ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Antipsychotics in the Elderly

FINAL Report: Pharmacoepidemiology Unit

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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Summary

Overall National and Provincial Trends in Antipsychotic Use in the Elderly

Prescriptions for antipsychotics (AP) to elderly patients in Canada have increased by nearly 32% over the past 4 years, from 2,954,248 prescriptions dispensed in the last quarter of 2009 to 3,912,013 prescriptions dispensed by the second quarter of 2014. A total of $75 million was spent on AP prescriptions dispensed to elderly patients nationally in the second quarter of 2014. The majority of AP prescription costs dispensed to elderly patients in Canada were for atypical AP (97%). Quetiapine was the most utilized atypical AP (50%) in Canada and the three most commonly used atypical AP (Quetiapine, risperidone, and olanzapine) accounted for 94% of all prescriptions across Canada. Newer atypical AP (aripiprazole, asenapine, paliperidone, lurasidone, ziprasidone) have increased in utilization growing from only 0.2% to over 5% of all atypical AP prescriptions between 2009 and 2014. This growth has meant that by the second quarter in 2014 they accounted for 19% of total atypical AP spending in Canada.

By the second quarter of 2014, Ontario had the third-highest rate of prescriptions for AP to elderly patients (592 prescriptions dispensed per 1,000 eligible population). The rate of AP prescribing was particularly high in Quebec compared to all other provinces (1,314 prescriptions dispensed per 1,000 eligible for Quebec vs. range of 303 to 625 prescriptions dispensed per 1,000 eligible for other provinces). When Ontario's rate of prescribing was compared to a national average that did not include Quebec (since Quebec is an outlier), Ontario's rate of prescribing (592 prescriptions per 1,000 eligible population) was higher the national average (495 prescriptions per 1,000).

National and Provincial Trends in Antipsychotic Use in the Elderly among Public Drug Plan Beneficiaries in 2013

In 2013, Ontario had the third lowest provincial rate of AP use in the elderly (58 users per 1,000 eligible) among public drug plan beneficiaries, in Canada. This rate was comparable to the national rate (comprised of 8 provinces) of 55 users per 1,000 eligible. This rate of use varied five-fold across provinces and age groups, with the lowest rates observed in PEI (29 users per 1,000 eligible), which has more restrictive public plan listings for AP. Over time, the rate of use of publicly-funded atypical AP in the elderly has increased in all provinces as the rate of use of typical AP in the elderly had decreased. Ratios of atypical AP compared to typical AP use ranged from 1.5 times in PEI to 5-times more use in New Brunswick. Annual costs per user varied across age groups with the highest costs found among users aged 65-74. Among those 65-74 years of age, Saskatchewan had the highest average annual drug cost per user ($185.69 per user) while Ontario had the lowest average annual drug cost per user ($151.25 per user).

Publically-funded Antipsychotic Use in the Elderly in Ontario

In the most recent 5 years (2009 to 2013) the overall rate of elderly atypical antipsychotic users has increased by 6% from 32.4 per 1,000 eligible in Q1-2009 to 34.4 per 1,000 eligible in Q4-2013. In this same time period, the rate of users in the community has increased 26% from 17.8 per 1,000 eligible in Q1-2009 to 22.4 per

1,000 eligible in Q4-2013. In contrast, the rate of users in LTC has decreased 1.7% from 333.5 per 1,000 eligible in Q1-2009 to 327.7 per 1,000 eligible in Q4-2013. Ontario has seen a sharp decrease in the use of publically-funded typical AP in the elderly and an increase in use of publically-funded atypical AP. In 2000, the rate of typical AP use was higher than the rate of atypical AP use; however in 2001, the rate of atypical AP use surpassed that of typical AP use. There has also been an overall increase in AP utilization over time, which may be driven by the introduction of newer agents since 2009. In 2013 the rate of total AP use in Ontario was 58 users per 1,000 eligible patients. Rates of atypical AP use were found to be much higher among older patients (85 and older; 123 users per 1,000 eligible) and those living in Long-Term Care (LTC) (367 users per 1,000 eligible).

Characteristics of Elderly Antipsychotic Users in Ontario

In 2013, there were 72,488 provincially-funded AP users aged 65 and older who resided in the community and 32,580 resided in LTC in Ontario. The majority of users were prescribed atypical AP in both the community (N=45,210, 62.4%) and LTC (N=26,903, 82.6%).The majority of patients lived in urban areas, had lower socioeconomic status, and were using a median of 11 to 14 medications depending on location of residence (community vs. LTC, respectively). AP users residing in LTC were more likely to have dementia than users residing in the community (88.3% vs. 34.6%, respectively). Psychiatrists were the most commonly visited specialist in the 3 months prior to initiating AP therapy for patients residing in the community and LTC (15.7% and 11.2%, respectively); however general practitioners prescribed the majority of initial prescriptions in both the community and LTC settings (59.1% and 95.2%, respectively).

Patterns of Antipsychotic Use and Discontinuation among new Elderly Users with Dementia in Ontario

Between April 2008 and March 2013, we identified 34,195 elderly patients with dementia newly initiated on an AP who resided in the community, and 24,804 who resided in LTC. The rate of typical new-use was found to be much higher in the community compared to LTC (37.6% vs. 17%, respectively). A third of new-users were initiated on a low-dose (36%) of less than 25 mg of chlorpromazine equivalents. One year after initiation of therapy, only one-half of patients in both the community and LTC remained on therapy (50-55%). Further, among patients who were still on therapy after one year, approximately half of patients in both the community and LTC had a change in dose category (56.5% and 55.0%, respectively). No differences in the rates of discontinuation were found for those living in LTC compared to those in the community, but patients initiated on higher doses were found to be more likely to discontinue therapy.

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Acknowledgments

This review was supported by the Ontario Drug Policy Research Network which is funded by grants from the Ontario Ministry of Health and Long-Term Care Health System Research Fund. This study was also supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). 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 or the Ontario MOHLTC is intended or should be inferred. Datasets provided by ICES were linked using unique encoded identifies and analyzed at ICES. 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 (GPM[12]), data period October 1 2009 – June 30 2014.

Introduction

Antipsychotics (AP) are a drug class with a variety of indications related to mental health. Twenty-four AP are currently available in Canada and can be divided into one of two classes, the older typical (first generation) and the newer atypical (second generation) class (**See Appendix A and B**). Both AP classes are available in tablets, sublingual tablets, injections, long-lasting injections and oral liquid formulations. Both classes have slightly different pharmacology and serious, but varied, safety profiles. Safety concerns are heightened in specific subpopulations, particularly in elderly patients due to increased risk of morbidity and mortality.[1-4] These concerns have driven considerable attention regarding the appropriate utilization of this class among elderly patients.

The objectives of this report are to describe national and provincial trends in the use of AP in the elderly and to identify patterns of use among elderly users. Specifically, this report aims to:

1. Present national utilization trends of AP in the elderly across Canada, including cross-provincial comparisons of population-adjusted rates of use
2. Present cross-provincial public drug program utilization comparisons of AP in the elderly across Canada using population-adjusted rates of use
3. Examine trends in use of AP dispensed through the Ontario Drug Benefit program to elderly patients
4. Describe the characteristics of elderly patients treated with AP in Ontario
5. Describe the characteristics of course and length of AP therapy among people with dementia newly initiated on these products 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 age groups. Data from IMS Geographic Prescription Monitor (GPM[12]) is available from the fourth quarter of 2009 to the second 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, British Columbia, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island. Data from

NPDUIS is available from 2000 to 2013.

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 and older. This database is of high quality, with an error rate of <1% and can be linked to other health administrative databases to obtain patient demographic information.[5] We analyzed data from the ODB between January 2000 and December 2013.

Methods

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

National Trends in Utilization of Antipsychotics

We used data from IMS Geographic Prescription Monitor (GPM[12]) to examine overall trends in the prescribing volumes of AP in the elderly, at both national and provincial levels. We examined the number of prescriptions dispensed for AP products between October 2009 and June 2014. The analyses were limited to those aged 65 and older. To conduct cross-provincial comparisons of AP paid for by publically funded drugs we leveraged the NPDUIS data. All cross-provincial analyses compared population-adjusted rates.

Population Adjustment – Overall Utilization

For measures examining provincially-funded utilization of AP products, we used the number of individuals eligible for provincial drug coverage in each year from 2000 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.

Provincial population estimates were obtained from Statistics Canada for each year from 2000 to 2013 and used to adjust the overall utilization rates (per 1,000 elderly population) of AP across the different provinces.

Trends in Provincially-Funded Antipsychotics in Ontario

We used claims data from ODB to perform additional analyses of utilization of AP among elderly patients in Ontario. These analyses included estimating the utilization and costs of publically-funded AP products. Users were defined in these analyses as individuals who received at least one prescription for an antipsychotic over the period of interest. We also looked at baseline characteristics of elderly patients dispensed AP products using linked administrative databases housed at the Institute for Clinical Evaluative Sciences including the

CIHI Discharge Abstract Database (inpatient hospitalizations), the Registered Persons Database (demographic information), the Ontario Health Insurance Plan (OHIP) database (physician visits), and the ICES Physician Database (physician characteristics). Dosing was calculated by calculating equivalent daily dose (eDD) for all AP prescribed on the date of initiation, where each eDD was calculated by multiplying the daily dose (determined from the quantity, strength, and days' supply fields) by the chlorpromazine dose equivalent (**See Appendix C**).

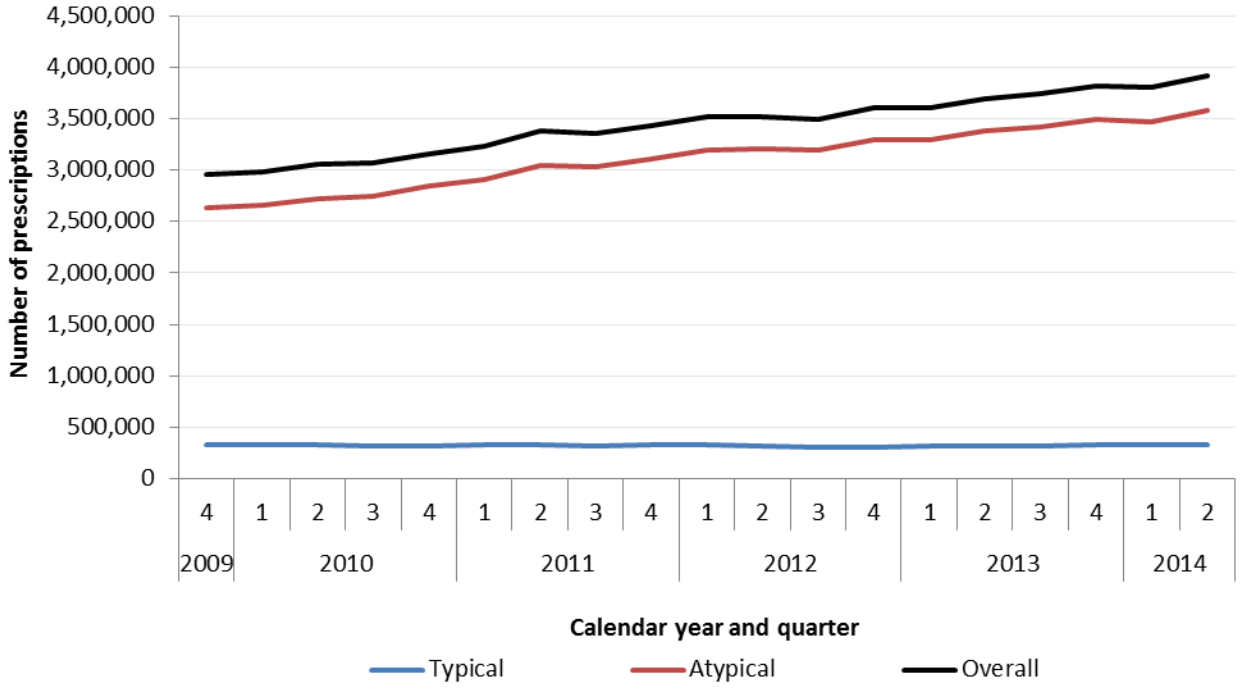
Adherence among New Users of Antipsychotics

We established a cohort of elderly patients with dementia (**See Appendix D**) who were new users of AP between January 1, 2009 and December 31, 2012, to examine the duration of AP use in Ontario. We used a validated dementia definition that used dementia diagnosis codes in the previous 5 years or a cognitive enhancer prescription dispensed to define patients for the cohort. 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 AP. We followed each individual forward from the time of their first prescription until they either discontinued therapy, died, had 2 years of follow-up or reached the end of the study period (December 31, 2013). Patients who switched drugs within the antipsychotic drug class were still considered to be persistent. Discontinuation of AP was defined on the basis of no subsequent prescription for an AP within 180 days of the previous prescription, which is consistent with previously published studies.[6,7] Due to the high proportion of death during follow-up for this cohort, competing risks analyses were used to estimate the time to discontinuation, overall and stratified by setting (community vs. LTC), dose level, and AP class. Gray's K-sample test was used to test for differences between stratified analyses.

