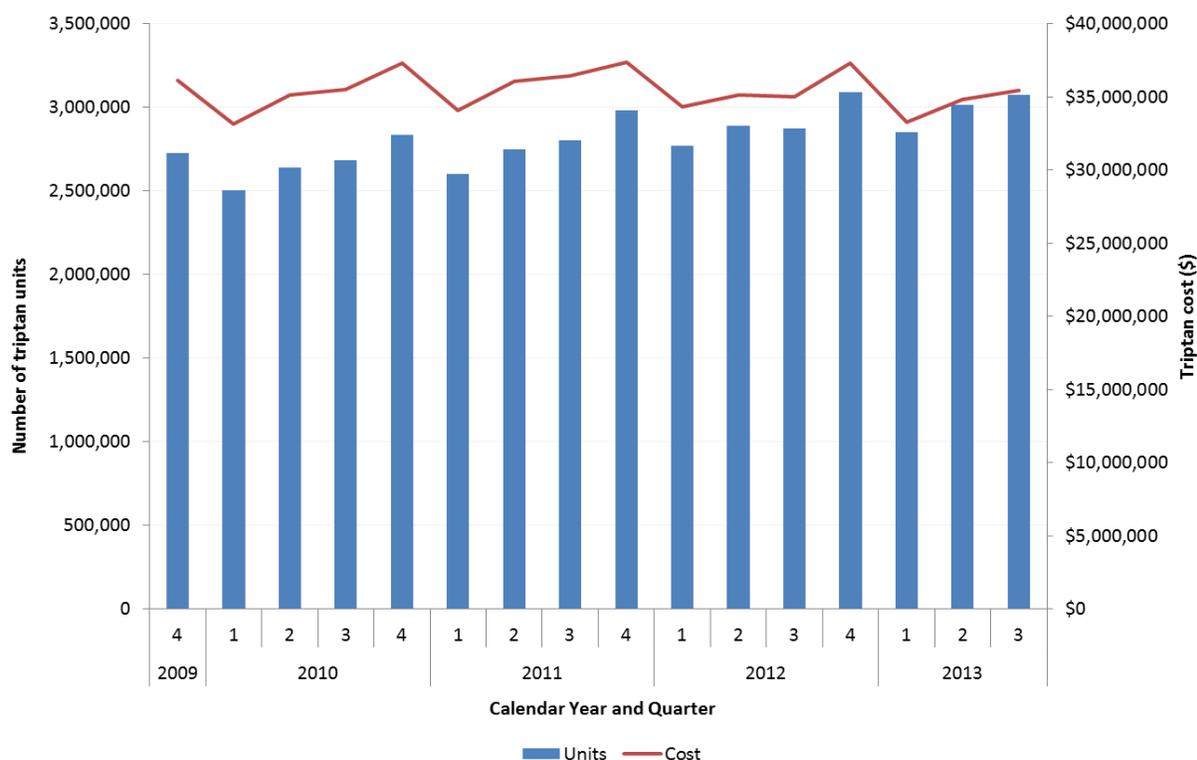
The first generic triptan to become available in Canada was sumatriptan (tablets), which was released on the market in August 2005. Sumatriptan was the only triptan to have a generic formulation available until December 2009, when generic naratriptan was released. Generic formulations of zolmitriptan, rizatriptan, eletriptan and almotriptan became available between June 2011 and July 2013. There are currently no generic formulations of oral frovatriptan available in Canada, or nasal preparations of sumatriptan or zolmitriptan. A detailed breakdown of generic availability is provided in Appendix D.

Exhibits and Findings

National Trends in Triptan Utilization

Volume of Triptan Utilization in Canada

Exhibit 1: Total cost and utilization of triptans in Canada, by quarter



Triptan use has increased slightly over the past 4 years. Over 3 million units were dispensed in Canada in the third quarter of 2013.

Summary of Findings for Exhibit 1

- Triptan utilization in Canada has increased 13% since Q4 2009, from 2.7 million units (Q4 2009) to 3.1 million units (Q3 2013).
- Despite the increase in utilization, triptan costs have remained relatively stable. On average, quarterly triptan costs were \$35 million over the last 4 years.

Exhibit 2: Total utilization of triptans in Canada, by triptan and quarter

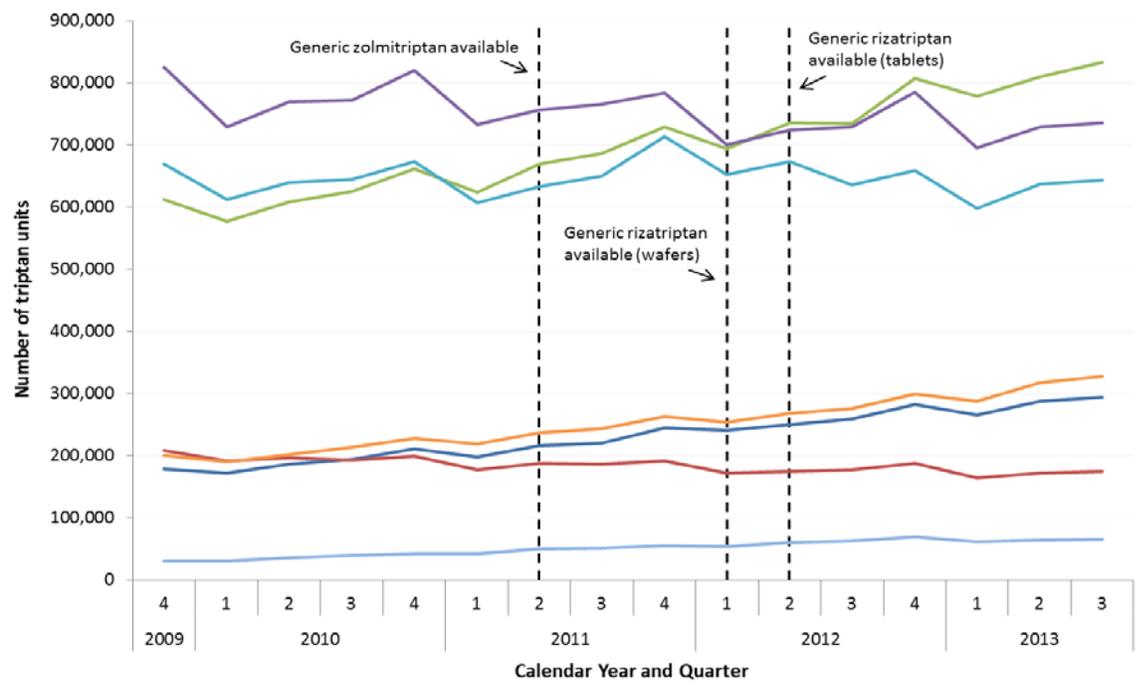
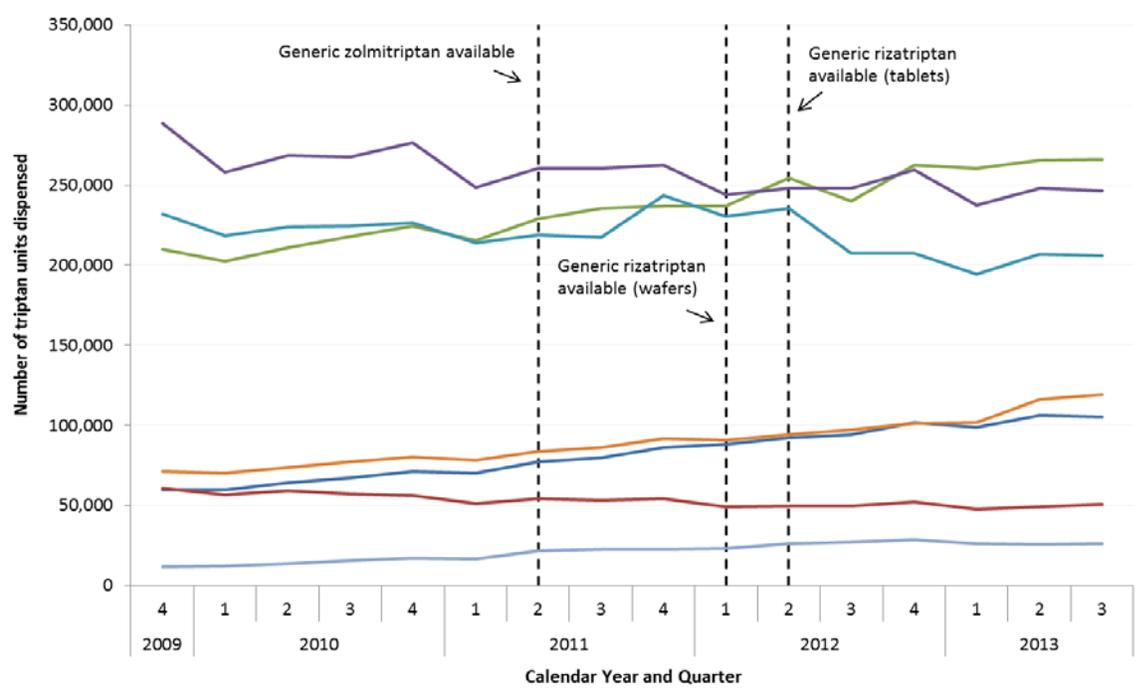
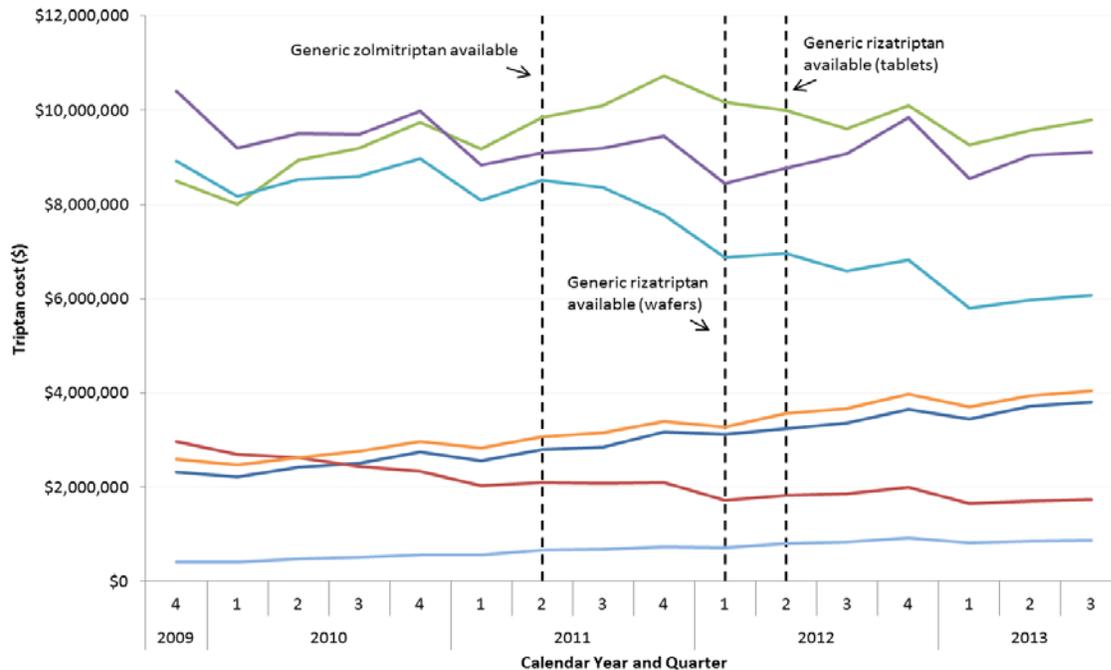


Exhibit 3: Total utilization of triptans in Ontario, by triptan and quarter.



Almotriptan Naratriptan Rizatriptan Sumatriptan Zolmitriptan Eletriptan Frovatriptan

Exhibit 4: Total cost of triptans in Canada, by triptan and quarter



Almotriptan Naratriptan Rizatriptan Sumatriptan Zolmitriptan Eletriptan Frovatriptan

Legend: See Appendix D for details on unit costs of brand name and generic triptans.

Rizatriptan, sumatriptan, and zolmitriptan are the three most commonly prescribed and most costly triptans in Canada and Ontario.

Summary of Findings for Exhibit 2, Exhibit 3, & Exhibit 4

1. Rizatriptan, sumatriptan and zolmitriptan are the most commonly prescribed triptans in Canada and are listed on the public drug formularies across all of the provinces. Frovatriptan is not listed on provincial drug formularies and was the least used triptan over the study period. Patterns of use in Ontario are consistent with national trends.
2. In the third quarter of 2013, rizatriptan had the greatest market share (27.1%; 832,908 units), followed by sumatriptan (23.9%; 736,042 units), zolmitriptan (20.9%; 643,013 units), eletriptan (10.7%; 328,314 units), almotriptan (9.6%; 294,594 units), naratriptan (5.7%; 174,888 units) and frovatriptan (2.1%; 65,859 units).

Impact of Generic Formulations on Utilization and Costs

3. At the beginning of the study period, sumatriptan was the most commonly dispensed triptan in Canada with the highest quarterly costs (825,434 units dispensed at a cost of \$10.4 million in Q4 2009).
4. In Q2 2012, sumatriptan utilization was surpassed by that of rizatriptan. This change aligned with the introduction of generic formulations of rizatriptan tablets and wafers in May 2012 and January 2012, respectively. Rizatriptan use and costs continued to increase to the end of the study period (832,908 units dispensed at a cost of \$9.8 million in Q3 2013). In comparison, in the last quarter of the study period, 736,042 units of sumatriptan were dispensed at a cost of \$9.1 million.
5. While utilization remained consistent, the quarterly costs of zolmitriptan decreased notably following the introduction of the generic formulation in June 2011, from \$8.5 million in Q2 2011 to \$6.1 million in Q3 2013.