Exhibits and Findings

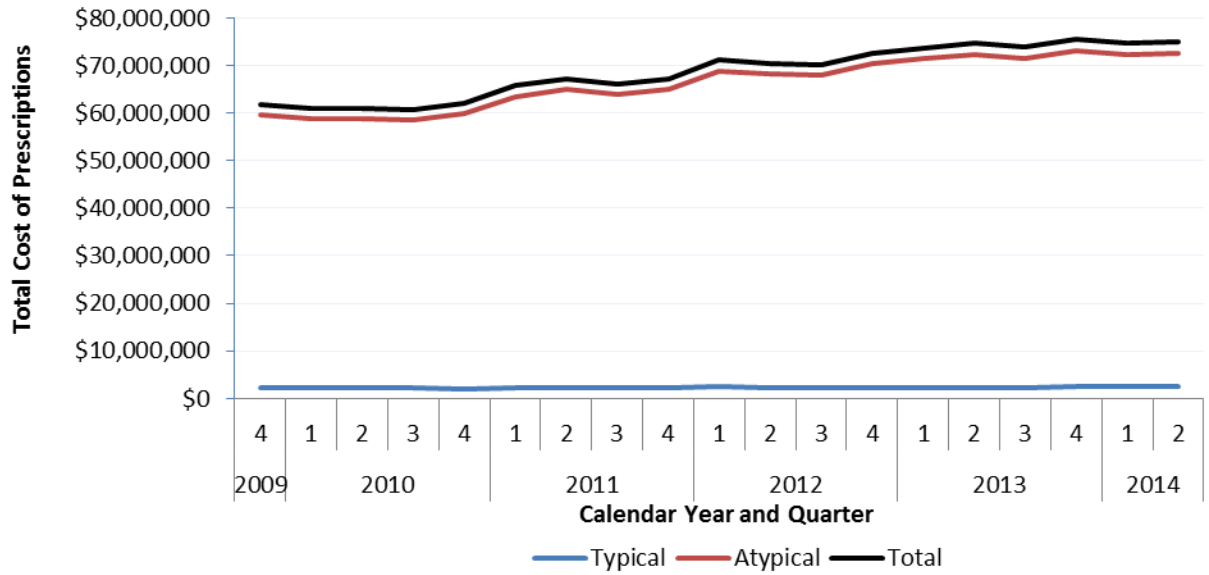
National Trends in Utilization of Antipsychotics in the Elderly

Exhibit 1: Total utilization of antipsychotics in Canada for patients 65 years of age and older, by class and quarter



Prescriptions for AP among elderly patients have increased by 32% over the past 4 years in Canada, with the majority of prescriptions for atypical AP. This growth in utilization is largely driven by increased atypical AP use and may also be driven by the growing elderly population.

Exhibit 2: Total cost of antipsychotics dispensed in Canada to elderly patients, by class and quarter

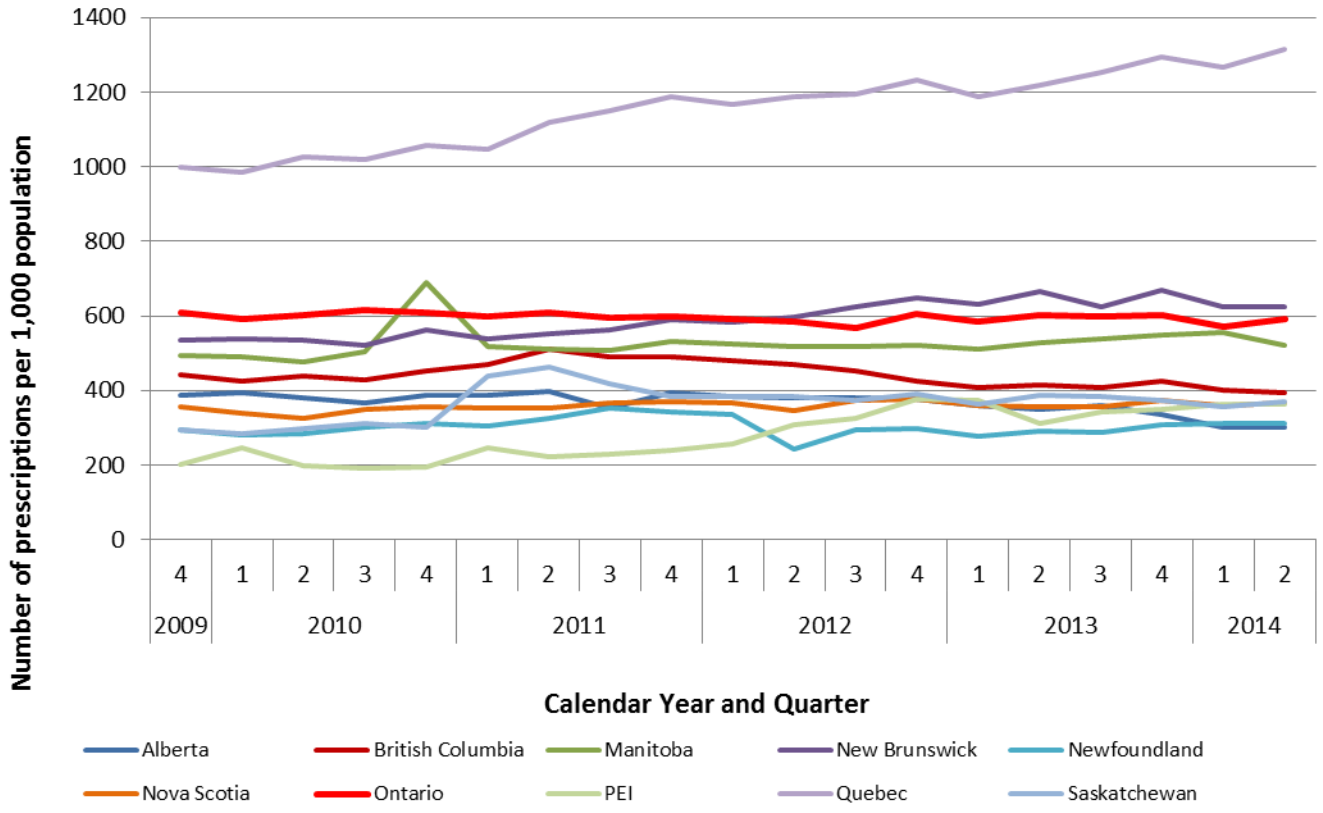


The cost of prescriptions for AP among elderly patients has increased by 21% over the past 4 years. The total cost of AP among the elderly was approximately $75 million in the second quarter of 2014.

Summary of Findings for Exhibit 1 and Exhibit 2

1. AP utilization in the elderly in Canada has increased 32% since Q4 2009, from a total of 2,954,248 prescriptions at the end of 2009 to 3,912,013 prescriptions by the second quarter of 2014.
2. By the second quarter of 2014, the majority (92%) of prescriptions dispensed in Canada were for atypical AP.
3. The number of prescriptions for atypical AP in the elderly has increased 27% over the study period (From 2,629,193 prescriptions in Q4-2009 to 3,578,862 prescriptions in Q2-2014), while prescriptions for typical AP have remained stable.
4. By the second quarter of 2014, a total of $75 million was spent on all AP products to elderly patients nationally, an increase of approximately 21% since Q4 2009 ($62 million). The majority of AP costs in Q2 2014 were attributable to atypical AP prescriptions (97%; $73 million).

Exhibit 3: Population-adjusted utilization of antipsychotics in the elderly in Canada by province



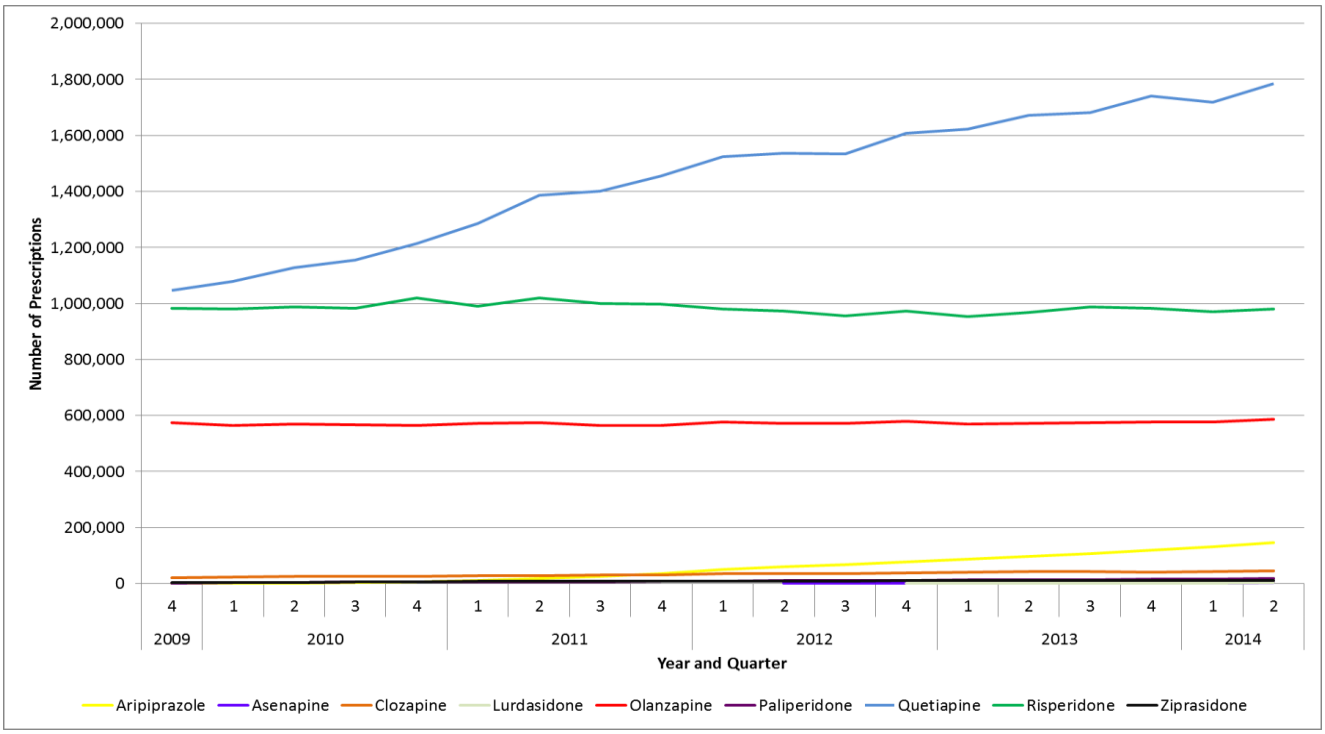
Ontario had the third highest rate of prescriptions for AP in the elderly in Canada by the end of the study period.

Summary of Findings for Exhibit 3

1. By the second quarter of 2014, Ontario had the third highest rate of AP prescriptions in the elderly (592 prescriptions per 1,000 elderly population compared to the national average of 701 prescriptions per 1,000 elderly population).
2. Quebec had the highest rates of AP prescriptions (1,314 prescriptions per 1,000 elderly population) and Alberta had the lowest rates of AP prescriptions (302 prescriptions per 1,000 elderly population).
3. Rate of AP use in Quebec were substantially higher (1,314 prescriptions per 1,000 elderly) than all other provinces. After excluding Quebec in calculations of national average, the national AP prescribing rate lowers to 495 prescriptions per 1,000 population. This places Ontario's AP prescribing rate well above the national average (592 prescriptions per 1,000 elderly population) when excluding Quebec's rate from the calculation.