NOTE: See Appendix D for details on unit costs of brand name and generic triptans.

Population Adjusted Rates of Triptan Utilization in Canada by Province

Exhibit 5: Population-adjusted utilization of triptans in Canada, by province

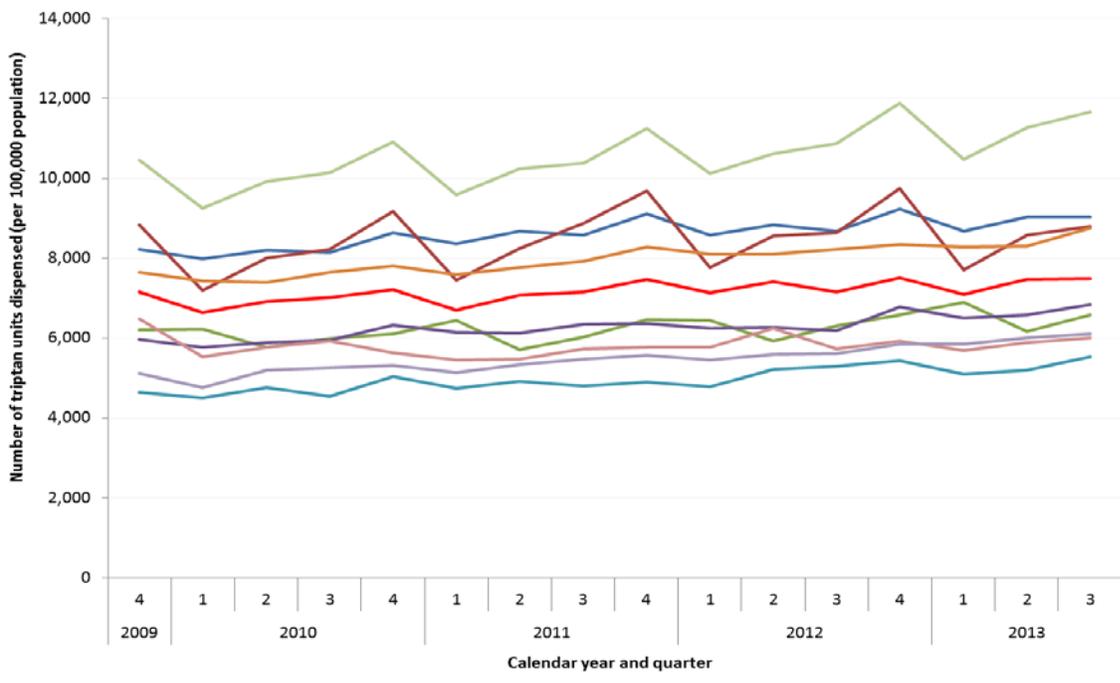
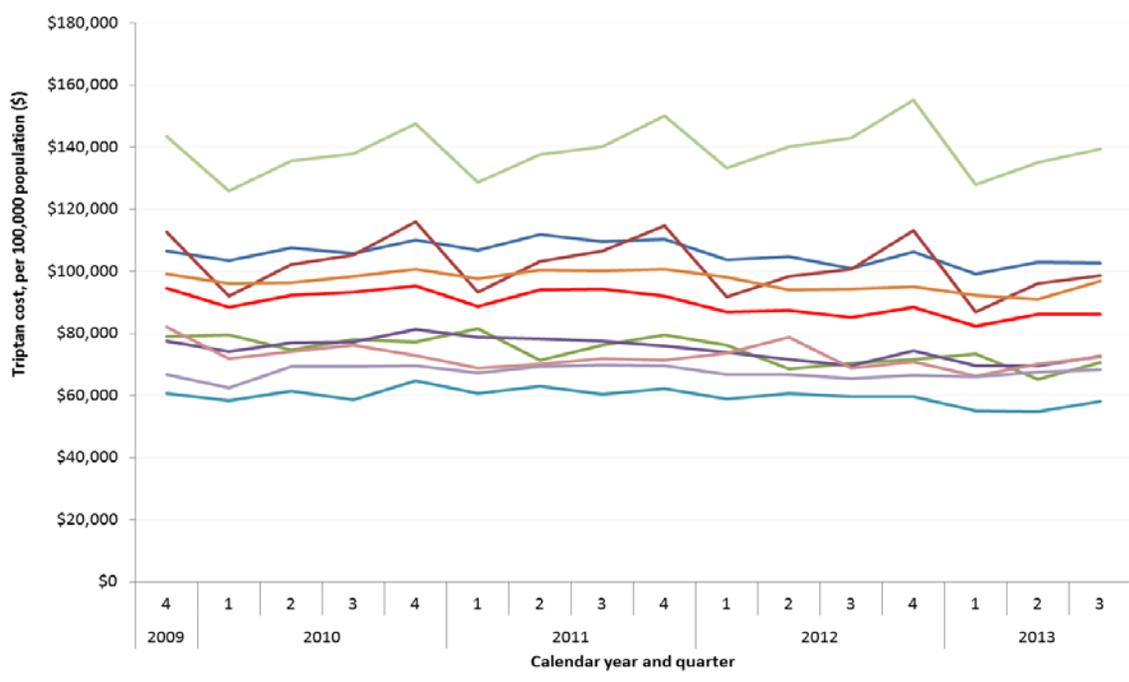


Exhibit 6: Population-adjusted costs of triptans in Canada, by province



- Alberta
- British Columbia
- Manitoba
- New Brunswick
- Newfoundland
- Nova Scotia
- Ontario
- PEI
- Quebec
- Saskatchewan

The overall rate of triptan use and costs in Ontario are average relative to other provinces (7,480 units and \$86,133 per 100,000 population in Q3 2013).

Summary of Findings for Exhibit 5 & Exhibit 6

1. There was wide variation in the rate of triptan units dispensed between provinces (range in Q3 2013: 5,532 [Newfoundland] to 11,661 [Quebec] units per 100,000 population).
2. In Ontario, triptan utilization and costs were average and did not change considerably over the study period. In the third quarter of 2013, the rate of triptan utilization and costs in Ontario were 7,480 per 100,000 population and \$86,133 per 100,000 population, respectively.
3. Quebec consistently exhibited the highest costs and rates of triptan use over the past 4 years. British Columbia, Alberta and Nova Scotia also demonstrated above-average rates of triptan use and costs.
4. Rates of use and costs of triptans were lowest in Newfoundland and Labrador (5,532 per 100,000 population and \$58,251 per 100,000 population, respectively in Q3 2013).

Population Adjusted Rates of Triptan 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

Exhibit 7: Population-adjusted utilization of non-provincially funded triptans in Canada by province

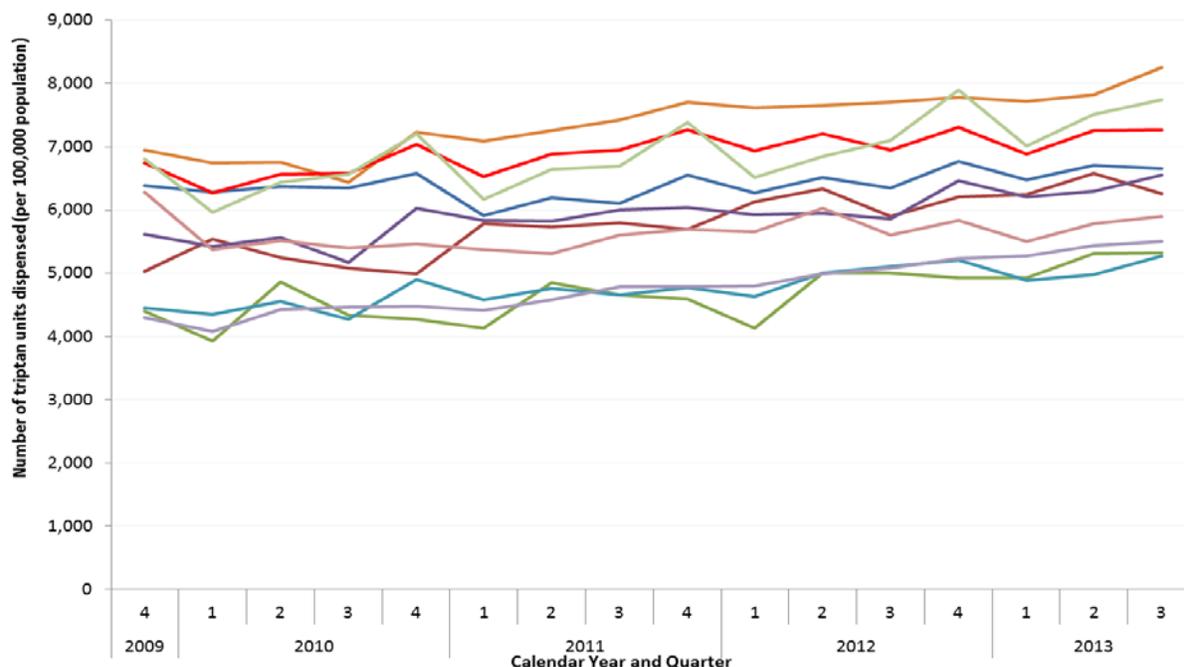
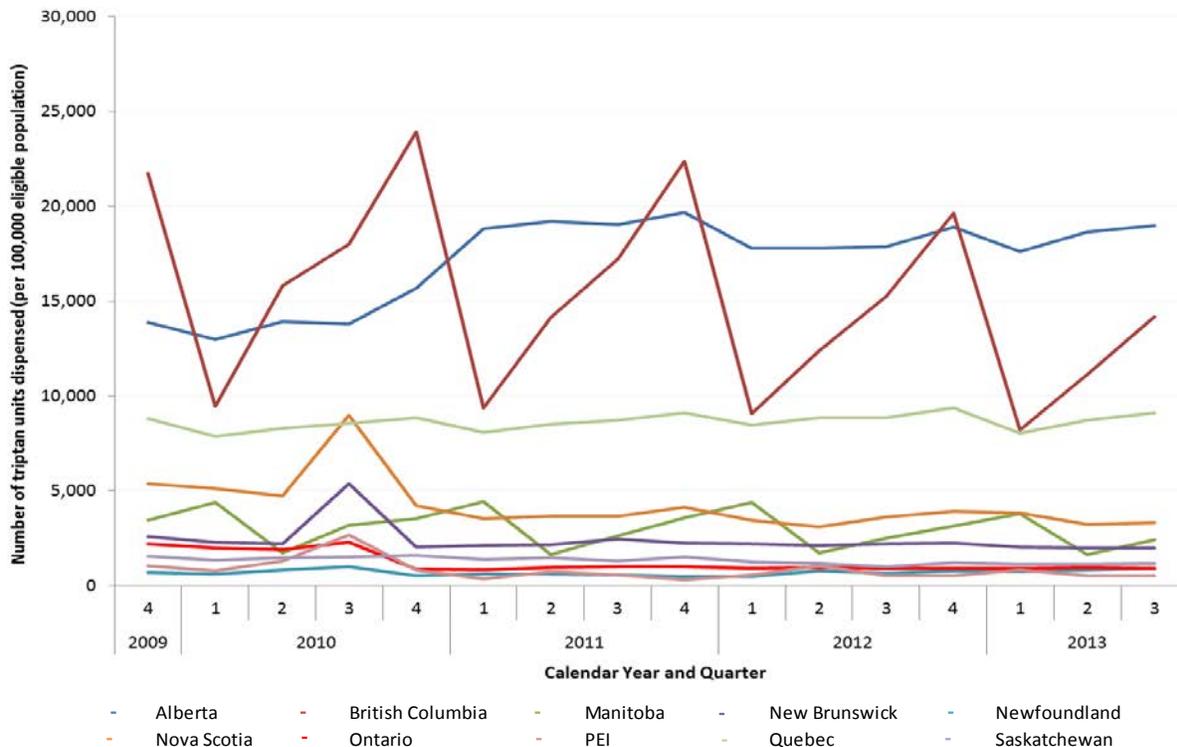


Exhibit 8: Population-adjusted utilization of provincially-funded triptans in Canada, by province



- Alberta
- British Columbia
- Manitoba
- New Brunswick
- Newfoundland
- Nova Scotia
- Ontario
- PEI
- Quebec
- Saskatchewan

Although Ontario has among the lowest rates of publically-funded triptan use in Canada, the rate of triptan use paid by other means (e.g. cash, private insurance) is the third highest in Canada.

Summary of Findings for Exhibit 7 & Exhibit 8

1. Although the Ontario Public Drug Program has established no quantity limits for triptans, it has among the lowest rates of provincially funded triptan use. This likely reflects the highly restrictive nature of triptan access in Ontario. In the third quarter of 2013, there were 931 triptan units dispensed per 100,000 eligible Ontarians, more than 5 times lower than the national average of 5,358 units per 100,000 eligible Canadians.
2. The rate of non-provincially funded triptan use in Ontario (7,271 units per 100,000 Ontarians in the third quarter of 2013) was the third highest rate in Canada (behind Quebec and Nova Scotia).

Provincial Comparisons

3. Quebec exhibited one of the highest rates of both provincially and non-provincially funded triptan use over the study period. This may reflect both the unrestricted access to these medications through public drug plans and the more widespread use of triptans in general in Quebec (Exhibit 5).
4. Alberta and British Columbia had among the highest rates of provincially-funded triptan use, which may reflect the lack of quantity limits on the number of triptan doses that can be dispensed per month in these provinces as well as less restricted coverage than some other provinces. This broader access to provincially-funded triptans was reflected in lower rates of triptan use paid for with other means.

Methodological Notes:

- There appears to be a cyclic trend in the rates of publically-funded triptan use in British Columbia and Manitoba. This is likely driven by deductibles in these PharmaCare programs that lead to medication stockpiling near the end of each funding period (calendar year in BC, fiscal year in Manitoba).
- National average per 100,000 eligible Canadians is only based on the provinces for which we have eligibility data (in other words, it does not include the territories or NIHB).

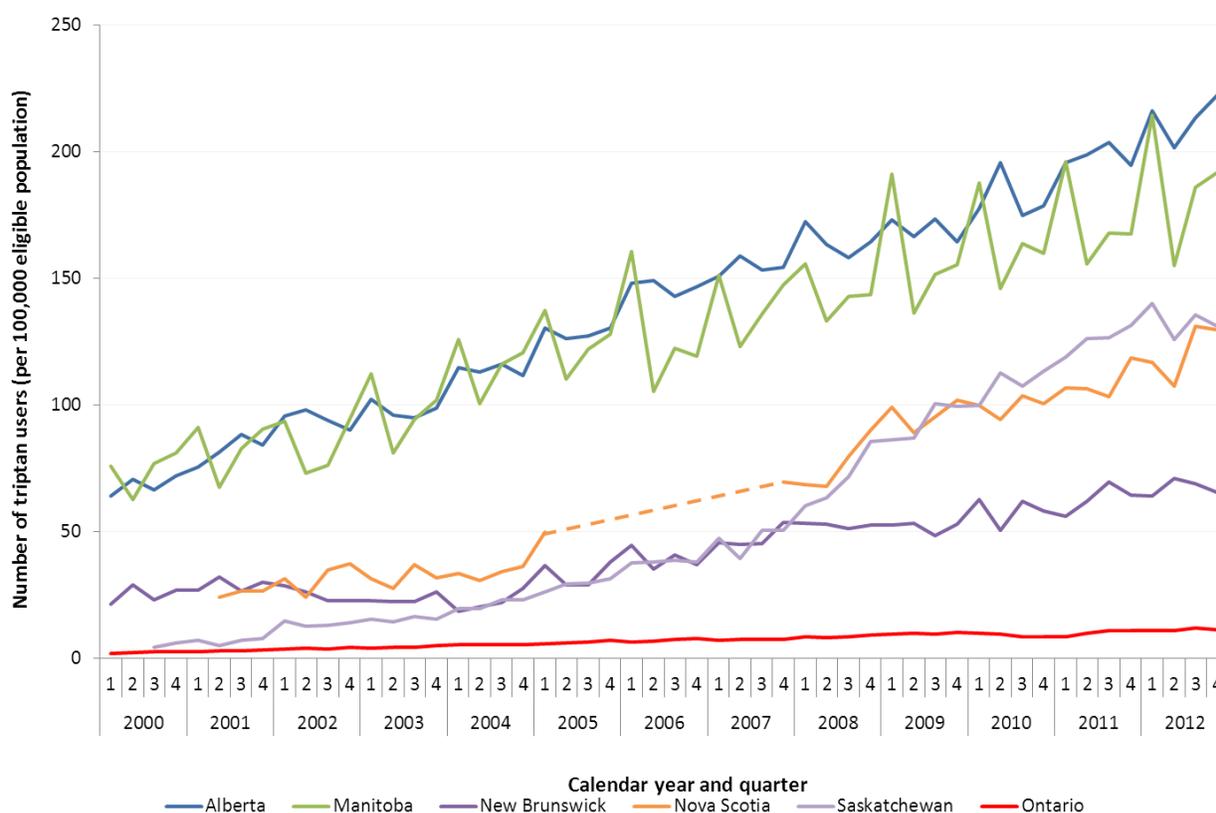
Cross-Provincial Analyses Among Public Drug Plan Beneficiaries

Methodological Note:

The following analyses are conducted using public drug beneficiary data collected by the Canadian Institute for Health Information and ICES. No data was available for British Columbia, New Brunswick, Newfoundland and Prince Edward Island.

Rate of Triptan Use, by Age

Exhibit 9: Rate of triptan use among public drug plan beneficiaries aged 65 and older, by province

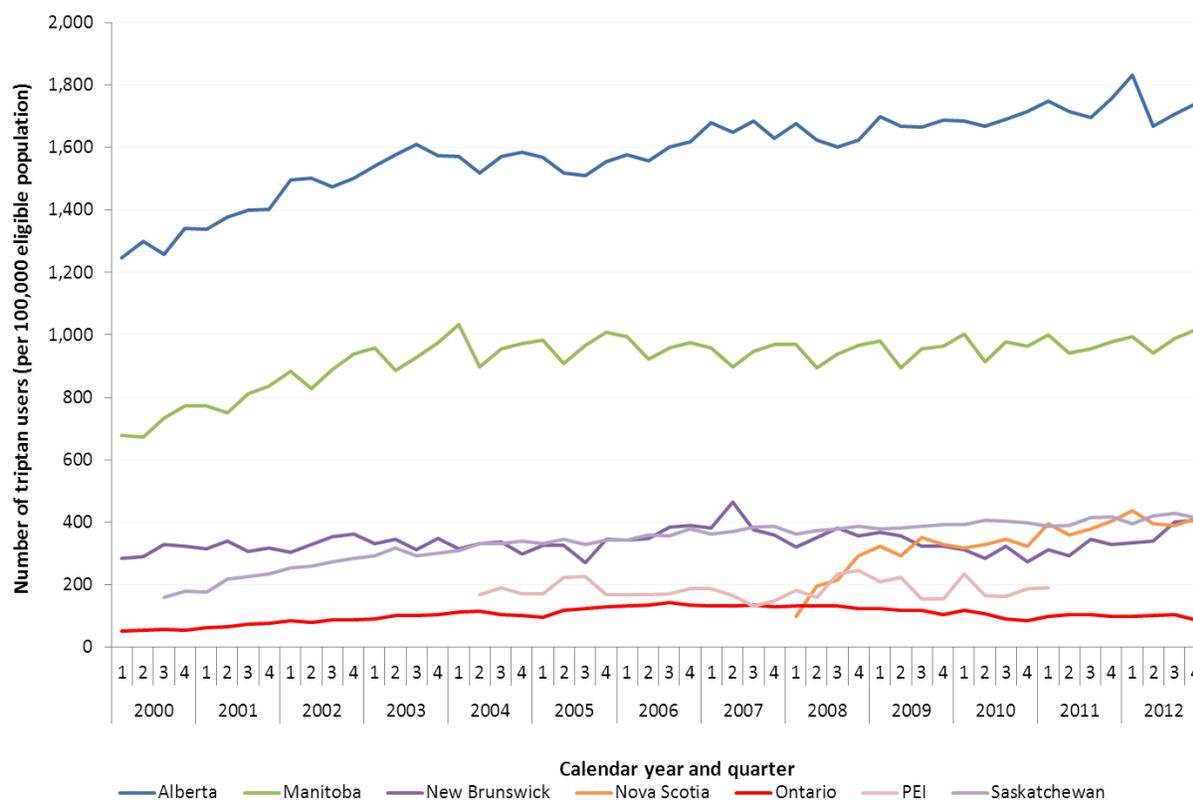


Legend: Dashed line represents time when Nova Scotia data not available.

The rate of triptan use among older public drug plan beneficiaries has increased across all provinces studied, but remains the lowest in Ontario.

Summary of Findings for Exhibit 9:

1. The rate of triptan use among older public drug plan beneficiaries (aged 65+) has increased across all provinces studied, but varies widely by province (range 11 per 100,000 in Ontario to 222 per 100,000 in Alberta at the end of 2012).
2. This increasing rate is not observed when looking at overall trends because of the low rate of use among older populations relative to younger populations.
3. The rate of use is lowest in Ontario, where triptans are listed under the Exceptional Access Program. The rate of triptan use in older beneficiaries increased slightly over the study period, from 2 users per 100,000 beneficiaries at the beginning of 2000 to 11 users per 100,000 beneficiaries at the end of 2012.
4. Alberta and Manitoba exhibited the highest rates of triptan use, with the rates increasing 247% (from 64 to 222 users per 100,000 beneficiaries) and 153% (from 76 to 192 users per 100,000 beneficiaries) over the 12 year period, respectively.
5. The rate of triptan use increased substantially in Saskatchewan at the beginning of 2008, when triptan coverage was extended to public drug plan beneficiaries aged 65 and older.

Exhibit 10: Rate of triptan use among public drug plan beneficiaries less than 65, by province

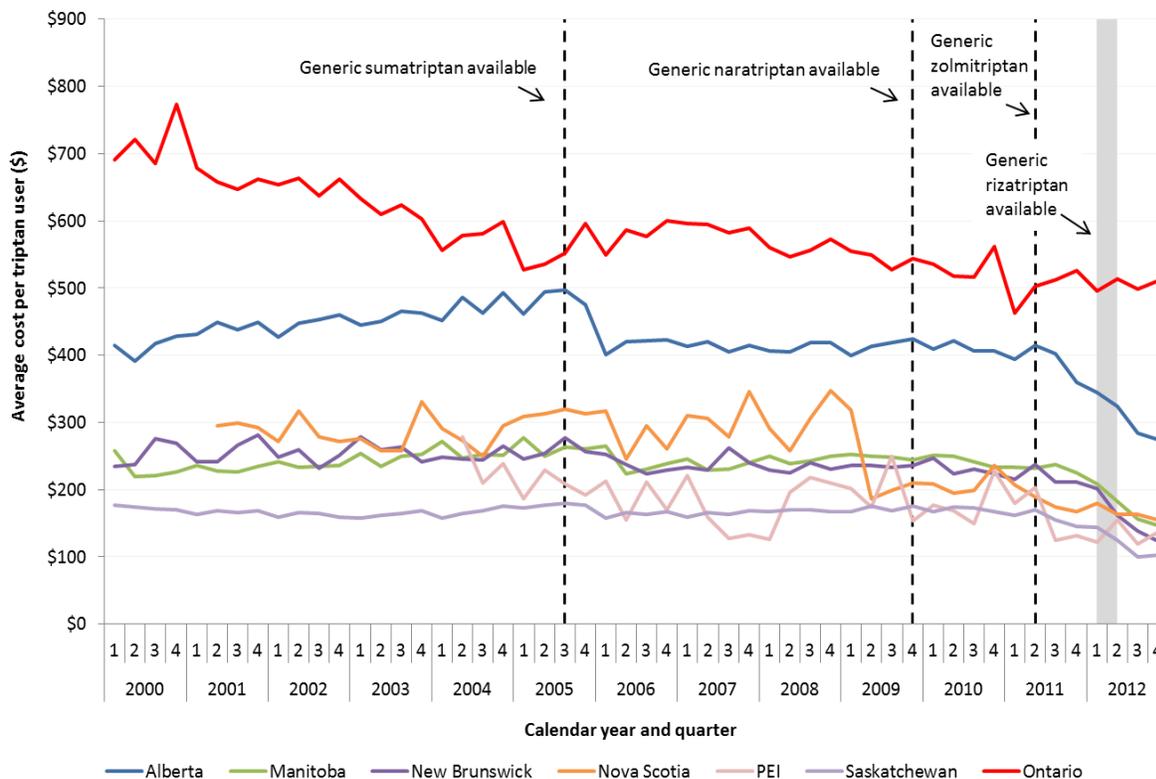
Rates of triptan use among younger public drug plan beneficiaries are much higher than rates in the older population.

Summary of Findings for Exhibit 10

1. Rates of triptan use among younger (<65 years) public drug plan beneficiaries are much higher than rates among the older population (range between 88 per 100,000 in Ontario and 1,739 per 100,000 population in Alberta), however these have largely remained stable over the study period.
2. Similar to the older age group, the rate of triptan use among younger beneficiaries is lowest in Ontario, and has changed only slightly over the study period (from 50 users per 100,000 beneficiaries at the beginning of 2000 to 88 users per 100,000 beneficiaries at the end of 2012).
3. The rate of triptan use among younger public drug plan beneficiaries is much higher in Alberta compared to all other provinces, and has increased 39.5% over the study period (from 1,247 to 1,739 per 100,000 population).
4. Since data became available in 2008, the rate of triptan use in Nova Scotia has increased nearly 4-fold, from 98 per 100,000 at the beginning of 2008 to 411 per 100,000 at the end of 2012.

Triptan Costs, Per Person

Exhibit 11: Average triptan cost per user among public drug plan beneficiaries, by province



Average quarterly costs per user of triptans have lowered in all provinces, but remain highest in Ontario (\$511 per user at end of 2012)

Summary of Findings for Exhibit 11

1. Average quarterly costs of triptans per person have lowered consistently among all provinces over the study period, which has likely been driven by the introduction of generics in 2005, 2009, 2011 and 2012.
2. Despite a 26% decrease in the average quarterly costs per user over the study period, costs remain highest in Ontario (\$511 per user at the end of 2012), and were not impacted by the introduction of generics. This is likely because the Ontario Public Drug Program did not require preferential use of generic triptans (where available) due to coverage through the Exceptional Access Program.
3. Average costs per user are high in Alberta, however these dropped substantially following the introduction of generic sumatriptan in Q3 2005, and the introduction of generic zolmitriptan in Q2 2011, due to provincial generic pricing agreements. By the end of 2012, average quarterly costs per person in Alberta were \$275 per user.
4. In all other provinces studied, the costs per user were similar (range \$103/user in Saskatchewan and \$155/user in Nova Scotia).