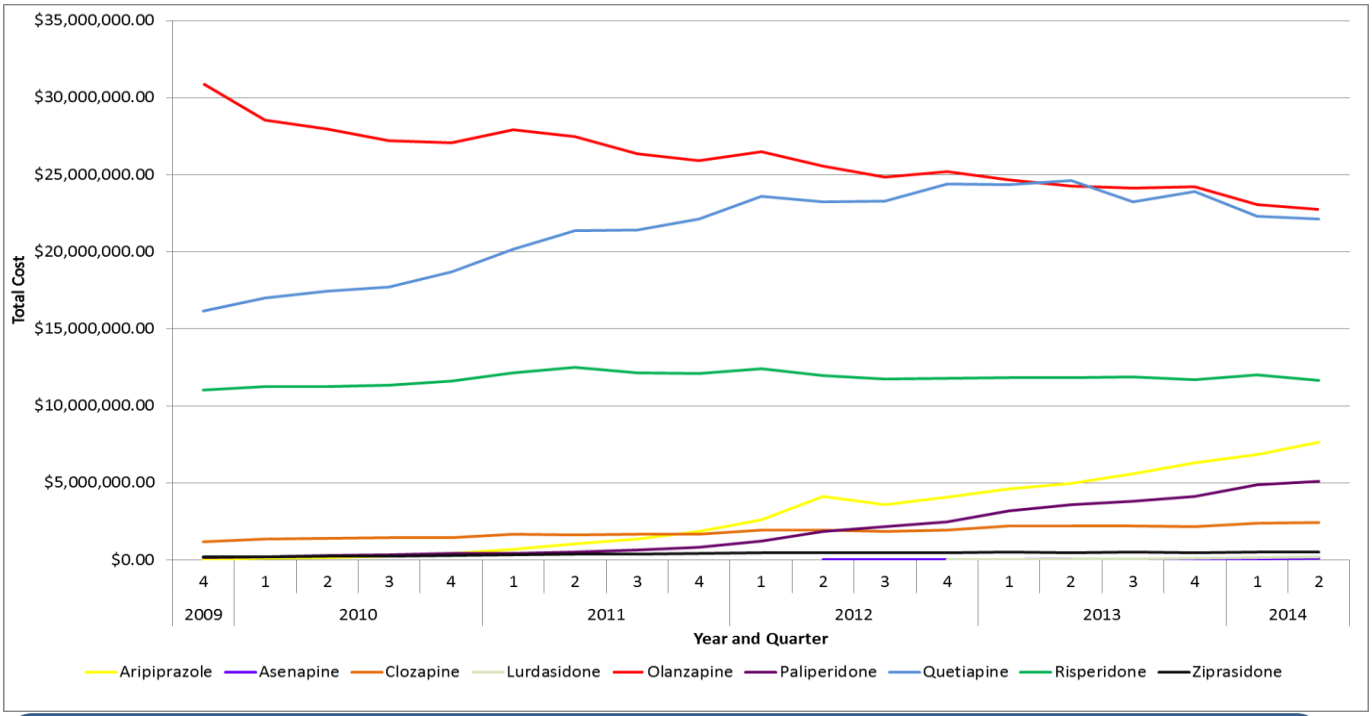
National Rates of Atypical Antipsychotic Use, by Drug

Exhibit 4: Total utilization of atypical antipsychotics in Canada among patients 65 years of age and older, by drug and quarter



Quetiapine is the most commonly prescribed atypical AP in Canada, and its use has increased in the past 5 years. By Q2-2014, 50% of all atypical AP prescriptions in Q2-2014 were for quetiapine.

Exhibit 5: Total cost of atypical antipsychotics in Canada for patients 65 years of age and older, by drug and quarter



Cost of newer atypical AP (aripiprazole, paliperidone, asenapine, lurasidone) is growing nationally among elderly patients. By Q2-2014, these newer agents accounted for 18% of spending but only 5% of prescriptions.

Summary of Findings for Exhibit 4 and Exhibit 5

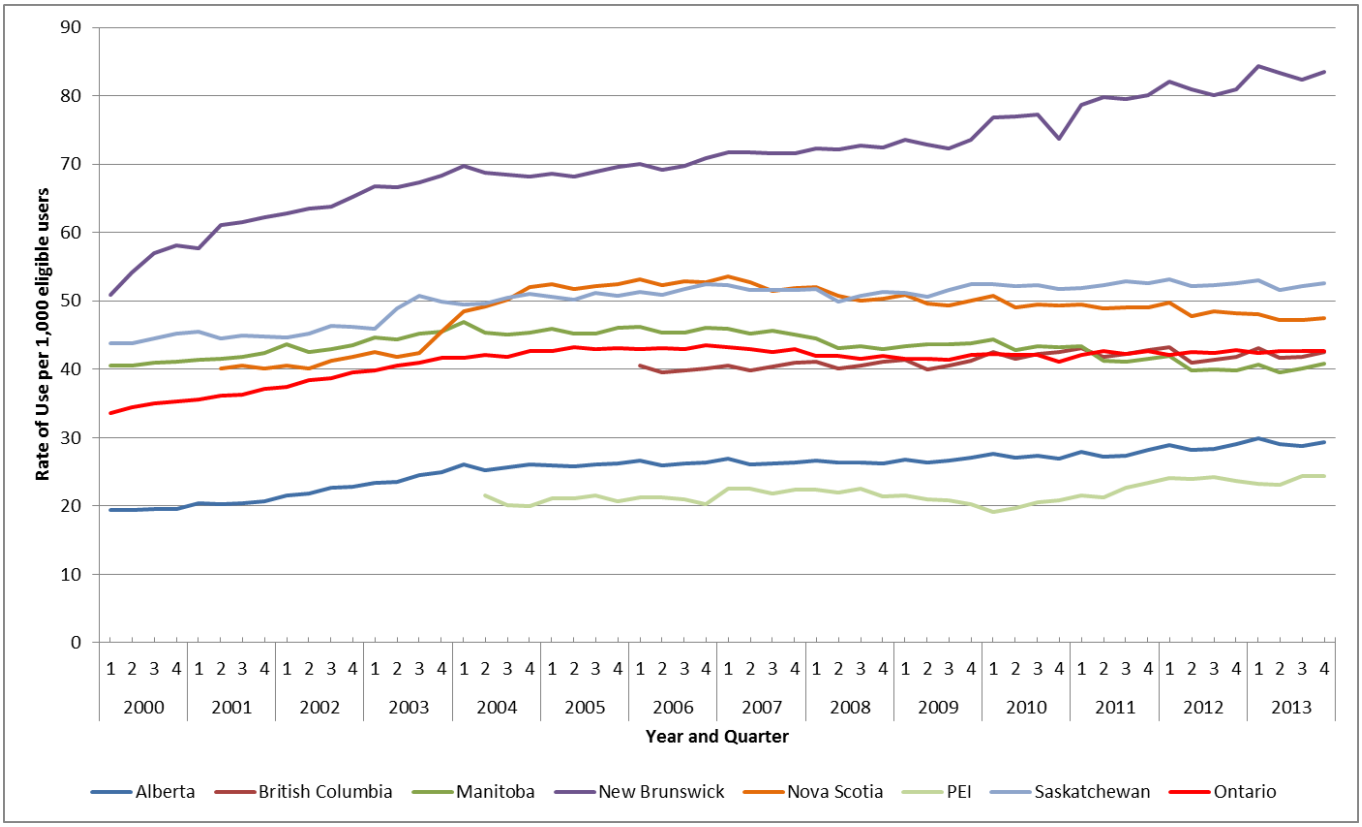
1. Quetiapine is the most commonly prescribed atypical AP in Canada, accounting for 50% of all atypical AP prescriptions to elderly patients in the second quarter of 2014. Quetiapine use has increased 71% over time growing from 1,045,776 prescriptions in Q4-2009 to 1,784,179 in Q2-2014.
2. Quetiapine, risperidone, and olanzapine are the 3 most prescribed atypical AP and account for 94% of atypical AP prescriptions (3,351,076 prescriptions in Q4-2014) and 78% of total cost ($56,555,847 in Q4-2014) across Canada.
3. Use of newer atypical AP has grown from being only 0.2% of all atypical prescriptions (5,979 prescriptions in Q4-2009) to 5% of total atypical AP prescriptions (181,443 prescriptions in Q2-2014).
4. In the second quarter of 2014, newer atypical AP (aripiprazole, asenapine, paliperidone, lurasidone, ziprasidone) accounted for just 5% of prescriptions (169,752) but 19% of total costs ($13, 536,377) in Q4-2014.

Population-adjusted Rates of Antipsychotic Utilization, Among Public Plan Beneficiaries

Methodological Note:
The following analyses are conducted using public drug beneficiary data collected by the Canadian Institute for Health Information NPDUIS and ICES. No data was available for Quebec and Newfoundland & Labrador.

Due to incomplete historical data, trends over time are not available for the full study period in some provinces.

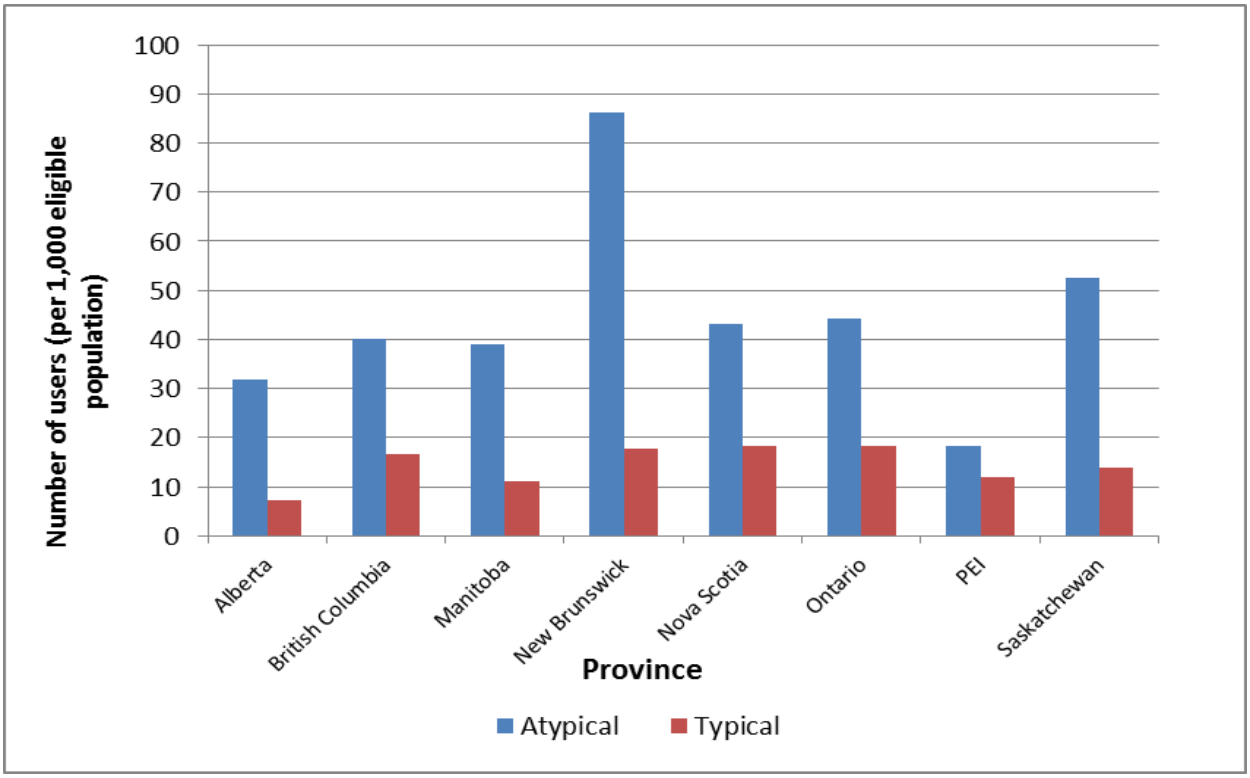
Exhibit 6: Population-adjusted utilization of provincially-funded antipsychotics among elderly patients in Canada by province, 2000-2013



All provinces have seen an increase in the rate of AP use among publically-funded elderly patients. Ontario's rate of AP use was approximately similar to the average national rates by the end of 2013. Alberta and PEI had the lowest rates of use in Canada.