Characteristics of Triptan Users

Exhibit 12: Characteristics of Triptan Users, By Province in 2012

	AB	SK	MB	NB	NS	PEI	ON
Number eligible for coverage	503,192	560,107	663,657	108,774	133,756	29,908	2,938,205
Triptan users (N, %)	3,731 (0.7%)	2,142 (0.4%)	6,555 (1.0%)	237 (0.2%)	313 (0.2%)	17 (0.1%)	1,090 (0.04%)
Ergot alkaloid users (N, %)	288 (0.1%)	68 (0.01%)	54 (0.01%)	31 (0.03%)	32 (0.02%)	0	1,538 (0.1%)
Butalbital-containing analgesic users (N, %)	541 (0.1%)	0	6 (0.00%)	66 (0.1%)	249 (0.2%)	0	0
Butorphanol users (N, %)	0	0	9 (0.00%)	0	≤5	0	14 (0.00%)
TRIPTAN USERS	N = 3,731	N = 2,142	N = 6,555	N = 237	N = 313	N = 17	N = 1,090
Triptan units dispensed	245,213	56,576	239,054	9,073	12,220	634	109,235
Triptan units dispensed/person (Median, IQR)	36 (12 - 84)	24 (10 - 42)	18 (6 - 48)	30 (12 - 54)	30 (12 - 54)	36 (18 - 54)	60 (24 - 126)
Age (Median, IQR)	60 (52 - 66)	52 (43 - 60)	49 (40 - 56)	54 (45 - 66)	66 (52 - 70)	49 (42 - 64)	52 (44 - 63)
Male (N, %)	528 (14.2%)	317 (14.8%)	971 (14.8%)	33 (13.9%)	65 (20.8%)	≤5	208 (19.1%)

Exhibit 13: Characteristics of Triptan Users aged <65 years, By Province in 2012

	AB	SK	MB	NB	NS	PEI	ON
Number eligible for drug coverage	109,887	413,218	497,244	37,001	24,243	7,980	1,071,382
Triptan users (N, %)	2,522 (2.3%)	1,875 (0.5%)	6,076 (1.2%)	172 (0.5%)	125 (0.5%)	≤5	846 (0.1%)
Ergot alkaloid users (N, %)	112 (0.1%)	61 (0.01%)	47 (0.01%)	17 (0.05%)	8 (0.03%)	0	840 (0.1%)
Butalbital-containing analgesic users (N, %)	184 (0.2%)	0	≤5	38 (0.1%)	67 (0.3%)	0	0
Butorphanol users (N, %)	0	0	≤5	0	≤5	0	≤5
TRIPTAN USERS	N = 2,522	N = 1,875	N = 6,076	N = 172	N = 125	N ≤ 5	N = 846
Triptan units dispensed	156,682	48,482	216,726	6,488	4,280	514	83,242
Triptan units dispensed/person (Median, IQR)	32 (12 - 78)	21 (10 - 42)	18 (6 - 48)	30 (12 - 54)	24 (12 - 54)	36 (18 - 54)	60 (24 - 126)
Age (Median, IQR)	55 (48 - 60)	50 (41 - 57)	48 (39 - 54)	49 (42 - 56)	48 (42 - 54)	43 (42 - 57)	49 (41 - 55)
Male (N, %)	314 (12.5%)	267 (14.2%)	887 (14.6%)	22 (12.8%)	18 (14.4%)	≤5	164 (19.4%)

Exhibit 14: Characteristics of Triptan Users aged 65 years and older, By Province in 2012

	AB	SK	MB	NB	NS	PEI	ON
Number eligible for drug coverage	393,305	146,889	166,413	71,773	109,513	21,928	1,866,823
Triptan users (N, %)	1,209 (0.3%)	267 (0.2%)	479 (0.3%)	65 (0.1%)	188 (0.2%)	≤5	244 (0.01%)
Ergot alkaloid users (N, %)	176 (0.04%)	7 (0.00%)	7 (0.00%)	14 (0.02%)	24 (0.02%)	0	698 (0.04%)
Butalbital-containing analgesic users (N, %)	357 (0.1%)	0	≤5	28 (0.04%)	182 (0.2%)	0	0
Butorphanol users (N, %)	0	0	≤5	0	0	0	≤5
TRIPTAN USERS	N = 1,209	N = 267	N = 479	N = 65	N = 188	N ≤ 5	N = 244
Triptan units dispensed	88,531	8,094	22,328	2,585	7,940	120	25,993
Triptan units dispensed/person (Median, IQR)	39 (18 - 96)	24 (12 - 48)	24 (12 - 60)	40 (14 - 54)	30 (12 - 54)	42 (12 - 66)	72 (36 - 126)
Age (Median, IQR)	68 (66 - 72)	69 (66 - 72)	68 (66 - 72)	69 (67 - 73)	69 (67 - 72)	68 (68 - 70)	70 (67 - 73)
Male (N, %)	214 (17.7%)	50 (18.7%)	84 (17.5%)	11 (16.9%)	47 (25.0%)	≤5	44 (18.0%)

Note: IQR = interquartile range

The median number of triptan units dispensed per public drug plan beneficiary varies considerably between provinces, and aligns with differences in quantity limits. In Ontario, where no quantity limits are in place, the quantity dispensed per person is highest.

Summary of Findings for Exhibit 12, Exhibit 13, & Exhibit 14

1. 1,090 individuals (0.04% of ODB beneficiaries) received publically-funded triptans in Ontario in 2012. The majority of these individuals (N=846, 77.6%) were aged less than 65 years, and only 19.1% (N=208) were men.
2. The rate of triptan use was between 1.5-fold (PEI) and 27-fold (Manitoba) higher in all other provinces studied compared to the rate in Ontario.
3. Ergot alkaloid use was higher than triptan use in Ontario in 2012 (1,538 users and 1,090 users, respectively). In all other provinces, ergot alkaloid use was minimal. This may be driven by Ontario's listing of these drugs on the formulary, as a general benefit with therapeutic notes indicating that ergotamine should be considered the drug of choice for acute migraines.
4. The median number of triptans dispensed per person varied considerably between provinces.
 - In Manitoba, where quantity limits are in place (maximum 12/month), the median number of units dispensed per person annually was the lowest among all provinces studied (18 units, IQR 6 to 48 units).
 - In Ontario, where no quantity limits are in place, the median number of units dispensed annually was highest (60 units, IQR 24 to 126 units).
 - Despite differences in quantity limit policies, all other provinces were similar with respect to the median number of triptan units dispensed per person (range between 24 units and 36 units, annually).
5. Overall, the median number of triptan units dispensed per person was higher among older triptan users (aged 65 and older) compared

Triptan Overuse

Exhibit 15: Characteristics of Triptan Overuse, by Province and Age in 2012

Province	Quantity Limit Imposed by Province	Overuse Definition: 6 units/month	Overuse Definition: 12 units/month	Overuse Definition: 18 units/month
Ontario	None	40-45%	15-20%	10-15%
Alberta	None	30-35%	10-15%	5-10%
Manitoba	12 units/month	15-20%	0-5%	0-5%
New Brunswick & PEI	6 units/month	15-20%	--*	--
Nova Scotia	6 units/month	10-15%	--	--
Saskatchewan	6 units/month	0-5%	--	--

*Suppressed due to small cell sizes

Approximately one in five publically-funded triptan users in Ontario received more than 12 triptan units per month, putting them at risk for medication overuse headache.

Summary of Findings for Exhibit 15:

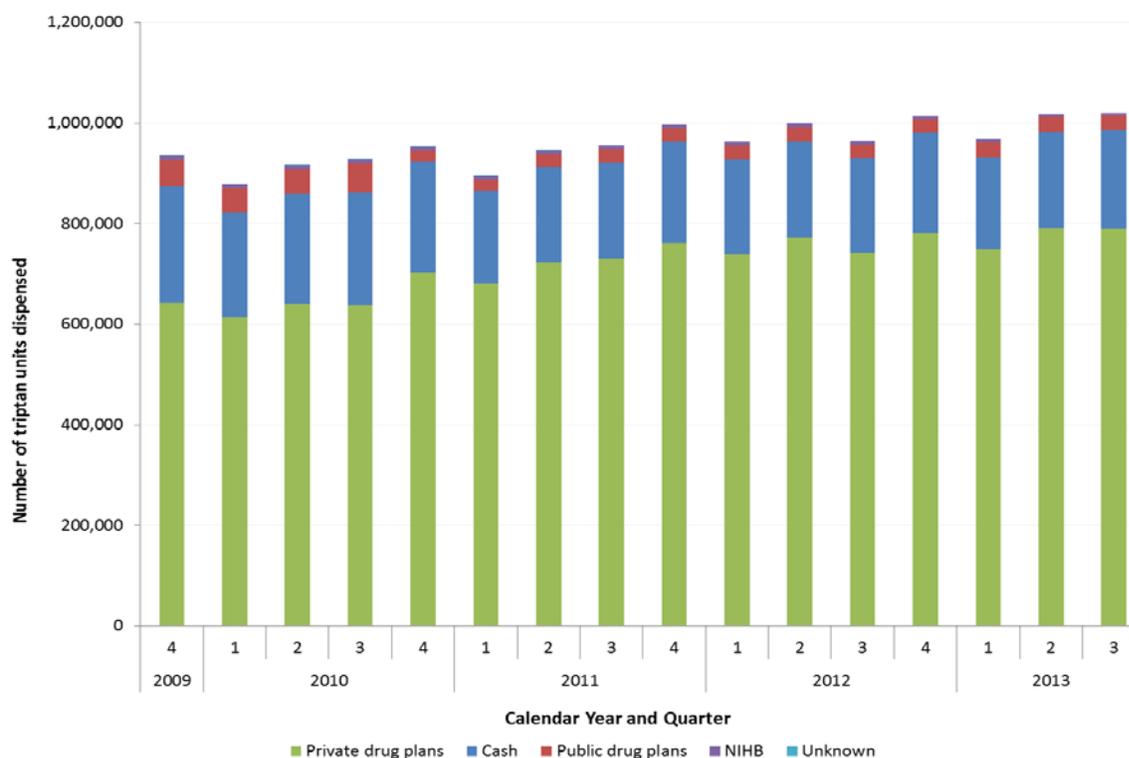
1. The prevalence of triptan overuse was highest in Ontario, where more than one in ten publically-funded triptan users were dispensed more than 18 units per month.
2. In Alberta, which (in addition to Ontario) has not established quantity limits for reimbursement, the prevalence of triptan overuse in public drug beneficiaries was also high (between 5% and 35% depending on the quantity limit used).
3. All other provinces studied have established quantity limits on triptan reimbursement (either 6 or 12 doses, monthly). In these provinces the prevalence of triptan overuse was much lower.
4. In general, the prevalence of triptan overuse was higher among older adults (data not shown).

Methodological Note: Due to plans for peer-reviewed publication of the results of this analysis, specific numbers and percentages have been replaced with ranges so as not to preclude publication. The full details of these results will be available upon publication in a peer-reviewed journal.

Triptan Use Among Public Drug Plan Beneficiaries in Ontario

Distribution of Payers for Triptans in Ontario

Exhibit 16: Total Utilization of Triptans in Ontario, by Coverage



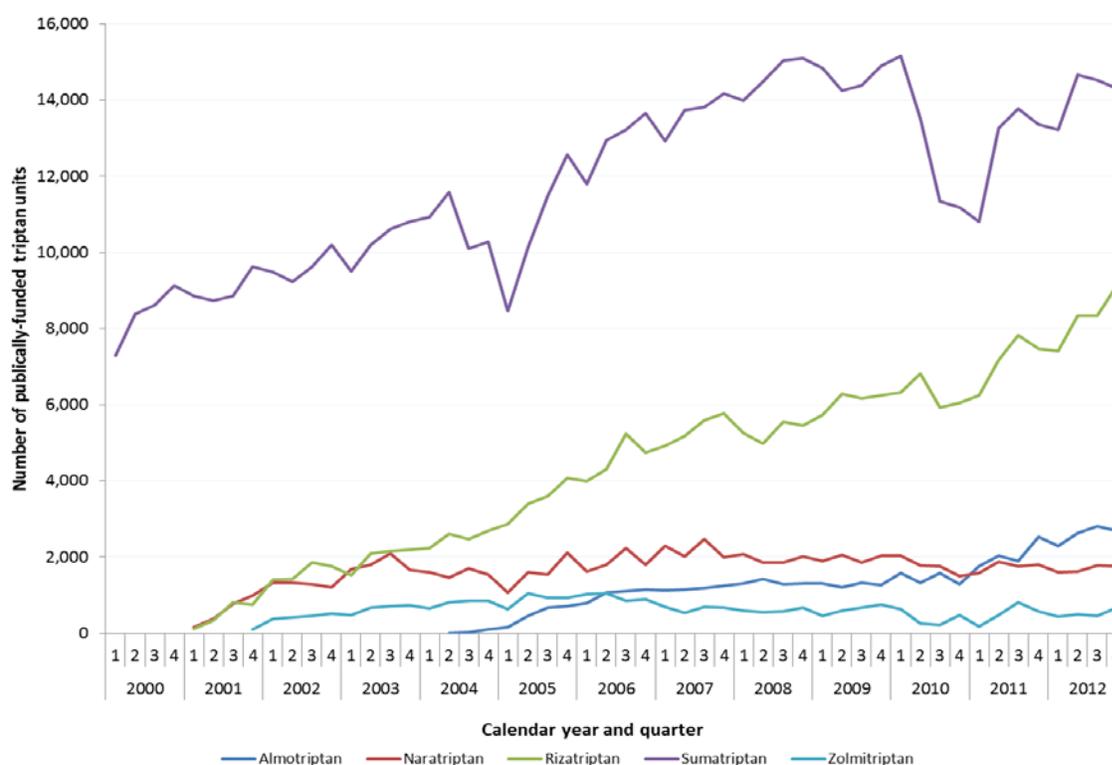
In the third quarter of 2013, the Ontario Public Drug Plan only paid for 2.8% of all triptan prescriptions dispensed in Ontario. The majority of triptans are paid for by private drug plans (77.4%).

Summary of Findings for Exhibit 16:

1. The number of triptan units dispensed in Ontario has increased 9.1%, from 934,168 units at the end of 2009 to 1,019,577 units at the end of 2013.
2. The majority of triptan prescriptions dispensed in Ontario are paid by private drug plans, which increased 22.8% from 642,622 units in Q4 2009 to 789,075 units in Q3 2013.
3. A small proportion of triptan units dispensed in Ontario are paid for by public drug plans, which declined in Q3 2010 but have remained steady since.
4. By Q3 2013, the market share of triptan units dispensed in Ontario was 77.4% private, 2.8% public, 19.3% cash and 0.5% Non-Insured Health Benefits (NIHB).

Trends in Triptan Use and Costs

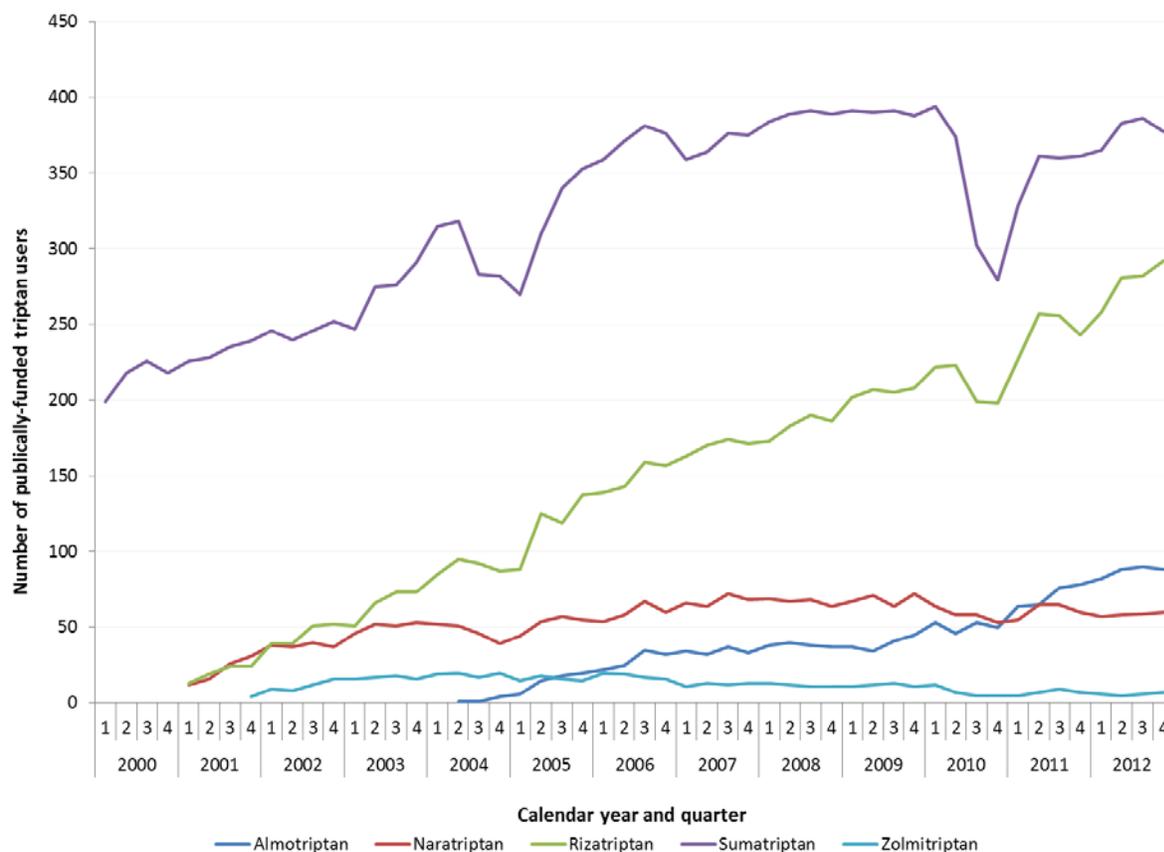
Exhibit 17: Total Utilization of Publically-Funded Triptans in Ontario, by Triptan



Trends in the selection of publically prescribed triptans in Ontario are not consistent with national trends. The number of publically-funded sumatriptan and rizatriptan units dispensed in Ontario has increased markedly in Ontario since 2000, but sumatriptan was still the most utilized publically funded triptan in 2012.

Summary of Findings for Exhibit 17:

1. The number of publically funded triptan units in Ontario has increased 291%, from 7,294 units in Q1 2000 to 28,571 units in Q4 2012.
2. Sumatriptan was the most commonly prescribed triptan in Ontario between 2000 and 2012, where the number of units dispensed increased 96.2% in the past 13 years (from 7,294 units in Q1 2000 to 14,313 units in Q4 2012).
3. Rizatriptan use increased markedly over the study period (from 116 units in Q1 2001 to 9,140 units in Q4 2012), becoming the second highest triptan dispensed in 2012.
4. At the end of 2012, sumatriptan was the most commonly dispensed publically funded triptan in Ontario (50.1%), contrary to national trends (where rizatriptan was most commonly dispensed; Exhibit 2).
5. Zolmitriptan is the least commonly prescribed, publically-funded triptan in Ontario, whereas it is the third most commonly prescribed triptan nationally. This is likely driven by strict funding criteria which require patients to have failed or demonstrated intolerance to other triptans.

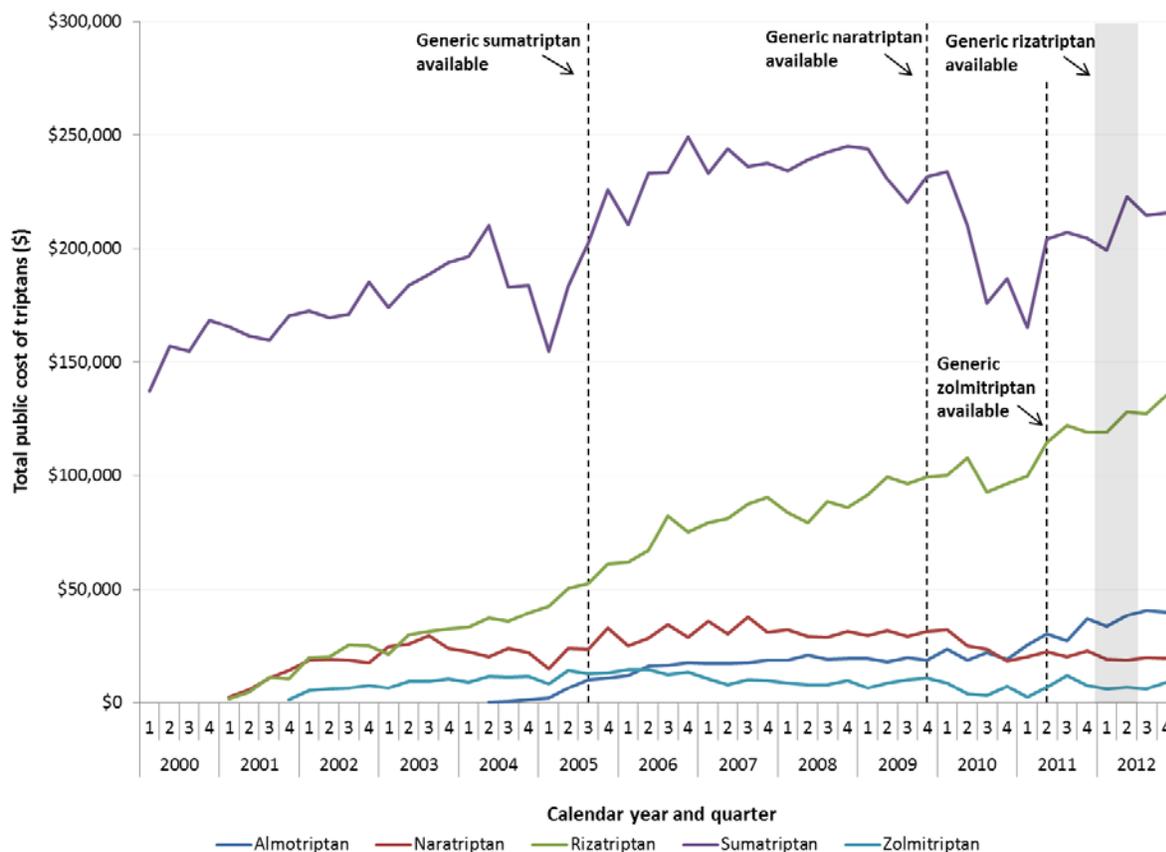
Exhibit 18: Number of Users of Publically-Funded Triptans in Ontario, by Triptan

The number of people using sumatriptan and rizatriptan has increased markedly over the past 13 years. By 2012, they were the two most commonly used triptans.

Summary of Findings for Exhibit 18:

1. The number of publicly funded triptan users in Ontario has increased 314% over the past 13 years, and aligns with prescribing trends (Exhibit 17).
2. At the end of 2012, 377 individuals received prescriptions for sumatriptan, 292 for rizatriptan, 88 for almotriptan, 60 for naratriptan, and 7 for zolmitriptan.
3. Zolmitriptan is the least frequently used triptan, aligning with reimbursement criteria, which require patients to have failed or demonstrated intolerance to other triptans.
4. The drop in number of users of sumatriptan and rizatriptan during 2010 was likely due to a temporary administrative delay in approval of EAP requests that occurred during this time.

Exhibit 19: Total Cost of Publically-Funded Triptans in Ontario, by Triptan



At the end of 2012, quarterly costs for the most commonly prescribed triptans (sumatriptan and rizatriptan) were \$215,954 and \$135,668, respectively.

Summary of Findings for Exhibit 19:

1. In general, public drug plan costs align with utilization trends and the availability of generics.
2. Sumatriptan had the highest public costs in Ontario between 2000 and 2012 (57% rise from \$137,358 to \$215,954). This is followed by the cost of rizatriptan, which has increased considerably since its introduction in 2001 (from \$1,723 at the beginning of 2001 to \$135,668 at the end of 2012).
3. Costs of sumatriptan did not change substantially upon introduction of generics. The main drop in the costs associated with this triptan aligned with the temporary drop in utilization in 2010.
4. The costs of almotriptan prescriptions have been increasing in Ontario since 2009, and it was the third most costly triptan by the end of 2012.
5. The use and costs of naratriptan have been slightly decreasing since the availability of generics in 2009 (from \$31,338 (2,034 units) in Q4 2009 to \$19,713.4 (1,762 units) at the end of 2012).

Exhibit 20: Distribution of generic versus brand name triptans paid for by the Ontario Public Drug Program, 2012

	OVERALL N	Generic N (%*)	Brand Name N (%*)
Number of triptan units			
Overall	109,235	44,473 (40.7%)	64,762 (59.3%)
Almotriptan	10,408	0 (0.0%)	10,408 (100.0%)
Naratriptan	6,782	4,564 (67.3%)	2,218 (32.7%)
Rizatriptan	33,235	7,697 (23.2%)	25,538 (76.8%)
Sumatriptan	56,740	31,762 (56.0%)	24,978 (44.0%)
Zolmitriptan	2,070	450 (21.7%)	1,620 (78.3%)

* row percent

Despite generic alternatives for 4 of 5 triptans available in Ontario, only 40.7% of all triptans dispensed in 2012 were generics.

Summary of Findings for Exhibit 20:

1. Overall, only 40.7% (N=44,473) of all triptans dispensed through the Ontario Public Drug Program were for generic formulations in 2012.
2. This varied substantially by triptan. Sumatriptan and naratriptan were the first two triptans to have generic formulations, and had the highest proportion of generic use in 2012 (56.0% and 67.3%, respectively).
3. Zolmitriptan and rizatriptan had the lowest prevalence of generic use (21.7% and 23.2%, respectively). This may be driven by the fact that these drugs were not genericized until 2011 and 2012, respectively.