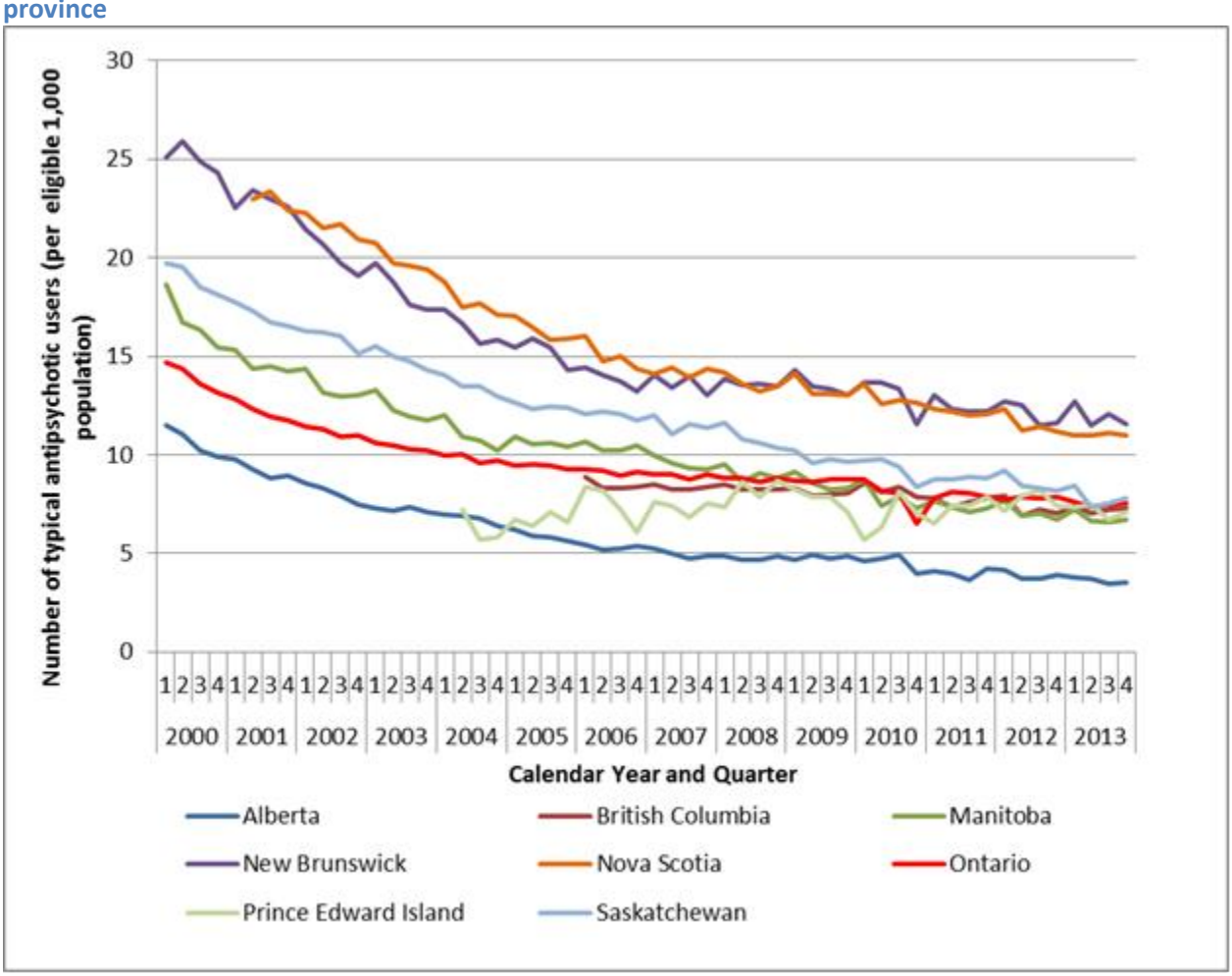
Provincially-funded Rates of Antipsychotic Use, by Class

Exhibit 7: Population-adjusted utilization of provincially-funded antipsychotics in the elderly in Canada by province and antipsychotic class, 2013



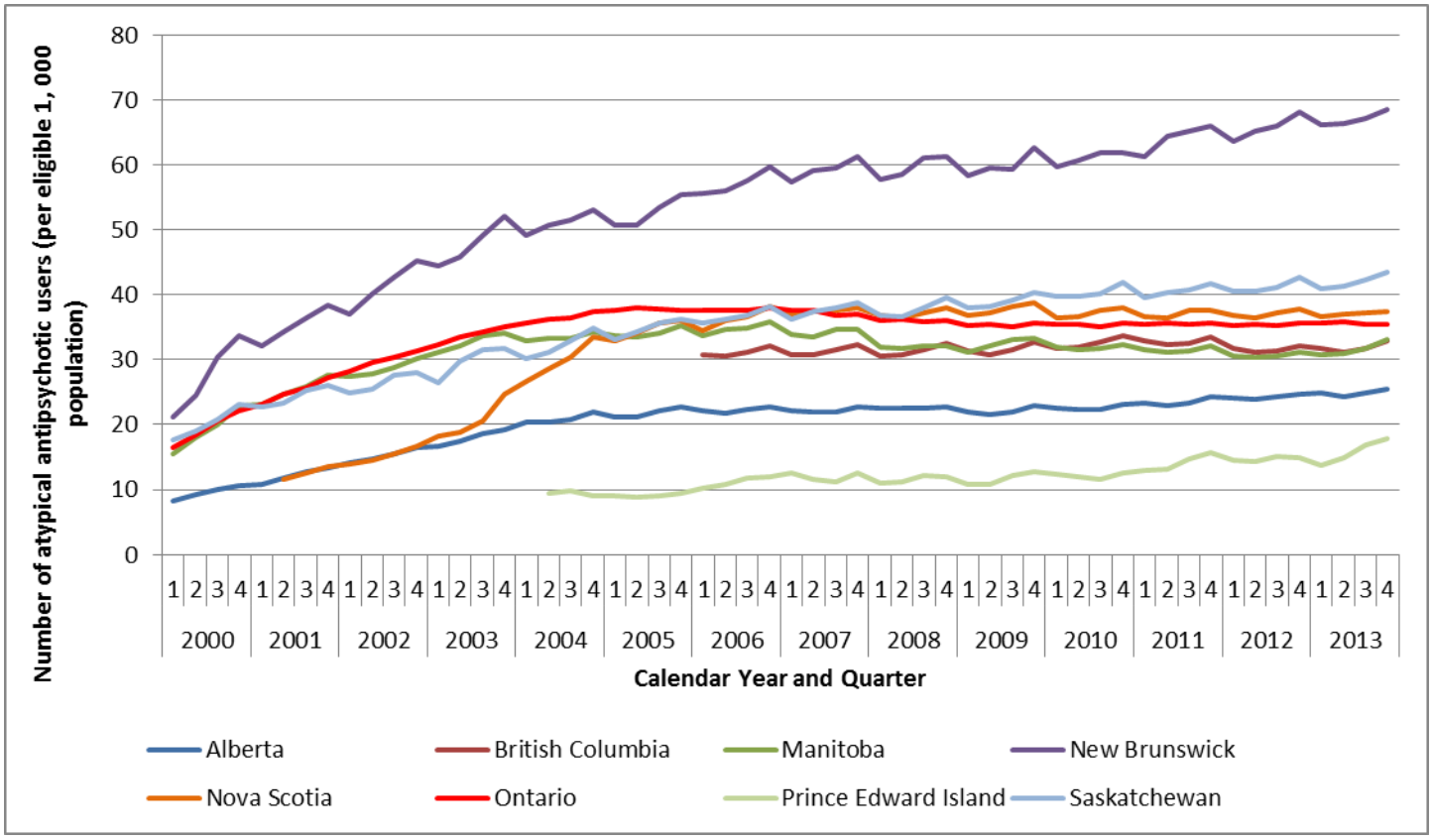
The prevalence of atypical AP users was higher than typical AP users across all provincial drug plans in 2013

Exhibit 8: Rate of Typical Antipsychotic use among Public Drug Plan Beneficiaries over 65 years of age, by province



All provinces, with the exception of PEI, have seen a decrease in the rate of use of typical AP among publically-funded elderly patients. Ontario rates were comparable to the average rates of publically-funded use nationally by the end of 2013.

Exhibit 9: Rate of Atypical Antipsychotic use among Public Drug Plan Beneficiaries over 65 years of age, by Province



All provinces have seen an increase in the rate of use of atypical AP among publically-funded elderly patients. Rate of atypical antipsychotic users in Ontario rose quickly between 2000 and 2004 before plateauing in 2005. By the end of 2013, Ontario's rate of publically-funded atypical AP use was similar to the national average.

Exhibit 10: Characteristics of antipsychotic users among elderly public drug program beneficiaries in 2013, by province and age group

Province	Total Number of Antipsychotic Users	Total Number of Eligible Population	Mean Age	Rate of Use per 1,000 Eligible Population					
					Age Group			Class of Antipsychotic	
				Overall	65-74	75-84	85+	Typical	Atypical
Alberta	15,429	411,322	77	38	34	43	77	7	32
British Columbia	34,825	669,940	79	52	43	59	134	17	40
Manitoba	7,966	171,195	80	47	36	51	108	11	39
Saskatchewan	9,248	149,505	81	62	42	67	143	14	52
Nova Scotia	6,432	112,780	79	57	44	63	124	18	43
New Brunswick	7,181	73,482	79	98	78	99	207	18	86
PEI	660	23,051	79	29	22	32	71	12	18
Ontario	**114,805**	**1,970,479**	**79**	**58**	**44**	**64**	**123**	**18**	**44**

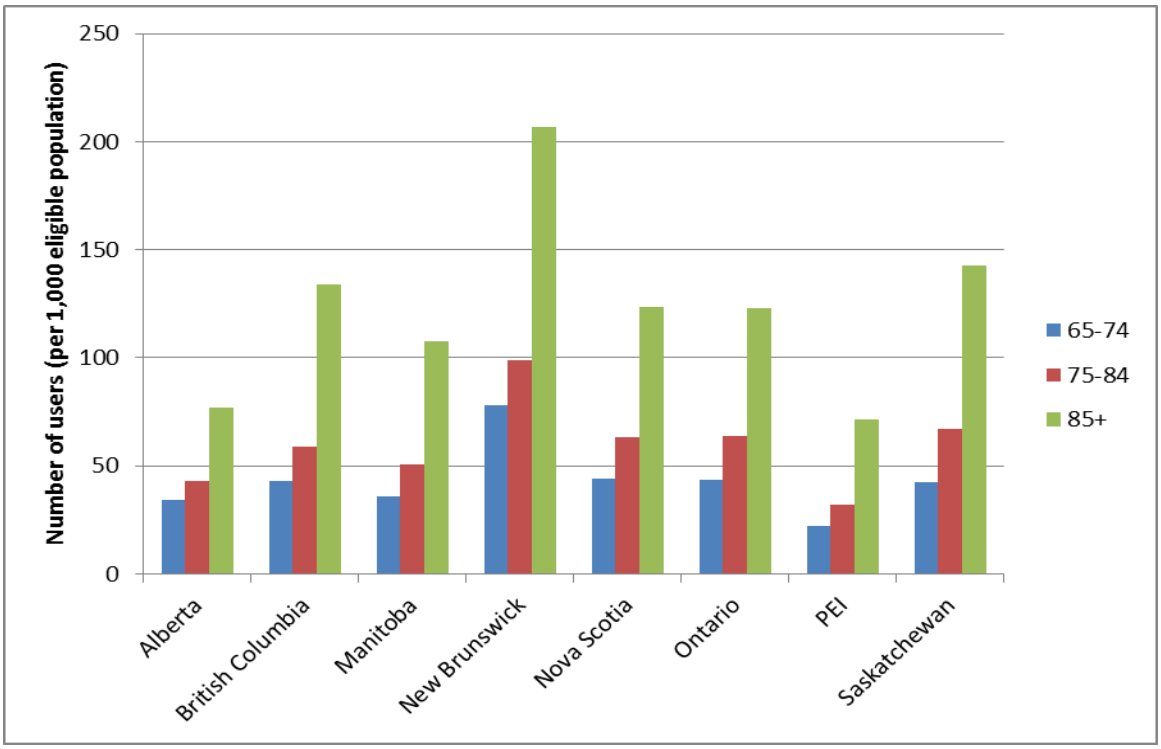
AP utilization rates vary among elderly public drug plan beneficiaries across Canada, with the lowest rates in Prince Edward Island and the highest rates in New Brunswick in 2013.

Summary of Findings for Exhibit 6 to 10

1. Ontario's rate of both atypical and typical AP use was close to the national average.
    a. Typical AP: 8 users per 1,000 elderly eligible in Ontario vs. 8 users per 1,000 elderly eligible nationally
    b. Atypical AP: 35 users per 1,000 elderly eligible in Ontario vs. 37 users per 1,000 elderly eligible nationally
2. Rates of atypical AP users were higher than rates of typical AP users across all provinces. The greatest difference was seen in New Brunswick where the rate of atypical AP use was 5-fold higher than typical AP use (86 users per 1,000 eligible population vs. 16 users per 1,000 eligible population, respectively).
3. The prevalence of atypical AP use varied considerably between provinces, ranging from 18 users per 1,000 eligible population in PEI to 86 users per 1,000 eligible population in New Brunswick.
4. Prevalence of typical AP use varied less between provinces, ranging from 7 users per 1,000 eligible population in Alberta to 18 users per 1,000 eligible population in New Brunswick, Ontario and Nova Scotia
5. In Ontario, the rate of atypical AP has increased by 214% and the rate of typical has decreased by 43% between the Q1-2000 and Q4-2013. This suggests that increases in rate of atypical AP prescribing is not simply due to replacement of typical antipsychotic prescribing.
6. In Ontario, the increase in the rate of atypical use occurred from Q1-2000 to Q4-2004 with rates growing from 16 per 1,000 eligible to 37 per 1,000 eligible. In contrast, from 2004 to 2013 the rate has dropped slightly and appeared steady over that period of time (37 per 1,000 eligible in Q4-2004 to 36 per 1,000 eligible in Q4-2013).