Exhibit 21: Characteristics of Triptan Users in Ontario, 2012

	OVERALL N (%)	AGE <65 N (%)	AGE 65+ N (%)
Number eligible for drug coverage	2,938,205	1,071,382	1,866,823
Number of triptan users¹			
Overall	1,090 (0.0%)	846 (0.1%)	244 (0.0%)
Almotriptan	131 (0.0%)	120 (0.0%)	11 (0.0%)
Naratriptan	76 (0.0%)	56 (0.0%)	20 (0.0%)
Rizatriptan	400 (0.0%)	340 (0.0%)	60 (0.0%)
Sumatriptan	484 (0.0%)	332 (0.0%)	152 (0.0%)
Zolmitriptan	7 (0.0%)	*	*
Number of ergot alkaloid users	1,538 (0.1%)	840 (0.1%)	698 (0.0%)
Number of butorphanol users	14 (0.0%)	*	*
SUBGROUP ANALYSIS: TRIPTAN USERS	N=1,090	N=846	N=244
Number of triptan units dispensed¹			
Overall	109,235	83,242	25,993
Almotriptan	10,408 (9.5%)	9,370 (11.3%)	1,038 (4.0%)
Naratriptan	6,782 (6.2%)	5,430 (6.5%)	1,352 (5.2%)
Rizatriptan	33,235 (30.4%)	28,422 (34.1%)	4,813 (18.5%)
Tablets	17,854 (16.3%)	15,889 (19.1%)	1,965 (7.6%)
Wafers	15,381 (14.1%)	12,533 (15.1%)	2,848 (11.0%)
Sumatriptan	56,740 (51.9%)	38,850 (46.7%)	17,890 (68.8%)
Tablets	52,571 (48.1%)	35,219 (42.3%)	17,352 (66.8%)
Injection	3,460 (3.2%)	2,942 (3.5%)	518 (2.0%)
Nasal spray	709 (0.6%)	689 (0.8%)	20 (0.1%)
Zolmitriptan ¹	2,070 (1.9%)	1,170 (1.4%)	900 (3.5%)
Tablets	2,070 (1.9%)	1,170 (1.4%)	900 (3.5%)
Total cost of triptans (average cost per user)			
Overall	\$1,622,420 (\$1,488)	\$1,247,788 (\$1,475)	\$374,632 (\$1,535)
Almotriptan	\$152,565 (\$1,165)	\$137,521 (\$1,146)	\$15,044 (\$1,368)
Naratriptan	\$77,825 (\$1,024)	\$61,836 (\$1,104)	\$15,989 (\$799)
Rizatriptan	\$510,415 (\$1,276)	\$436,355 (\$1,283)	\$74,060 (\$1,234)
Sumatriptan	\$853,038 (\$1,762)	\$597,505 (\$1,800)	\$255,533 (\$1,681)
Zolmitriptan	\$28,578 (\$4,083)	\$14,572 (*)	\$14,006 (*)
Number of new triptan users			
Overall ^a	281 (25.8%)	238 (28.1%)	43 (17.6%)
Almotriptan	47 (4.3%)	*	*
Naratriptan	*	*	*
Rizatriptan	128 (11.7%)	114 (13.5%)	14 (5.7%)
Sumatriptan	99 (9.1%)	77 (9.1%)	22 (9.0%)
Zolmitriptan	*	*	0 (0.0%)
Urban Location of Residence	939 (86.1%)	739 (87.4%)	200 (82.0%)
Prescriptions Dispensed to Long Term Care Residents	80 (0.9%)	*	*
Socioeconomic status			
Quintile 1 (lowest)	385 (35.3%)	320 (37.8%)	65 (26.6%)
Quintile 2	243 (22.3%)	196 (23.2%)	47 (19.3%)
Quintile 3	173 (15.9%)	128 (15.1%)	45 (18.4%)
Quintile 4	152 (13.9%)	109 (12.9%)	43 (17.6%)
Quintile 5 (highest)	133 (12.2%)	90 (10.6%)	43 (17.6%)
Plan²			
Seniors	1,730 (20.0%)	0 (0.0%)	1,730 (96.6%)
Ontario Disability Support Program	4,698 (54.4%)	4,666 (68.1%)	32 (1.8%)
Ontario Works	710 (8.2%)	710 (10.4%)	0 (0.0%)
Trillium	1,430 (16.5%)	1,416 (20.7%)	14 (0.8%)
Other	73 (0.9%)	59 (0.9%)	14 (0.8%)

*In accordance with the ICES privacy policy, in cases where the number of total users is less than 6, this number has been suppressed to ensure confidentiality. In cases where there is only one record being suppressed, the next record with the second-lowest value has been suppressed as well in order to avoid residual disclosure issues.

¹ Note: eletriptan, frovatriptan, and zolmitriptan nasal spray are not covered on the Ontario formulary

² Note: No triptan users were covered under the Homes for Special Care, Special Drugs, or Other plan codes

There were 1,090 publically funded triptan users in Ontario in 2012, 281 of which were new users. Triptan users tended to be less than 65 years of age, and live in urban areas.

Summary of Findings for Exhibit 21:

1. There were 1,090 publically-funded triptan users in Ontario in 2012. The majority of these triptan users were aged less than 65 (N=846, 77.6%) and lived in urban areas (N=939, 86.1%).
2. The majority of the prescriptions for triptans dispensed in Ontario in 2012 were dispensed to users that did not reside in a long term care facility (99.1%; 8,561 prescriptions).
3. The majority of prescriptions for older users (aged 65+) were covered under the seniors plan (96.6%; 1,730 prescriptions), whereas the majority for younger users were covered under the Ontario Disability Support Program (68.1%; 4,666 prescriptions).
4. The annual cost of triptans aligned with utilization and was highest for sumatriptan prescriptions (\$853,038) and lowest for zolmitriptan prescriptions (\$28,578). However, the average annual cost per user was highest among zolmitriptan users (\$4,083), followed by sumatriptan users (\$1,762) and rizatriptan users (\$1,276).
5. Among the 281 new triptan users in Ontario in 2012, 46% (N=128) initiated rizatriptan, 35% (N=99) initiated sumatriptan, 4% (N=47) initiated almotriptan, and the remaining 2.5% (N=7) initiated naratriptan or zolmitriptan.

Patterns of Triptan Use and Discontinuation

Exhibit 22: Time to Discontinuation of Triptan Therapy

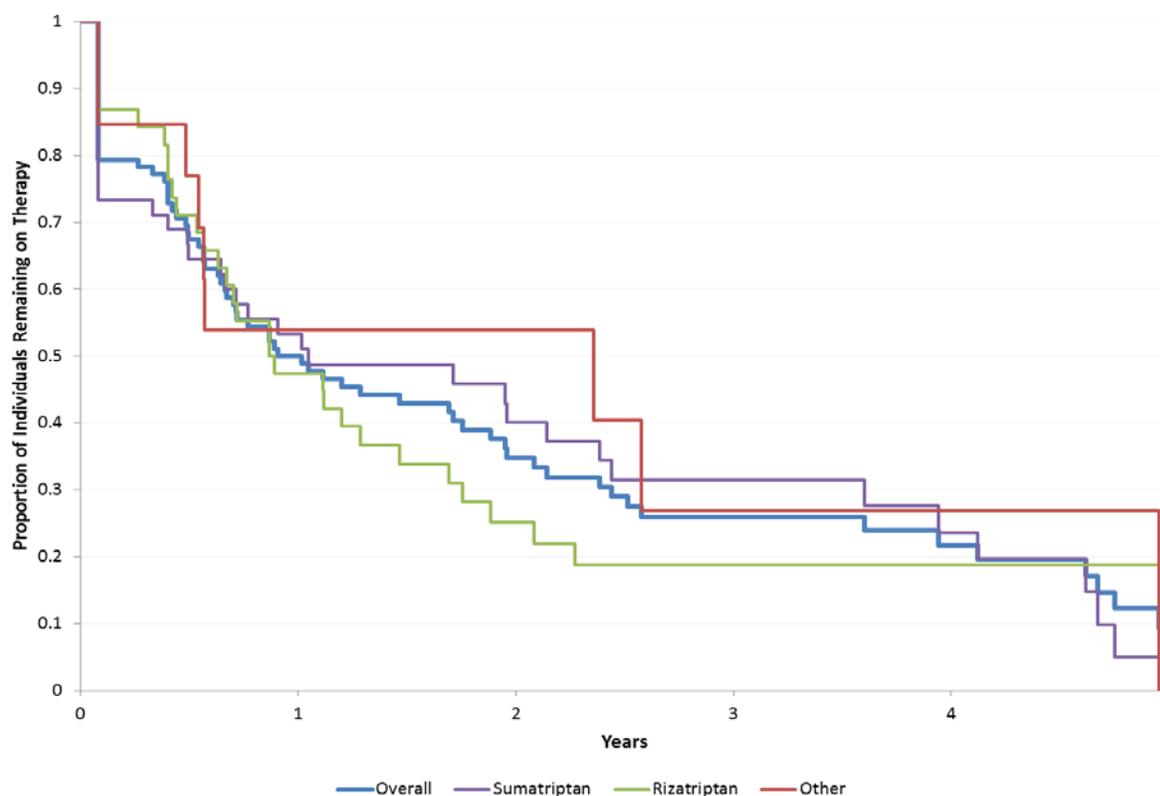


Exhibit 23: Patterns of Triptan Use among New Users Aged 66 and Older, 2008-2012

	OVERALL	Rizatriptan	Sumatriptan	Other ³
Number of new users	N=92	N=38	N=45	N=13
Duration of therapy, Median (IQR)	333 (147-772)	322 (154-673)	372 (30-891)	334 (198-862)
<i>Less than 1 year of therapy</i>	48 (52.17%)	20 (52.63%)	22 (48.89%)	7 (53.85%)
<i>Only 1 prescription for triptan</i>	19 (20.65%)	*	12 (26.67%)	*
<i>Early discontinuation¹</i>	40 (43.48%)	14 (36.84%)	20 (44.44%)	6 (46.15%)
Concomitant therapies ²				
NSAIDs	36 (39.13%)	16 (42.11%)	16 (35.56%)	6 (46.15%)
Opioids	52 (56.52%)	23 (60.53%)	23 (51.11%)	8 (61.54%)

*In accordance with ICES privacy policies, in cases where the number of total users is less than 6, this number has been suppressed to ensure confidentiality.

¹ Defined as receipt of ≤ 5 prescriptions

² There was little (≤ 5 users) to no use of ASA, acetaminophen, ergots and antiemetics

³ Consists of almotriptan, naratriptan and zolmitriptan. Grouped due to small numbers

The median time to discontinuation of triptans was approximately 1 year, and did not differ significantly between triptans.

Summary of Findings for Exhibit 22 & Exhibit 23:

1. 92 individuals aged 66 and older started publically funded triptan therapy in Ontario between 2008 and 2012. Their median duration of therapy was 333 days (IQR 147 to 772 days).
2. Among these individuals, 20.7% received only 1 prescription for a triptan, and 43.5% received ≤ 5 prescriptions.
3. There was no significant difference in the time to discontinuation between different triptans ($p=0.8054$).
4. More than 50% of the new triptan users received concomitant prescriptions for opioids, and almost 40% received concomitant prescriptions for NSAIDs.

Methodological Note:

1. Data holdings for publically funded prescription data in Ontario do not capture the indications for medications. We are therefore unable to determine whether opioids and NSAIDs are being prescribed for the treatment of migraines or for other conditions.

Key Findings

Provincial Variation in Rates of Triptan Use

Near the end of 2013, 3 million triptan units were dispensed quarterly in Canada, at a cost of \$35 million. The three most commonly prescribed triptans in Canada were rizatriptan, sumatriptan and zolmitriptan. Although this is comparable to overall rates of triptan use in Ontario, this is not reflected among publically funded triptan users in Ontario, where zolmitriptan is the least commonly prescribed triptan due to more restricted reimbursement criteria.

Rates of publically funded triptan use are increasing in all provinces, particularly among individuals aged 65 and older. The exception to this is within Ontario where rates of publically funded triptan use have stayed fairly consistent over the last 13 years (13 users per 100,000 beneficiaries in Q1 2000 to 34 users per 100,000 beneficiaries in Q4 2012).

Overall, Ontario's rate of triptan utilization in the third quarter of 2013 (7,480 units per 100,000 population) was slightly lower than the national average (8,677 units per 100,000 population). However, Ontario had among the lowest rates of triptan use among public drug plan beneficiaries (931 units vs. national rate of 5,358 units per 100,000 population) and one of the higher rates of triptan use paid for through non-public means (7,271 units vs. national rate of 6,473 units per 100,000 population). This is in direct contrast to all other provinces, where rates of triptan use in provincial drug programs are comparable to rates of triptan use paid through other means. Trends in Ontario align with the considerable restrictions for public drug access to triptans through the OPDP, and suggest that people are instead obtaining triptans through other means (private insurance, out-of-pocket).

Provincial Variation in Risk of Triptan Overuse

In 2012, the median number of triptan units dispensed per person was highest in Ontario (median 60 units annually), where no quantity limits are in place. This is in stark contrast to other provinces studied, where the median annual number of units dispensed per person ranged between 18 and 36 units. In an analysis of potential triptan overuse, more than 40% of publically funded triptan users in 2012 in Ontario exceeded a treatment frequency of 6 units per month, which is the quantity limit established in 5 provinces in Canada. In those provinces where monthly triptan quantities were limited to 6 units, the prevalence of overuse (defined as more than 6 units/month) was reduced to between approximately 0% and 20%. In Alberta, where no quantity limits were in place, the prevalence of overuse was also high (30-35%), but lower than that observed in Ontario. If quantity limits were expanded to a monthly limit of 12 units or 18 units, only 10 to 20% of triptan users in Ontario would have exceeded this limit in 2012.