Provincially-funded Rates of Antipsychotic Use, by Age Group

Exhibit 11: Population-adjusted utilization of provincially-funded antipsychotics among elderly patients in Canada in 2013, by province and age group



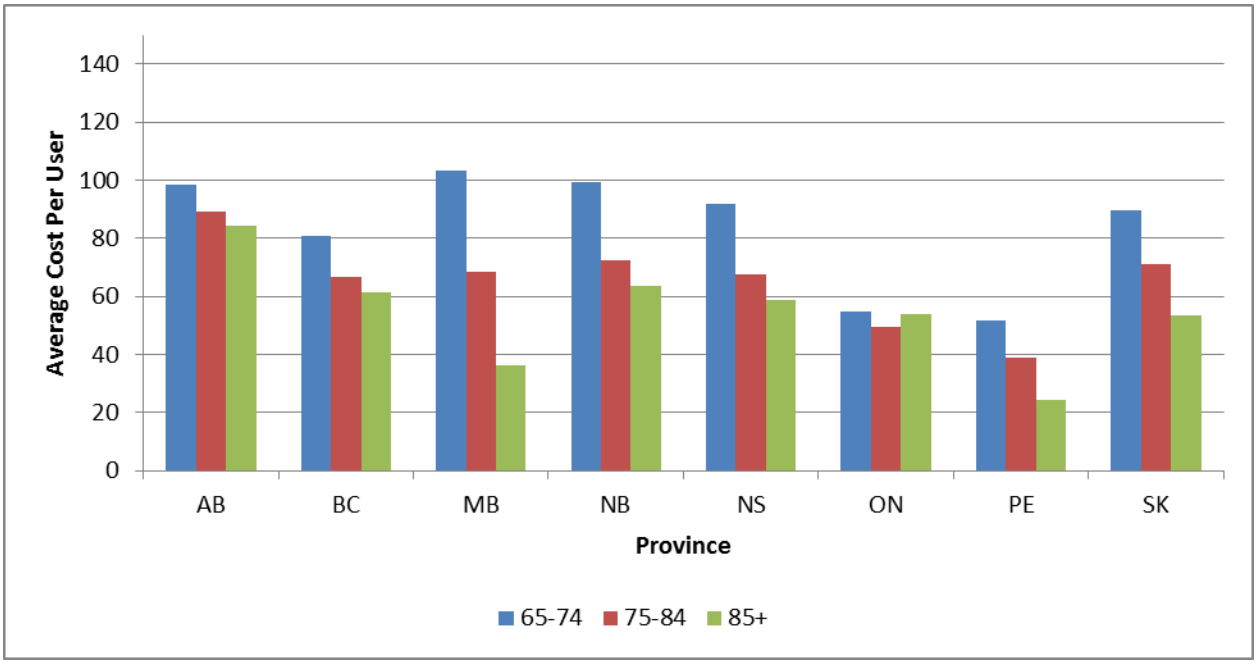
Rates of AP utilization increase with increasing age in all provinces studied. New Brunswick had the highest rate of publically-funded AP use in 2013 for all age groups.

Summary of Findings for Exhibit 10 and Exhibit 11

1. The prevalence of AP use increased with age in all provincially-funded drug programs. Ontario's rate of AP use was approximately similar to the average national rates by the end of 2013.
2. AP utilization rates varied considerably across provinces for elderly drug plan beneficiaries. The lowest rates were observed in Prince Edward Island (29 users per 1,000 population eligible) and the highest in New Brunswick (98 users per 1,000 population eligible) in Q4 2013. Ontario rates of AP use (58 users per 1,000 eligible population) were approximately the national average (55 users per 1,000 eligible population).
3. New Brunswick had the highest rates of AP utilization across all age groups (78 users per 1,000 per eligible population, 99 users per 1,000 eligible population, and 207 users per 1,000 eligible population for ages 65-74, 75-84, and 85+, respectively).
4. PEI had the lowest rates of AP utilization across all age groups (22 per 1,000 eligible population, 32 per 1,000 eligible population, and 71 per 1,000 eligible population for ages 65-74, 75-84, and 85+, respectively).
5. The average age of AP users was similar across provinces and ranged from 77 years in Alberta to 81 years in Saskatchewan. The average age for users in Ontario was 79.

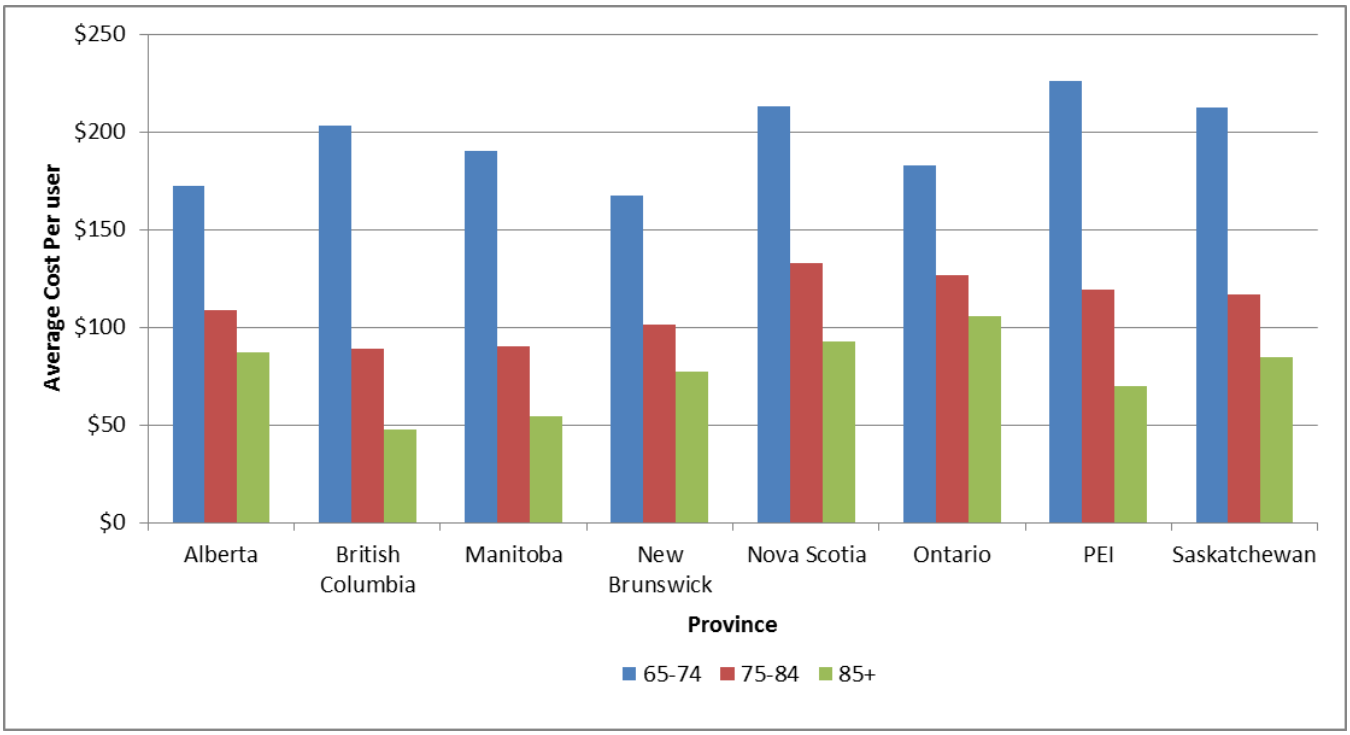
Publicly-Funded Antipsychotics Costs, Overall and Per Person

Exhibit 12: Average cost per user of typical antipsychotics for the last quarter of 2013, by age and province



Across all provinces the average cost per typical AP user is higher among younger elderly patients (65-74) and decreases with increasing age-group with the exception of Ontario where costs per user are similar by age.

Exhibit 13: Average cost per user of atypical antipsychotic for the last quarter of 2013, by age and province



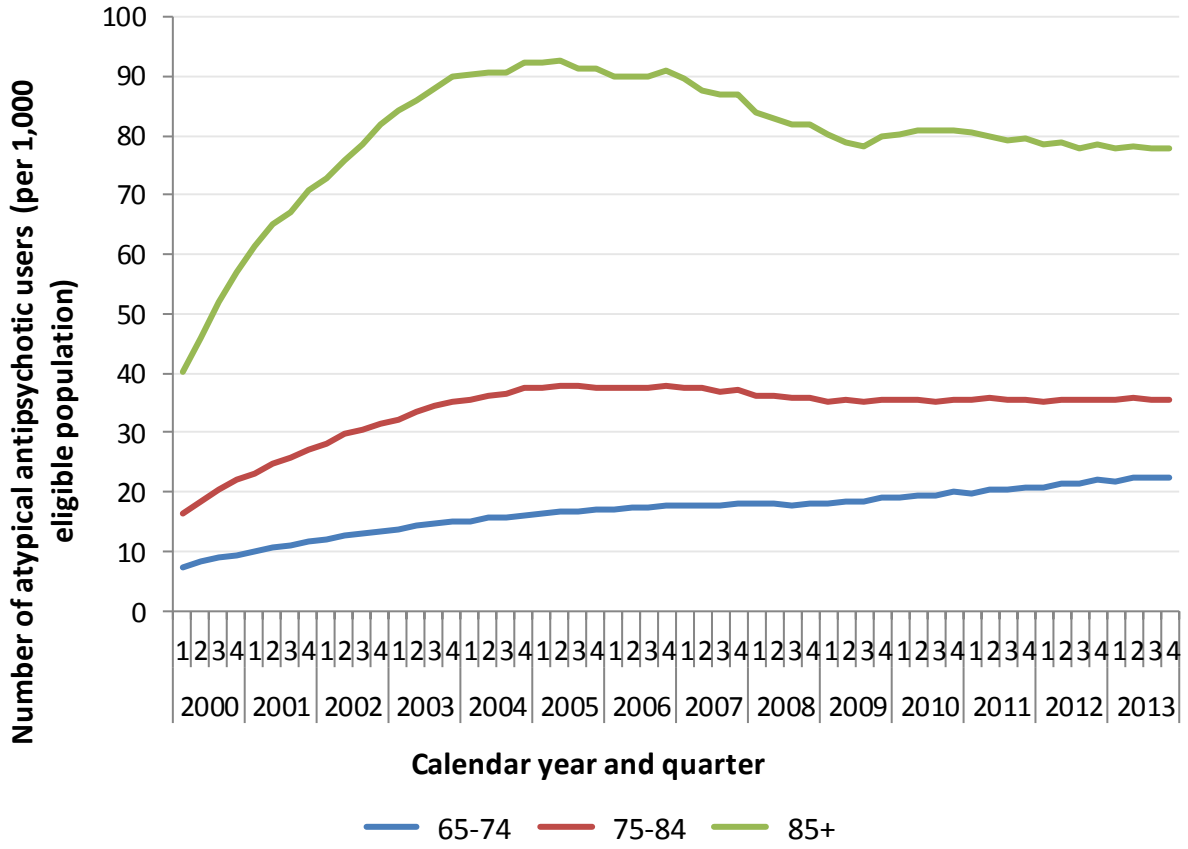
Across all provinces the average cost per atypical AP user is higher among younger elderly patients (65-74) and decreases with increasing age-group

Summary of Findings for Exhibit 12 and Exhibit 13

1. In general, the average cost per user is higher among the elderly aged 65-74 compared to those aged 75 and older across Canada. Similarly, costs per user are higher among users of atypical vs. typical AP.
2. Among users aged 65 to 74, the average cost per user ranged from $151.25 in Ontario to $185.69 in Saskatchewan.
3. Among users aged 75-84, the average cost per user ranged from $85.54 in British Columbia $112.72 in Ontario.
4. Among users aged 85 years and older, the average cost per user ranged from $50.49 in British Columbia to $99.11 in Ontario.
5. In Ontario in 2013:
    a. The overall cost of AP was $151.25 per user among those aged 65-74, $112.72 per user among those aged 75-84 and $99.11 per user among those aged 85 years and older.
    b. The cost of atypical AP ranged from $105.33 per user (age 85 years and older) to $183.82 per user (age 65 to 74). The costs of typical AP were similar by age group (range $49.31 to $54.78)

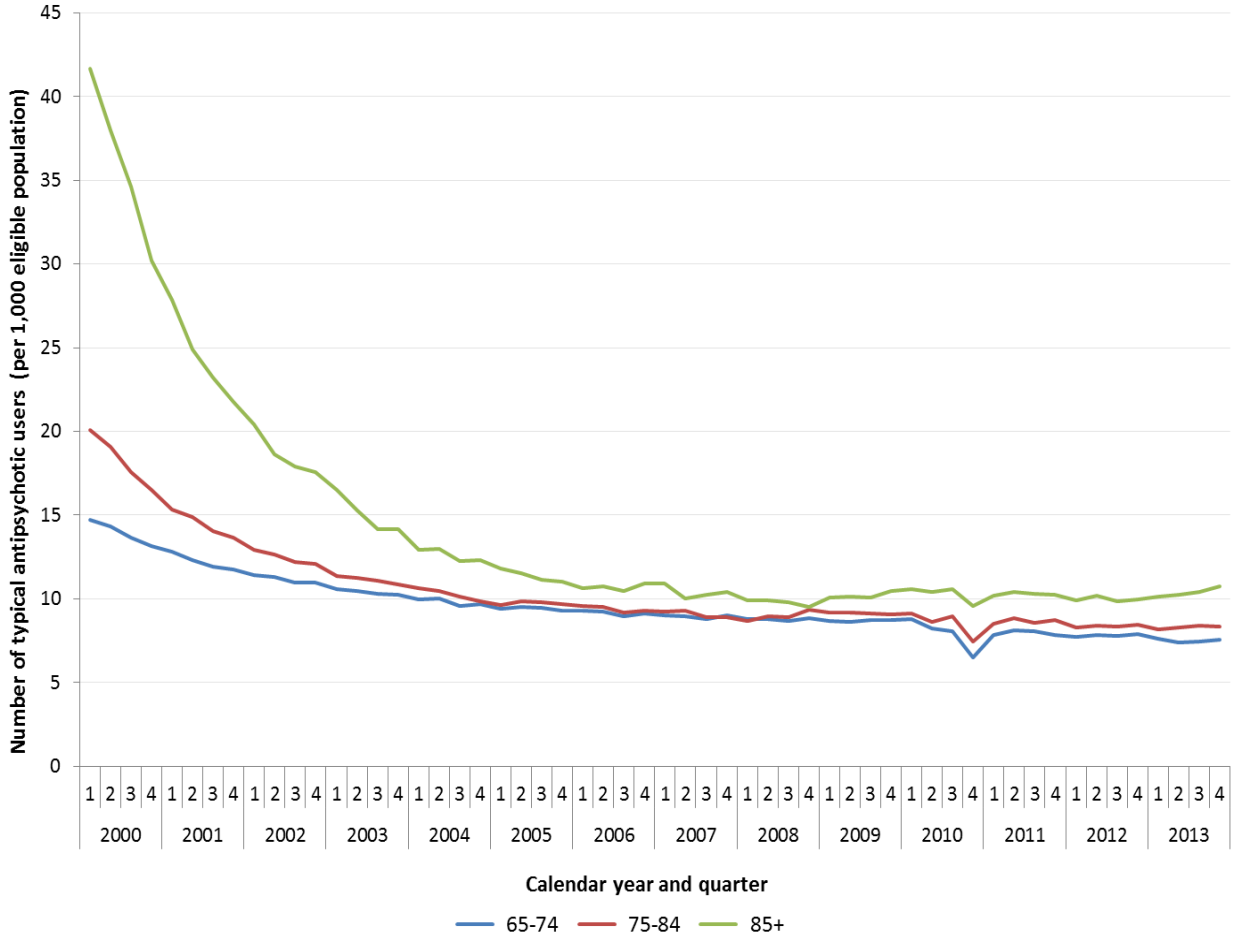
Trends in Provincially-Funded Antipsychotic Products in Ontario

Exhibit 14: Rate of Users of Atypical Antipsychotic Products in Ontario, by Age Group



The prevalence of atypical AP users in Ontario was highest in those 85 years of age and older. This age group has also seen the greatest increase in use from 2000 to 2013, with the majority of this increase occurring between 2000 and 2004.

Exhibit 15: Rate of users of Typical Antipsychotic products in Ontario, by age group



The prevalence of typical AP users among elderly in Ontario dropped drastically in the past 14 years. In 2013, the rate of use was similar by age group.

Summary of Findings for Exhibit 14 and Exhibit 15

1. Similar to national trends, Ontario has seen a sharp decrease in the use of typical AP in the elderly and an increase in use of atypical AP. In 2000, the rate of typical use was higher than atypical AP rates, however by 2013 the inverse was found. This trend was similar across all three age groups (65-74, 75-84, and 85+).

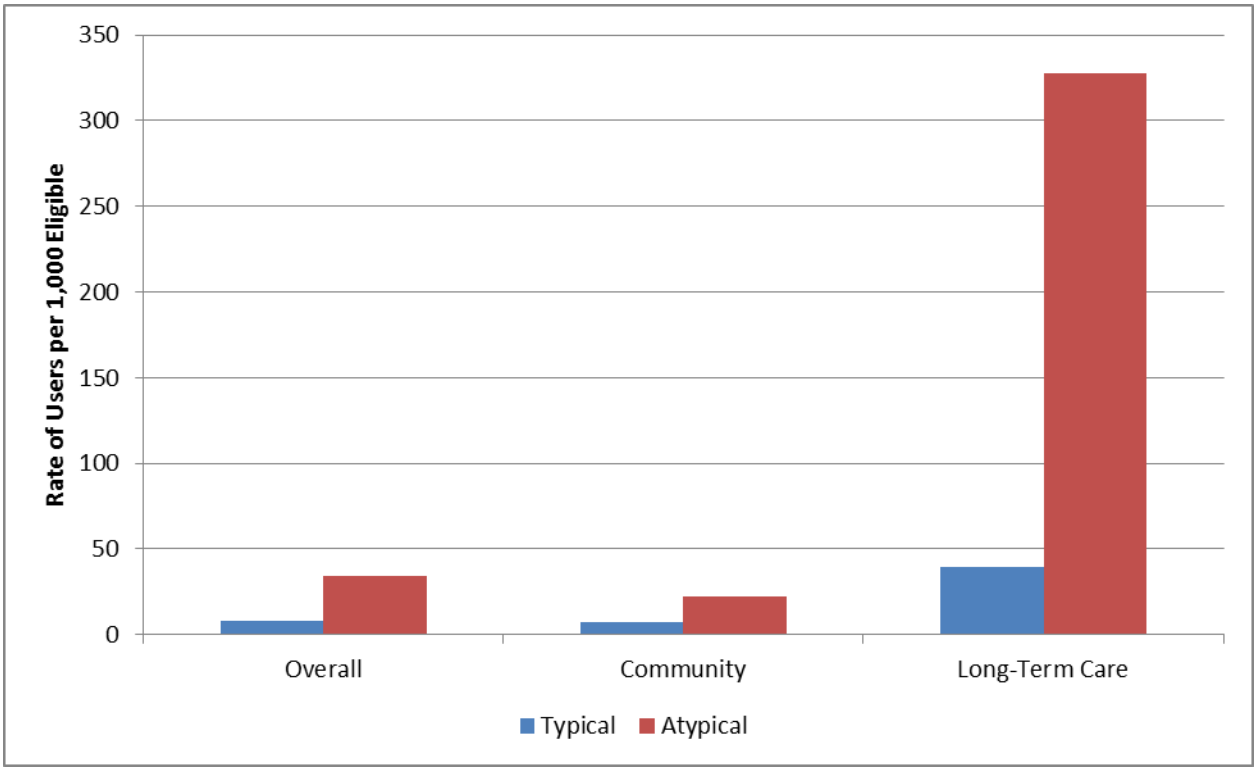
2. By the end of 2013, rates of atypical AP prescribing were still highest among elderly aged 85 years and older (77 users per 1000 eligible) compared to those aged 65-74 (22 users per 1000 eligible) and 75-84 (36 users per 1,000 eligible).

3. In Ontario, elderly patients 85 years and older had a much higher rate of typical AP prescribing at the beginning of 2000 (42 per 1,000 eligible compared to 20 per 1,000 eligible and 15 per 1,000 eligible among those aged 65-74 and 75-84. However, by the end of 2013, rates of typical AP prescribing were similar between age groups.

4. An increase in the rate of atypical AP users occurred from 2000 to 2004 in all 3 age groups (65-74, 75-84, and 85+), rates grew from 7, 16, and 40 per 1,000 eligible in Q1-2000 to 16, 37, and 92 per 1,000 eligible in Q4-2004, respectively. In contrast, from 2004 to 2013 the rates have remained stable or dropped in all 3 age groups (16, 37, and 92 per 1,000 eligible in Q4-2004 to 22, 35, and 77 per 1,000 eligible in Q4-2013, respectively).

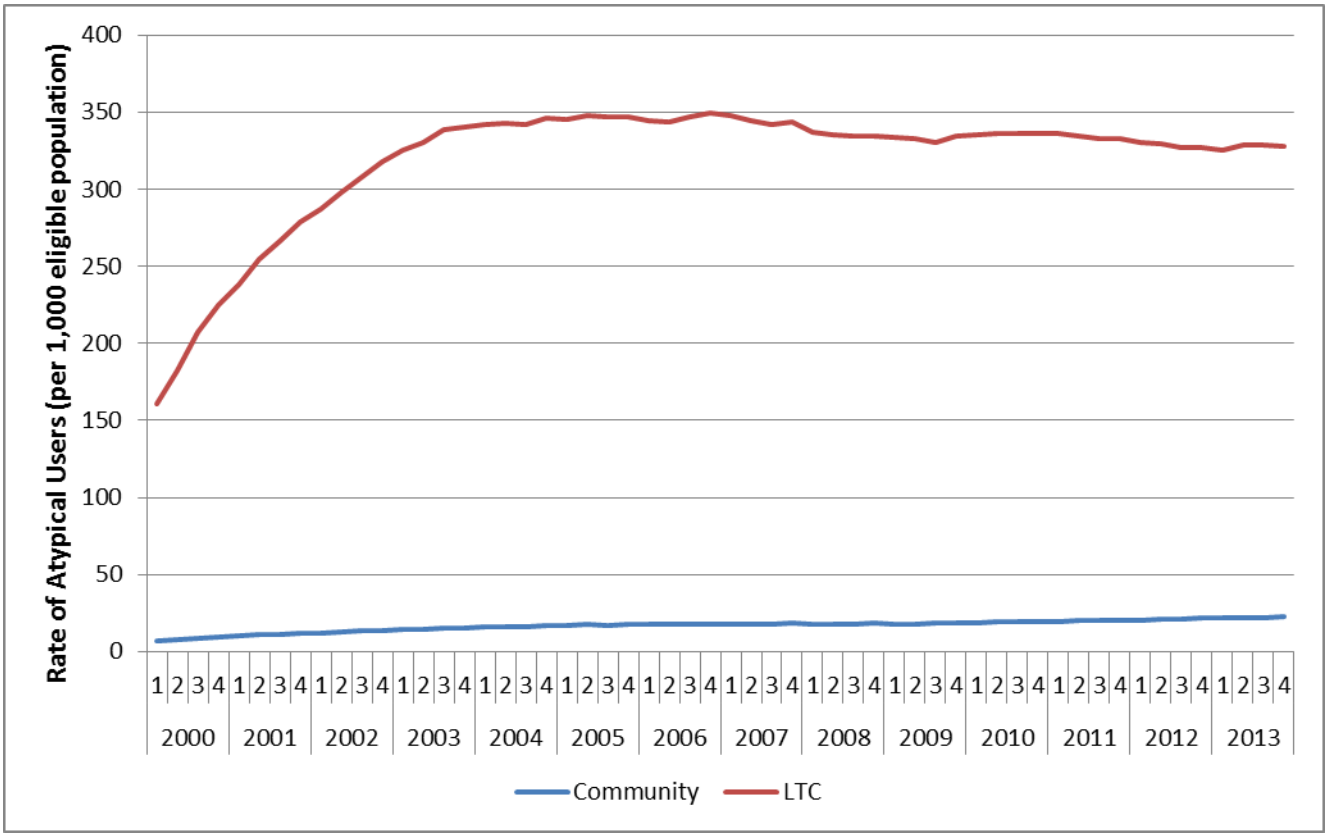
Users of Provincially-funded Antipsychotic Products in Ontario, by Living Status (Community and Long-term Care)

Exhibit 16: Rate of antipsychotic use among elderly public drug plan beneficiaries in Ontario, by setting and antipsychotic class



In Ontario the rate of AP use in the elderly is much higher in LTC settings than in the community. Atypical AP is the primary antipsychotic class used in both settings.