Triptan Use in Ontario

The majority of triptan use in Ontario is through non-public payers. Private drug plans pay for over three-quarters (77%) of triptan units dispensed in Ontario, and the provincial drug plan pays for <5% of all units dispensed. Overall, there were 1,090 publically-funded triptan users in Ontario in 2012, 281 of which were new users. In general, triptan users were aged less than 65 years and lived in urban areas.

When considering adherence to therapy, approximately half of older triptan users discontinued therapy within 1 year, and 21% received only 1 triptan prescription. These rates are slightly higher than those found in the American Migraine Prevalence and Prevention (AMPP) study, in which just over one-third of triptan users discontinued therapy within 1 year.⁶ The high rate of discontinuation in Ontario may reflect a failure to tolerate or respond to these drugs, or discontinuation due to medication overuse headaches.⁷ It is unlikely that this lack of adherence is due to access issues since the vast majority (84%) of renewal requests through EAP are granted.⁸

Finally, over half of older triptan users in Ontario were prescribed opioids over their course of triptan therapy, despite the fact that our systematic review found no clinical trials investigating the safety or effectiveness of this combination in migraine therapy. Although the indication for opioid therapy is unknown, this finding suggests that opioids are likely being used in conjunction with triptans in the management of migraines.

Impact of Generic Triptans on Rates of Use in Ontario

Ontario has had the highest cost per person of publically funded triptans in Canada over the past 13 years (\$511 per user in Q4 2012). This is likely driven by two factors. The first is that costs for these drugs are not regulated by provincial drug pricing policies, and therefore unit costs may be higher than in other provinces. Secondly, there is no requirement for preferential use of generic forms of triptans (where available) within the triptan drug class, and therefore the majority of triptans dispensed in Ontario are brand name agents (59.3% in 2012), not generic formulations. This is in direct contrast to most other provinces where generic pricing agreements are in place and where preferential generic use is required when available.

The introduction of a generic form of oral sumatriptan in 2005 had no impact on total provincial costs for this triptan over time. However, the introduction of a generic form of naratriptan at the end of 2009 led to a reduction in overall costs for this triptan (19% reduction in annual provincial cost, from \$121,725 in 2009 to \$99,023 in 2010) that was sustained to the end of 2012.

Cyclic Trends

We observed a major cyclic trend in rates of publically funded triptan use in British Columbia, with triptan 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).

Health Equity

Stratified analyses suggest that there isn't a major equity issue in access to these medications by age or gender. Overall, triptans were more widely used by women (approximately 80%), which aligns with the

higher prevalence of migraines among women. A rising prevalence of use of triptans among older (aged 65+) adults was observed in all provinces studied, with the exception of Ontario. This suggests that there may be an increasing demand of these drugs among older adults that is not being met in Ontario. Of note is that rates of triptan overuse appear to be higher among older adults treated with this class of drugs. This discrepancy between younger and older triptan users highlights an important safety issue that should be considered.

This analysis suggests that highly restricted public drug coverage in Ontario has led to poorer access to these medications through public drug plans compared to most other provinces. Indeed, near the end of 2013, more than 75% of triptan prescriptions in Ontario are paid for by private drug plans, and 20% are paid for out of pocket. This suggests that many Ontarians who cannot afford either private drug insurance or out of pocket purchases may not have access to triptans.

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 Compuscript does not collect patient-level data, and therefore information on privately funded triptan use is only available at the prescription and unit (e.g. tablet) level.
3. NPDUIS does not have data from public drug plans in British Columbia, Quebec, or Newfoundland & Labrador. Furthermore, prescription data for PEI is only available as of 2004. Therefore, we were unable to make comparisons between Ontario rates and rates of use in these provinces.
4. 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.

Concomitant Drug Therapy

Some acute pharmacologic treatment options for migraines (e.g. ASA, acetaminophen) are available over the counter in Ontario, and are not captured in our databases. Therefore we will underestimate the true prevalence of concomitant therapy use. For this reason, rates of use of many concomitant therapies were low, and we were only able to report rates of use of NSAIDs and opioids.

Generalizability

All analyses using IMS Compuscript data reflect triptan use among the entire population. Furthermore, analyses of prescribing trends conducted among public drug beneficiaries were restricted to those aged

18 and older, and therefore are generalizable to the entire adult population. However, 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 triptan users to patients aged 66 and older. Therefore, these findings may not be generalizable to the younger population of triptan users.

Indication

First, we cannot isolate migraine diagnoses in any of the data holdings used in these analyses. Therefore, we are unable to exclude triptans that may have been prescribed for cluster headaches. In most provinces (including Ontario), access to these drugs through public drug plans is highly restricted, and therefore it is unlikely that any of these prescriptions were prescribed to patients without migraines. However, we may have over-estimated rates of triptan use for migraine therapy paid by other means (e.g. private drug plans, cash) due to use of these drugs for other indications (e.g. cluster headaches). Second, because we do not have information on the indication for prescriptions in our study, we do not know whether concomitant use of opioids or NSAIDs is meant for migraine therapy or treatment of other conditions.

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 reflected by the large proportion of individuals who only received one triptan prescription.

Review of the Observational Literature

Although clinical trials typically report rates of adverse events, given their size, duration, and strict inclusion criteria, these rates are not generalizable to the general population and typically lack the power to determine their clinical and statistical significance. Furthermore, most trials do not include individuals over the age of 65,⁹ and product monographs do not recommend the use of triptans in the elderly (with the exception of almotriptan) because of lack of evidence in this population. Despite this, these medications continue to be used in the elderly, both in Ontario (as described earlier in this report) and elsewhere.^{10;11} Observational studies can often provide sufficient power and valuable insights into studying issues related to drug safety.

Objectives

We conducted a rapid review of the literature to investigate the prevalence and risk of adverse events among triptan users in observational studies. Secondary objectives were to assess these risks specifically among the elderly population and the relationship between triptan dose and adverse events.

Methods

We performed a PubMed search for articles relating to triptan safety using combinations of the search terms “triptans”, “adverse events”, “cardiovascular disease”, “migraines”, “safety” and “elderly”. In order to capture real world prescribing trends, we included any articles so long as their study population did not exclude seniors over 65. We further restricted our search to English-language only observational studies published in the last 20 years, and excluded single case reports. We searched the reference list of all articles that met our inclusion criteria to identify any additional relevant articles.

Results

Triptans and Vascular Events

We identified two studies from the United States and the United Kingdom that investigated serious cardiac and cerebrovascular events among triptan users and a review of reports submitted to the United States Food and Drug Administration (FDA) Adverse Events Reporting System database. Furthermore, the American Headache Society convened an Expert Panel to review the cardiovascular safety of triptans, which is summarized below.

In 2004, Velentgas et al reported the findings of a retrospective cohort study of 260,822 UnitedHealthcare members in the United States (average age 38.2 years).¹² This study compared rates of serious outcomes between triptan users and non-users. This study found no significantly increased risk of myocardial infarction (MI; rate ratio (RR), 0.80, 95% confidence interval (CI) 0.58-1.11), stroke (RR 0.90, 95% CI 0.64-1.26), serious ventricular arrhythmia (RR 1.00, 95% CI 0.45-2.20), or transient ischemic attacks (TIA) (RR 0.98, 95% CI 0.66-1.45) among current triptan users versus non-users. Current triptan users were found to have a slightly reduced risk of unstable angina (RR 0.72, 95% CI 0.55-0.94) and death (RR 0.64, 95% CI 0.45-0.89) compared to non-users. No significant findings were observed when comparing recent triptan users to non-users. This study had several limitations, including invalidated outcome definitions and an inability to adjust for several important confounders (e.g. smoking status).

Therefore, it is possible that the findings of a protective effect of triptans for unstable angina and death are due to unmeasured confounding.

An epidemiologic study of the General Practice Research Database (GPRD) in the United Kingdom¹³ compared rates of MI, stroke, TIA, non-MI ischemic heart disease (IHD), ventricular arrhythmias and all-cause mortality among 13,664 triptan users (6.8% of whom were aged 60 or older) and 27,328 matched controls. This study found that triptans were not associated with increased risks of stroke (adjusted hazard ratio [aHR] 1.13, 95% CI 0.78-1.65), MI (aHR 0.93, 95% CI 0.60, 1.43), IHD (aHR 1.22, 95% CI 0.96-1.53), or death (aHR 0.81, 95% CI 0.65, 1.01). Analyses were not performed for TIA and ventricular arrhythmia due to data quality and sample size concerns. Furthermore, triptan exposure was defined by any prescription during the study period; due to the “as needed” nature of triptan therapy, the exact timing of exposure in relation to each outcome could not be determined. The authors also note that patients with cardiovascular risk factors were less likely to receive triptans, and therefore these findings cannot be extrapolated to migraine patients in which triptan therapy is contraindicated.

In response to questions on the cardiovascular safety of triptans, the American Headache Society (AHS) convened the Triptan Cardiovascular Safety Expert Panel in 2002 to review existing evidence and form recommendations on triptan prescribing as it pertained to cardiovascular risks.¹⁴ The panel was composed of a variety of experts in neurology, primary care, cardiology, pharmacology, women’s health, and epidemiology. Several different sources of information were reviewed, including epidemiological studies, clinical trial data, post marketing surveillance data, pharmacologic and pharmacodynamic studies, and clinical risk assessments. The panel concluded that although serious cardiovascular adverse events can occur among triptan users, these are typically rare. Based on this, it was recommended that the benefits of triptans outweigh the risks among patients without contraindications. There was insufficient evidence for the panel to reach a conclusion on the safety of triptans among patients with known risk factors.

A more recent review of reports submitted to the United States (US) FDA Adverse Events Reporting System database between 2004 and 2010¹⁵ aimed to characterize the safety of triptans in clinical practice. The authors focused on evaluating the association between triptan use and risk of vascular events, particularly those that were rare or serious. Out of more than 2 million FDA reports, 7,808 involved triptans; of these, 2,593 (33.2%) involved serious cardiac or vascular events. The average age of patients was 44 (range 0-90 years), and the ratio of female to male reports was approximately 5 to 1. Reporting odds ratio (ROR) values were calculated from a case/non-case analysis. The authors found an association between triptans and cardiovascular signs and symptoms (i.e. feelings of heaviness or tingling in the chest or limbs, generally termed “triptan sensations”) (adjusted ROR 2.29, 95% CI 1.93-2.72). Ischemic cerebrovascular events such as ischemic stroke (22 cases) and cerebral infarction (26 cases) had adjusted reporting odds ratio (ROR) values of 2.73 (95% CI 1.75-4.22) and 1.71 (95% CI 1.14-2.54), respectively. These were considered unexpected as previous observational studies^{12;13} did not find significant associations between triptan use and cerebrovascular events. Aneurysms and artery dissections were also found to be related to triptan use. In particular, the authors found a strong association between triptans and carotid artery dissections (8 cases; adjusted ROR 27.21, 95% CI 12.09-

58.21), although the authors note that there have not been any published case reports to date. This study has several notable limitations. Firstly, because reports have to be submitted to the FDA Adverse Event Reporting System proactively by healthcare professionals, patients, or manufacturers, underreporting, duplicate reporting, or selective reporting of events are very real concerns. Secondly, the reports that are submitted may contain only incomplete information. In particular, the exact timing of exposure to the drug of interest is often unclear, thereby forcing the authors to make assumptions as to whether the drug was related to the event. Lastly, the case/non-case method of analysis is less robust than others.

Key Findings

Evidence relating to the vascular safety of triptans is sparse and inconsistent. Although two population based studies and an Expert Panel did not find evidence of cardio- or cerebrovascular risks with triptan use, a more recent study of FDA adverse events reports suggests that there may be a significant, although rare, risk of severe ischemic events among triptan users in the US. However, the quality and validity of these studies is highly variable.

Triptans and Vascular Events in the Elderly

Evidence relating to the cardiovascular safety of triptans among the elderly is sparse. In a review conducted by Haan et al. in 2007,⁹ the authors concluded that triptans can generally be used after the age of 60 years if, and as long as, there are no cardiac contraindications. Similar conclusions were also generated in one study examining overall management of migraines in the elderly population.¹⁶ However, both authors noted the lack of evidence related to the cardiovascular safety of triptans in the elderly, and conclusions are typically based primarily on clinical advice and consensus.

A case-control study published as a conference abstract by Salem et al. in 2012¹⁷ investigated whether the risk of death, myocardial infarction, ischemic heart disease and ischemic stroke was increased in elderly migraineurs treated with triptans in the United States compared to non-migraineurs who did not receive a triptan. A total of 27,059 migraineurs over the age of 65 were identified of whom 3,726 (13.8%) used triptans. The authors found no association between triptan use and risk of death (odds ratio (OR) 0.73, 95% CI 0.53-1.02), MI (OR 0.86, 95% CI 0.59-1.26), or ischemic stroke (OR 1.15, 95% CI 0.84-1.59) compared with non-migraine controls (who did not use triptans). However, this study found that triptan users had fewer cardiovascular risk factors than non-triptan treated patients with migraines (including less hypertension, hyperlipidemia, diabetes, prior stroke, MI or ischemic heart disease), suggesting that triptans were preferentially prescribed to older patients with low risk of cardiovascular disease.