Exhibit 17: Rate of Atypical Antipsychotic Use among Elderly Public Drug Plan Beneficiaries in Ontario, by setting



In the last 5 years (2009 to 2013) the rate of atypical antipsychotic users in LTC has decreased 1.7% but increased in the community by 26%.

Summary of Findings for Exhibit 16 and Exhibit 17

1. Rates of both typical and atypical AP use in the elderly are substantially higher in the LTC setting (39 and 328 per 1,000 eligible users, respectively) than in the community setting (7 and 22 per 1,000 eligible users, respectively).
2. In the most recent 5 years (2009 to 2013) the overall rate of atypical antipsychotic users has increased by 6% from 32.4 per 1,000 eligible in Q1-2009 to 34.4 per 1,000 eligible in Q4-2013.
3. In this same time period the rate of users in the community has increased 26% from 17.8 per 1,000 eligible in Q1-2009 to 22.4 per 1,000 eligible in Q4-2013. In contrast, the rate of users in LTC has decreased 1.7% from 333.5 per 1,000 eligible in Q1-2009 to 327.7 per 1,000 eligible in Q4-2013.
4. In the LTC setting, rates of atypical AP use have increased over time (161 per 1,000 eligible in Q1-2000 to 328 per 1,000 eligible in Q4-2013). The increase in the rate of use occurred from 2000 to 2004 with rates growing from 161 per 1,000 eligible to 346 per 1,000 eligible. In contrast, from 2004 to 2013 the rate has dropped slightly and appears steady over that period of time (346 per 1,000 eligible in Q4-2004 to 328 per 1,000 eligible in Q4-2013).
5. In the community setting, the rates of atypical AP use have increased over time (7 per 1,000 eligible in Q1-2000 to 22 per 1,000 eligible in Q4-2013). This rate has continually increased over each quarter in this time period.

Exhibit 18: Characteristics of provincially-funded Antipsychotic users over 66 in Ontario, by setting and antipsychotic class, calendar year 2012

	Setting							
	Community				Long-Term Care			
	Overall	Atypical	Typical	Both	Overall	Atypical	Typical	Both
Total number of users	**N=72,488**	**N=45,210**	**N=22,958**	**N=4,320**	**N=32,580**	**N=26,903**	**N=2,508**	**N=3,169**
Number of New Users	**33,143 (45.7%)**	**15,296 (33.8%)**	**15,914 (69.3%)**	**1,933 (44.7%)**	**8,055 (24.7%)**	**5,598 (20.8%)**	**1,554 (62.0%)**	**903 (28.5%)**
Age -Mean (SD)	77.4（8.0)	78.1（8.2)	76.0（7.1)	77.5（8.1)	84.3（7.7)	84.4 (7.6)	84.8（8.3)	82.9 (7.9)
Sex - Male (%)	28,665 (39.5%)	16,986 (37.6%)	9,858 (42.9%)	1,821 (42.2%)	10,604 (32.5%)	8,593 (31.9%)	780 (31.1%)	1,231 (38.8%)
Urban Residence	63,433 (87.5%)	39,811 (88.1%)	20,029 (87.2%)	3,593 (83.2%)	27,540 (84.5%)	22,965 (85.4%)	1,999 (79.7%)	2,576 (81.3%)
Income Quintile								
1	15,873 (21.9%)	10,272 (22.7%)	4,586 (20.0%)	1,015 (23.5%)	8,027 (24.6%)	6,672 (24.8%)	625 (24.9%)	730 (23.0%)
2	15,130 (20.9%)	9,485 (21.0%)	4,800 (20.9%)	845 (19.6%)	6,012 (18.5%)	4,935 (18.3%)	483 (19.3%)	594 (18.7%)
3	14,107 (19.5%)	8,688 (19.2%)	4,577 (19.9%)	842 (19.5%)	6,221 (19.1%)	5,153 (19.2%)	455 (18.1%)	613 (19.3%)
4	13,810 (19.1%)	8,402 (18.6%)	4,593 (20.0%)	815 (18.9%)	6,308 (19.4%)	5,200 (19.3%)	503 (20.1%)	605 (19.1%)
5	13,298 (18.3%)	8,188 (18.1%)	4,327 (18.8%)	783 (18.1%)	5,773 (17.7%)	4,752 (17.7%)	424 (16.9%)	597 (18.8%)
Number of unique medications in last year (Median (IQR))	11 (7-16)	11 (7-16)	12 (7-17)	13 (9-18)	14 (10-19)	14 (10-18)	15 (11-21)	14 (10-19)
Number with 1 or more hospitalizations	24,218 (33.4%)	12,075 (26.7%)	10,196 (44.4%)	1,947 (45.1%)	10,232 (31.4%)	7,753 (28.8%)	1,235 (49.2%)	1,244 (39.3%)
Physician office visits within the last year Median (IQR)	12 (6-19)	10 (5-16)	15 (9-22)	13 (7-21)	2 (0-5)	2 (0-5)	2 (0-7)	3 (0-7)
Specialist visits within 3 months								
Psychiatrists	11,367 (15.7%)	9,531 (21.1%)	992 (4.3%)	844 (19.5%)	3,653 (11.2%)	2,900 (10.8%)	176 (7.0%)	577 (18.2%)
Geriatricians	4,533 (6.3%)	3,619 (8.0%)	624 (2.7%)	290 (6.7%)	1,375 (4.2%)	1,035 (3.8%)	135 (5.4%)	205 (6.5%)
Neurologists	3,501 (4.8%)	2,517 (5.6%)	785 (3.4%)	199 (4.6%)	828 (2.5%)	654 (2.4%)	74 (3.0%)	100 (3.2%)

Setting								
	Community				Long-Term Care			
	Overall	Atypical	Typical	Both	Overall	Atypical	Typical	Both
Total number of users	**N=72,488**	**N=45,210**	**N=22,958**	**N=4,320**	**N=32,580**	**N=26,903**	**N=2,508**	**N=3,169**
Charlson Morbidity Index								
No hospitalization	36,430 (50.3%)	24,939 (55.2%)	9,730 (42.4%)	1,761 (40.8%)	14,014 (43.0%)	12,081 (44.9%)	755 (30.1%)	1,178 (37.2%)
0	8,669 (12.0%)	6,247 (13.8%)	2,009 (8.8%)	413 (9.6%)	3,240 (9.9%)	2,592 (9.6%)	303 (12.1%)	345 (10.9%)
1	7,147 (9.9%)	5,472 (12.1%)	1,222 (5.3%)	453 (10.5%)	6,502 (20.0%)	5,391 (20.0%)	405 (16.1%)	706 (22.3%)
2	7,218 (10.0%)	3,534 (7.8%)	3,158 (13.8%)	526 (12.2%)	3,472 (10.7%)	2,789 (10.4%)	315 (12.6%)	368 (11.6%)
3+	13,024 (18.0%)	5,018 (11.1%)	6,839 (29.8%)	1,167 (27.0%)	5,352 (16.4%)	4,050 (15.1%)	730 (29.1%)	572 (18.0%)
Concomitant psychotropic use (%)								
Antidepressants	33,765 (46.6%)	25,862 (57.2%)	5,948 (25.9%)	1,955 (45.3%)	22,035 (67.6%)	18,322 (68.1%)	1,498 (59.7%)	2,215 (69.9%)
Benzodiazepine	22,465 (31.0%)	14,047 (31.1%)	6,684 (29.1%)	1,734 (40.1%)	9,130 (28.0%)	7,174 (26.7%)	859 (34.3%)	1,097 (34.6%)
Mood Stabilizer	7,061 (9.7%)	5,056 (11.2%)	1,466 (6.4%)	539 (12.5%)	3,197 (9.8%)	2,513 (9.3%)	272 (10.8%)	412 (13.0%)
Stimulants	409 (0.6%)	264 (0.6%)	106 (0.5%)	39 (0.9%)	70 (0.2%)	55 (0.2%)	7 (0.3%)	8 (0.3%)
Cognitive enhancers	10,684 (14.7%)	9,534 (21.1%)	578 (2.5%)	572 (13.2%)	11,863 (36.4%)	10,309 (38.3%)	473 (18.9%)	1,081 (34.1%)
Dementia	25,059 (34.6%)	21,030 (46.5%)	2,502 (10.9%)	1,527 (35.3%)	28,753 (88.3%)	24,072 (89.5%)	1,882 (75.0%)	2,799 (88.3%)
Prescriber of Initial AP prescriptions								
Specialist±	11,816 (16.3%)	10,289 (22.8%)	791 (3.4%)	736 (17.0%)	196 (0.6%)	145 (0.5%)	12 (0.5%)	39 (1.2%)
General Practitioner	42,864 (59.1%)	29,492 (65.2%)	10,682 (46.5%)	2,690 (62.3%)	31,026 (95.2%)	25,652 (95.3%)	2,382 (95.0%)	2,992 (94.4%)
Average Dose Mean (SD)**	169.5 (259.8)	102.3 (143.5)	269.0 (322.6)	344.1 (483.5)	133.6 (213.4)	102.3 (137.9)	298.3 (372.8)	269.2 (385.7)

*** Dosing based on converting all AP doses to Chlorpromazine equivalents. (See appendix C)*

± Specialist of interest are psychiatrists, geriatricians, or neurologists

Summary of Findings for Exhibit 18

1. There were 72,488 community-dwelling elderly and 32,580 LTC residents over the age of 65 in Ontario who were treated with provincially-funded AP in 2013. Among these, 33,143 (45.7%) of those in the community, and 8,055 (24.7%) of those residing in LTC were new users. The average age of users was higher in LTC compared to community (84.3 and 77.4, respectively), which likely reflects different overall age distributions between community-dwelling seniors and LTC residents.
2. The majority of treated patients were using atypical AP in both community (N=45,210, 62.4%) and LTC (N=26,903, 82.6%). In both settings, those treated with typical AP were sicker (higher Charlson comorbidity score), more likely to have visited a hospital in the past year, but less likely to have seen a specialist compared to those treated with atypical antipsychotics.
3. Approximately two-thirds (67.6%) of AP users in LTC and one half (46.6%) of those residing in the community had concomitant use of an antidepressant. One-third of those in both settings (31.0% and 28.0% in community and LTC, respectively) had concomitant use of a benzodiazepine. Concomitant use of cognitive enhancers was higher in the LTC setting (36.4%) compared to the community setting (14.7%). Atypical AP users in the community were more likely to be on concomitant psychotropic medications than typical AP users in the community, this was true for all types of concomitant psychotropic medications.
4. AP users residing in LTC were more likely to have dementia (88.3%) compared to those residing in the community (34.6%). Atypical AP users were more likely than typical AP users to have dementia in both community (46.5% vs. 10.9%) and LTC (89.5% vs. 75.0%) settings.
5. The average dose of chlorpromazine equivalents was found to be higher in community residents (169.5 mg) compared to LTC residents (133.6 mg). Atypical AP users were found to be on lower average chlorpromazine equivalent doses than typical AP users in both community (102.3 mg vs. 322.6 mg) and LTC (102.3 mg vs. 298.3 mg) settings.
6. Community AP users were more likely that LTC AP users to get the initial prescription from a specialist (16.3% vs. 0.6%, respectively). Atypical AP users in the community were also more likely to have received the initial prescription from a specialist when compared to typical AP users in the community (22.8% vs. 3.4%, respectively).
7. There was a wide variation in the utilization of AP across Local Health Integration Networks (LHINs) for the elderly living in both the community and in LTC. This variation can be explored on our interactive map found on our website (http://odprn.ca/antipsychotics-in-the-elderly/)
    a. Rates of use in LTC resident ranged from 378 per 1,000 population in the Mississauga-Halton LHIN to 518 per 1,000 population in the North West LHIN.
    b. Rates of use in community-dwelling elderly resident ranged from 32 per 1,000 population in the North West LHIN to 48 per 1,000 population in the North Simcoe Muskoka LHIN.