Key Findings

Meagre evidence suggests that triptans may be safe in elderly patients with low risk of cardiovascular disease. The lack of evidence in the elderly may be attributable to several factors such as declining prevalence^{16;18} and disappearance of migraine symptoms with advancing age as well as prescriber preference not to prescribe triptans to elderly patients at risk of cardiovascular disease. More evidence is needed to elucidate whether older patients using triptans are at an elevated risk for any

cardiovascular events, irrespective of underlying cardiovascular risk factors.

Triptans and Other Adverse Events

Although most studies evaluating the safety of triptans focus on cardiovascular risks, two recent studies have investigated the association between triptan use and other risks.

The review of the FDA Adverse Event Reporting System¹⁵ highlighted several unexpected adverse events. Along with assessing the cardio- and cerebrovascular safety of triptans, the authors placed a particular focus on evaluating the association between triptan use and other rare or serious events. The authors found an association between triptans and pregnancy-related outcomes such as pregnancy-induced hypertension (5 cases; adjusted ROR 7.61, 95% CI 2.75-19.14) and placental infarction (3 cases; adjusted ROR 12.68, 95% CI 3.23-42.70). This raises questions regarding the safety of triptan use during pregnancy, however is based on a very small number of cases. More research would be needed to confirm these findings.

A case-control study by Spoenlin et al.¹⁹ using a large electronic medical record database (GPRD) in the United Kingdom explored the association between triptan use and risk of developing rosacea. In all, 53,927 incident rosacea cases were matched to the same number of rosacea-free controls. Almost one-quarter (23.7%) were aged 60 years or older and 62.8% were female. Overall, 2,836 (2.7%) subjects (1,590 cases and 1,246 controls) were dispensed at least one triptan prescription prior to their rosacea diagnosis date (or matched index date for controls). The authors found a small but significant association between triptan exposure and incident rosacea (aOR 1.30, 95% CI 1.20-1.40), regardless of duration of triptan therapy. Interestingly, this association was not significant in men of any age, including those above 60 (aOR for men aged ≥ 60 1.07, 95% CI 0.69-1.65). Among women, the risk of triptan-associated rosacea was significant in all age groups, and increased with age; among older women (aged ≥ 60 years), the authors found a 66% increased risk of developing rosacea (aOR 1.66, 95% CI 1.30-2.10).

Key Findings

There has been very little evidence on the relationship between non-vascular adverse events and triptan use, although limited evidence of variable quality suggests increased risks of pregnancy-related outcomes and rosacea among triptan users.

Triptan Dose and Adverse Events

Although guidelines recommend limiting triptan use to no more than 10 days per month [CHS, IHS] to avoid medication overuse headache, in real-world clinical practice many patients receive triptan quantities that exceed these.^{10-12;20-22} One small retrospective chart review and two case-control studies have investigated whether high levels of triptan use was associated with an increased risk of adverse events.

In 2004, Robbins²² performed a retrospective chart review of 118 long-term patients at the Robbins Headache Clinic (Illinois, USA) who used triptans more than 4 days a week for more than 6 consecutive months. All patients were routinely subjected to laboratory tests and electrocardiograms to screen for

any abnormalities that might have developed as a result of triptan therapy. The results of the blood tests, which included measures of liver and kidney function, did not show any abnormalities that were felt to be related to triptan use. The electrocardiograms found the majority of patients to have normal cardiac function; 8 patients (6.8%) had abnormal results, which were also deemed unrelated to triptan use. Further testing by echocardiogram with Doppler flow was performed on 57 patients; 10 (17.5%) had abnormal results. All cases were reviewed by a cardiologist, who concluded that the abnormalities were not associated with triptan use. Overall, 17 patients (14%) experienced mild adverse events related to triptan use such as fatigue (9 patients, 7.6%), nausea (3 patients, 2.5%) and feelings of tingling or heaviness in the limbs and chest (i.e. “triptan sensations”; 5 patients, 4.2%). Although no serious cardiac events were found to be associated with frequent, long-term use of these drugs, this was a small chart review with no comparator population of triptan non-users, and the criteria used to determine if abnormal results were deemed unrelated to triptan use were not clear.

Two retrospective case-control studies conducted in the Netherlands and France also investigated this question. In 2006, Wammes-van der Heijden et al. reported a retrospective, nested case-control study of community pharmacy dispensing records (PHARMO Record Linkage System) in The Netherlands examining the relationship between intensity of triptan use and ischemic events.²⁰ Cases were defined as triptan users who were hospitalized for ischemic heart disease, Raynaud syndrome, peripheral vascular disease, vascular insufficiency of intestine, gangrene, and cerebral ischemia. A total of 105 cases were matched to 407 controls selected from the population of triptan users who did not experience an ischemic event during the study period. More than two-thirds of the matched cohort was female (67.6% cases; 70.4% controls), and approximately 20% of the patients were over 65 years of age (21.3% cases; 19.2% controls). Medication overuse was defined as use of triptans on more than 10 days per month for at least 3 consecutive months, or ≥ 90 defined daily doses (DDD) per year. The authors found that triptan overuse did not increase the risk of ischemic events (adjusted odds ratio [OR] 0.96, 95% CI 0.49-1.90) when compared to non-use. In an analysis stratified by cardiovascular risk, the authors observed an increased, but non-significant, risk of ischemic events among patients with past use of cardiovascular medications (OR 2.28 [95% CI 0.68-7.65]).

Similarly, a case-control study of a French health system database²¹ investigated the association between the intensity of triptan use and risk of cardiac events. Cases and controls were selected from a nest population of 8,625 new triptan users. The authors identified 155 cases who had experienced an ischemic cardiac event between triptan initiation and December 2003, and 620 age- and sex-matched controls. On average, patients were 50 years of age, and 69% of the study population was female. Low, and intermediate/high triptan exposure were defined as ≤ 8 and > 8 defined daily doses per 30-day period, respectively. No cases were found to have 15 or more defined daily doses per 30-day period. Intermediate/high triptan users were not found to have an increased risk of cardiac events (OR 1.14, 95% CI 0.58-2.25) compared to non-triptan users. Similarly, no significant association was found between low triptan use and risk of cardiac events (OR 0.74, 95% CI 0.31-1.77).

Key Findings

There does not appear to be an increased risk of serious ischemic events among high dose users of triptans.

Key Findings of Literature Review

There have been several observational studies examining the association between triptans and adverse events that reflect triptan use in clinical practice. Overall, more than 12 years of evidence have demonstrated low rates of serious adverse events among triptan users. Furthermore, despite the pharmacologic plausibility of cardiovascular and ischemic events associated with triptan use, the risks of such events appear to be low and triptans have been deemed safe for use among patients without preexisting cardiovascular risk factors by various groups. However, evidence is sparse among the elderly and those with cardiovascular conditions, and therefore the safety of triptans has not been firmly established in these populations. Although triptan use is increasing among seniors, adverse events are difficult to measure in this group as triptans are typically preferentially prescribed to those without risk factors.

Conclusions

The findings of this analysis suggest that the restrictive nature of access to publically-funded triptans has led to very low use of these drugs through public drug programs in Ontario, and slightly higher than average access through private drug plans and out-of-pocket payments. Although this analysis cannot determine the appropriateness of restricted triptan access through the public drug program, evidence regarding the effectiveness and cost-effectiveness of triptans will help illuminate this issue. Triptans have been shown to be safe and effective among individuals without contraindications; however, there is limited evidence on the safety of these drugs among seniors. Furthermore, despite low rates of publically funded triptan use, the lack of triptan quantity limits in Ontario reimbursement policy has led to large quantities of these products being dispensed that are likely putting many patients at risk of medication overuse headache.⁵

Appendix A: Public drug plan benefit listings

Drug	Brand name	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB
Almotriptan	Axert, generic	Ben	Res# Pas##	Res	No	Res*	Ben	Res	Res	Res	Res	Ben	Ben***
Eletriptan	Relpax, gen	No	No	No	No	No	Ben	No	No	No	No	No	No
Frovatriptan	Frova	No	No	No	No	No	No	No	No	No	No	No	No
Naratriptan	Amerge, generic	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	Res	Res	Ben	Ben***
Rizatriptan	Maxalt, generic	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	No	Res	Ben	Ben***
Sumatriptan	Imitrex, generic	Ben**	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	Res	Res	Ben	Ben***
Zolmitriptan	Zomig, generic	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	Res	Res	Ben	Ben***
Quantity Limits (monthly)		None	None	6	12	None	None	6	6	6	6	None	12

No=not listed

Res=restricted listing - enforced

Pas= restricting listing - passive

Ben=unrestricted listing

*EAP=Exceptional Access Program

**Special authority required for injectable sumatriptan

***General benefit with quantity limits imposed

#Restricted listing enforced for patients 65 years and older

##Restricted listing passive for patients aged 18-64

Appendix B: Defined Daily Doses for Triptans

Generic name	Dosage forms	Usual dose	Maximum dose (per 24 hours)	Defined Daily Dose
Almotriptan	Tablets (6.25mg, 12.5mg)	12.5mg	25 mg	12.5
Eletriptan	Tablets (20mg, 40mg)	40mg	80mg*	40
Frovatriptan	Tablets (2.5 mg)	2.5mg	5mg	2.5
Naratriptan	Tablets (1 mg, 2.5 mg)	2.5mg	5mg	2.5
Rizatriptan	Tablets (5mg, 10mg)	10mg	20mg	10
	Wafers (orally disintegrating tablet) (5 mg, 10mg)	10mg	20mg	10
Sumatriptan	Tablets (25 mg, 50mg, 100mg)	100mg	200mg	50
	Tablets (fast-dissolving) 50mg, 100mg	100mg		50
	Injection (6mg/0.5mL)	6mg	12mg	6
	Nasal spray (5 mg/dose, 20 mg/dose)	20mg	40mg	20
Zolmitriptan	Tablets (2.5 mg)	2.5mg	10mg	2.5
	Orally disintegrating tablet (2.5 mg)	2.5mg	10mg	2.5
	Nasal spray (2.5 mg/spray, 5 mg/spray)	5mg	10mg	2.5

Appendix C: Public Drug Coverage by Province

Jurisdiction	Plan Description
Alberta	Non-Group, Seniors, Palliative Care
Manitoba	Employment and Income Assistance Program, Palliative Care, Pharmacare, Personal Home Care/Nursing Homes
New Brunswick	Seniors, Cystic Fibrosis, Individuals in Licensed Residential Facilities, Family and Community Services, Children in Care of the Minister of Family and Community Services, Multiple Sclerosis Patients, Organ Transplant, Human Growth Hormone, HIV, Nursing Home
Nova Scotia	Drug Assistance for Cancer Patients, Diabetic Assistance Pharmacare program, Pharmacare Long Term Care (Under 65), Seniors' Pharmacare Program, Family Pharmacare Program
Prince Edward Island	Diabetes Control, Family Health Benefit, High Cost Drug, Nursing Home, Drug Cost Assistance, Children-in-care Financial Assistance, Sexually Transmitted Diseases, Quit Smoking Program
Ontario	Seniors, Trillium Drug Program (high drug costs), Long-Term Care or Home for Special Care, Home Care, Social Assistance, Special Drugs Program, Inherited Metabolic Diseases Program, Respiratory Syncytial Virus Program, Visudyne Program
British Columbia	Fair PharmaCare Plan, Residence of Licensed Residential Care Facilities, Income Assistance, Cystic Fibrosis, Children in the At Home Program, No-Charge Psychiatric Medication Plan, Palliative Care Drug Plan, Smoking Cessation Program, Antiretroviral Medications
Quebec	Seniors, Persons who are not eligible for a private plan, Recipients of Last-Resort Financial Assistance, Children of Persons Covered by the Public Plan
Newfoundland and Labrador	Seniors, Income Support, High Drug Costs, Cystic Fibrosis, Growth Hormone Deficiency

Appendix D: Timeline for generic triptans

Drug Name	Generic available	Brand name/ generic	Dosage form	Cost (for 6 tablets or uses) ¹	Date commercially available
Almotriptan	Yes	Axert	Oral	\$82.57	8-Dec-03
		Generic	Oral	\$61.98	22-Jul-13
Eletriptan	Yes	Relpax	Oral	\$86.65	13-Oct-04
		Generic	Oral	\$60.51	11-Oct-12
Frovatriptan	No	Frova	Oral	\$87.19	4-Jan-08
Naratriptan	Yes	Amerge	Oral	\$89.70	5-May-98
				\$94.55	
		Generic	Oral	\$46.64	1-Dec-09
				\$49.28	
Rizatriptan	Yes	Maxalt	Oral, wafers	\$98.66	31-Aug-99
		Generic	Oral (tablets)	\$98.66	3-May-12
		Generic	Oral disintegrating tablet	\$66.69	30-Jan-12
Sumatriptan	Yes	Imitrex	Subcutaneous	\$251.40	30-Aug-99
		Generic	Subcutaneous	\$185.16	6-Jun-11
	Yes	Imitrex	Oral	\$95.95	11-Feb-97
				\$105.69	
				\$53.94	24-Aug-05
				\$54.39	
				\$59.92	
No	Imitrex	Transnasal	\$92.43	19-Feb-97	
			\$95.13		
Zolmitriptan	Yes	Zomig	Oral	\$88.69	5-Mar-01
		Generic	Oral	\$41.18	7-Jun-11
	Yes	Zomig	Rapid dissolving tablet	\$88.69	5-Mar-11
		Generic	Rapid dissolving tablet	\$41.18	7-Jun-11
	No	Zomig	Transnasal	\$88.71	23-Dec-04

¹ Price obtained from McKesson



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