Patterns of Antipsychotic Therapy Use and Discontinuation Among Elderly Patients with Dementia

Exhibit 19: Patterns of antipsychotic therapy use among elderly patients with dementia who are new users of provincially-funded antipsychotics in Ontario, by setting and antipsychotic class. January 2009 – December 2013

	Setting					
	Community			Long-Term Care		
	Overall	Atypical	Typical	Overall	Atypical	Typical
Number of users	**N=34,195**	**N=28,048**	**N=6,147**	**N=24,804**	**N=20,188**	**N=4,616**
Number of users with only 1 prescription date during period of continuous use (N, %)	**8,560 (25.0%)**	**5,182 (18.5%)**	**3,378 (55.0%)**	**4,995 (20.1%)**	**2,485 (12.3%)**	**2,510 (54.4%)**
Equivalent Daily doses dispensed at initiation	80.8 ± 153.7	60.1 ± 79.9	251.5 ± 365.3	103.9 ± 184.9	79.0 ± 125.8	313.0 ± 373.6
Equivalent daily dosing level at initiation*						
Low (<=25 mg)	9,841 (38.4%)	9,673 (42.3%)	168 (6.1%)	6,723 (33.9%)	6,582 (37.2%)	141 (6.7%)
Medium (25-62 mg)	7,880 (30.7%)	7,208 (31.5%)	672 (24.3%)	5,550 (28.0%)	5,218 (29.5%)	332 (15.8%)
High (>62 mg)	7,914 (30.9%)	5,985 (26.2%)	1.929 (69.7%)	7,536 (38.0%)	5,903 (33.3%)	1,633 (77.5%)
Average cost per user of antipsychotics over period of continuous use (mean, SD)	$410.26 ($563.95)	$441.11 ($580.69)	$155.52 ($295.05)	$588.00 ($701.40)	$617.32 ($714.32)	$341.60 ($519.94)
Number of users who enter LTC from community within 1 year	11,230 (43.8%)	10,602 (46.4%)	628 (22.7%)	--	--	--
Median time (days) to discontinuation**	700-750	Did not reach in 2 years	150-200	Did not reach in 2 years	Did not reach in 2 years	250-300
Patients who discontinued therapy within 1 year of follow-up**	35-40%	30-35%	60-65%	30-35%	30-35%	50-55%
Patients who died within 1 year of follow-up**	5-10%	5-10%	20-25%	15-20%	10-15%	20-25%
Among those persistent on therapy for 1 year:						
Number who Changed Antipsychotic Drug	3,474 (25.2%)	3,182 (23.9%)	292 (57.6%)	2,653 (26.8%)	2,229 (23.8%)	424 (76.7%)
Number who Changed Antipsychotic Class	1,086 (7.9%)	803 (6.0%)	283 (55.8%)	1,218 (12.3%)	812 (8.7%)	406 (73.4%)
Equivalent Daily dose dispensed (Mean (SD) at 1 year	117.48 (144.4)	116.92 (142.6)	132.36 (184.1)	131.80 (163.8)	129.91 (161.2)	165.03 (201.3)
Equivalent daily dosing level at 1 year						
Low (<=25 mg)	2,871 (20.8%)	2,781 (20.9%)	90 (17.8%)	1,721 (17.4%)	1,628 (17.4%)	93 (16.8%)
Medium (25-62 mg)	3,782 (27.4%)	3,640 (27.4%)	142 (28.0%)	2,459 (24.8%)	2,341 (25.0%)	118 (21.3%)
High (>62 mg)	7,158 (51.8%)	6,883 (51.7%)	275 (54.2%)	5,729 (57.8%)	5,387 (57.6%)	342 (61.8%)
Change of equivalent daily dosing level from index	7,400 (56.5%)	7,179 (56.8%)	221 (46.4%)	5,236 (55.0%)	5,047 (55.9%)	195 (37.9%)

** Dosing based on converting all antipsychotic doses to Chlorpromazine equivalents. (See appendix c). Dose levels were based on grouping of overall dose distribution.*
NOTE: See Appendix E for baseline characteristics of new-users.
***Estimated from competing risks analysis. Information is censored to allow for publication.*

Summary of Findings for Exhibit 19

1. The majority of patients in both the community (69.1%) and LTC (61.9%) were found to be on low or medium dose AP at time of drug initiation.
2. Overall, 43.8% (N=11,230) of individuals initiating AP in the community entered LTC within one year of initiation. This was higher among users who initiated atypical AP (46.4%) compared to those who initiated typical AP (22.7%).
3. Approximately half of new AP users persisted on therapy for at least one year (50-60%), with 35-40% of new users discontinuing therapy and the remaining 5-10% dying within one year of follow-up. Among individuals still on therapy after one year, only 7.9% of those in the community and 12.3% of those in LTC homes switched between AP classes (atypical to typical or vice versa) during their period of ongoing use.
4. Within 1 year of drug initiation, 56.5% of new AP users in the community and 55.0% of those in LTC had changed the dosing level of their AP therapy. Overall, the prevalence of high dose AP use rose in both the community (from 31% to 52%) and the LTC (from 38% to 58%) setting.
5. No major differences in persistence to AP therapy were found between those initiating AP therapy in LTC or community (censored data).

Key Findings

Overall National and Provincial Trends in Antipsychotic use in the elderly

Prescriptions for AP among elderly patients in Canada have increased by nearly 32% over the past 4 years, from 2,954,248 prescriptions dispensed in the last quarter of 2009 to 3,912,013 prescriptions dispensed by the second quarter of 2014. By the second quarter of 2014, $75 million was spent quarterly on AP dispensed to elderly patients in Canada, and the majority of these costs were attributable to atypical AP prescriptions ($72,511,714; 97% of all costs). Quetiapine was the most utilized atypical AP (50%) in Canada. The three most commonly used atypical AP (Quetiapine, risperidone, and olanzapine) accounted for 94% of all prescriptions across Canada. Newer atypical AP (aripiprazole, asenapine, paliperidone, lurasidone, ziprasidone) have increased in utilization growing from only 0.2% to over 5% of all atypical AP prescriptions between 2009 and 2014. This growth has meant that by the second quarter in 2014 they accounted for 19% of total atypical AP spending in Canada.

By the second quarter of 2014, Ontario had the third-highest rate of prescriptions for antipsychotics to elderly patients (592 prescriptions per 1,000 eligible population). The rate of AP prescribing was particularly high in Quebec compared to all other provinces (1,314 prescriptions dispensed per 1,000 eligible for Quebec vs. range of 303 to 625 prescriptions dispensed per 1,000 eligible for other provinces). When Ontario's rate of prescribing was compared to a national average that did not include Quebec (since Quebec is an outlier), the rate of prescribing (592 prescriptions per 1,000 eligible population) was higher the national average (495 prescriptions per 1,000).

National and Provincial Trends in antipsychotic use in the elderly among Public Drug Plan Beneficiaries

In 2013, Ontario had the third lowest provincial rate of AP use in the elderly (58 users per 1,000 eligible) among public drug plan beneficiaries, in Canada. This rate was comparable to the national rate (comprised of 8 provinces) of 55 users per 1,000 eligible. This rate of use varied five-fold across provinces and age groups, with the lowest rates observed in PEI (29 users per 1,000 eligible), which has more restrictive public plan listings for AP. Over time, the rate of use of publicly-funded atypical AP in the elderly has increased in all provinces as the rate of use of typical AP in the elderly had decreased. Ratios of atypical AP compared to typical AP use ranged from 1.5 times in PEI to 5-times more use in New Brunswick. Annual costs per user varied across age groups, with the highest costs general found among users aged 65-74. Among those 65-74 years of age, Saskatchewan had the highest average cost per user ($185.69 per user) while Ontario had the lowest average annual drug cost per user ($151.25 per user). The inverse trend of increased cost in younger age groups of elderly patients is likely due to use of higher doses and severity of disease in younger patients.

Antipsychotic use in the elderly in Ontario

In the most recent 5 years (2009 to 2013) the overall rate of elderly atypical antipsychotic users has increased by 6% from 32.4 per 1,000 eligible in Q1-2009 to 34.4 per 1,000 eligible in Q4-2013. In this same time period, the rate of users in the community has increased 26% from 17.8 per 1,000 eligible in Q1-2009 to 22.4 per 1,000 eligible in Q4-2013. In contrast, the rate of users in LTC has decreased 1.7% from 333.5 per 1,000 eligible in Q1-2009 to 327.7 per 1,000 eligible in Q4-2013. Ontario has seen a sharp decrease in the use of publically-funded typical AP in the elderly and an increase in use of publically-funded atypical AP. In 2000, the rate of typical AP use was higher than the rate of atypical AP use; however in 2001, the rate of atypical AP use surpassed that of typical AP use. There has also been an overall increase in AP utilization over time, which may be driven by the introduction of newer agents since 2009. In 2013 the rate of total AP use in Ontario was 58 users per 1,000 eligible patients. Rates of atypical AP use were found to be much higher among older patients (85 and older; 123 users per 1,000 eligible) and those living in Long-Term Care (LTC) (367 users per 1,000 eligible).

Characteristics of Elderly Antipsychotic Users in Ontario

In 2013, 72,488 community-dwelling elderly and 32,580 LTC residents over the age of 65 were users of provincially-funded AP in Ontario. The majority of users were prescribed atypical AP in both community (N=45,210, 62.4%) and LTC (N=26,903, 82.6%) settings. The rate of typical use was found to be much higher in the community compared to LTC (37.6% vs. 17%, respectively). The majority of users were prescribed atypical AP in both the community (N=45,210, 62.4%) and LTC (N=26,903, 82.6%).The majority of patients lived in urban areas, had lower socioeconomic status, and were using a median of 11 to 14 medications depending on location of residence (community vs. LTC, respectively). AP users residing in LTC were more likely to have dementia than users residing in the community (88.3% vs. 34.6%, respectively). Psychiatrists were the most commonly visited specialist in the 3 months prior to initiating AP therapy for patients residing in the community and LTC (15.7% and 11.2%, respectively); however general practitioners prescribed the majority of initial prescriptions in both the community and LTC settings (59.1% and 95.2%, respectively).

Patterns of Antipsychotic use and discontinuation in the elderly in Ontario

Between April 2008 and March 2013, we found 34,195 community and 24,804 LTC newly-initiated AP users over the age of 65 with dementia. A third of new-users were initiated at a dose less than 25 mg chlorpromazine (CZD) equivalents (38.4%). One year after initiation of therapy close to half in both the community and LTC (50-60%) still remained on therapy. A large proportion of users in both community and LTC (56.5% and 55.0%, respectively) had a change in dose category over continuous use. Among the new-users living in the community, a considerable number (43.8%) were living in LTC by the end of the

year. No major differences in persistence to AP therapy were found between those initiating AP therapy in LTC or community (censored data); however patients initiated on higher doses were likely to discontinue therapy than those initiated on low or moderate doses (censored data).

Health Equity

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

Limitations

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. There is no data available for publically paid prescriptions in Quebec and Newfoundland & Labrador from NPDUIS. Therefore, we were unable to make comparisons between Ontario rates and rates of use in these provinces.
4. Data on the number of active beneficiaries eligible for public drug coverage was estimated based on active prescription in each quarter and annually. Therefore, these may slightly underestimate the true size of the public beneficiary population; however, this does reflect the number of active beneficiaries (e.g. those filling at least one prescription over a given year) each year.
5. All data presented are based on prescriptions filled. We are unable to confirm whether a patient actually took the medication.

Generalizability

1. All analyses were restricted to elderly aged 65 and older. Therefore these findings are not necessarily generalizable to a younger population.

Dosing

Chlorpromazine equivalents have been determined based on adult populations and use in schizophrenia

(See Appendix), and not elderly patients treated for dementia. This may not be representative of differences between agents that may be inconsistent between adult and elderly populations. This approach was taken to help simplify the complexity of AP dosing due to the large number of drugs and available formulations, practice variation, indications, and differences in dosing (ex. scheduled vs. as needed). Due to a lack of information of reasonable thresholds for dose levels in the elderly, we stratified our data into low, moderate and high dose using tertiles based on the distribution of the data.

Adherence

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

Overall Conclusion

Utilization of AP in the elderly continues to grow over time both nationally and in Ontario. With a growing elderly population, extended life-expectancy, the introduction of new products, and lack of alternate treatment options we do not expect this trend to change in the future. The growth in utilization is largely due to the increased utilization of atypical AP in this population. Because newer atypical AP are only available as brand name products, which are particularly costly, the rise in utilization has the potential to lead to considerably increased costs in this drug class in the near future. Although rates of AP use in LTC remain high, there is some evidence of leveling off of AP use in the LTC setting which may be due to growing attention surrounding the overuse of AP in this setting. Despite this, AP use in the community continues to grow, and close to half of elderly patients with dementia newly initiating an AP entered a LTC home within the year.

Review of the Observational Literature

The safety and efficacy of antipsychotics in the elderly have been established in randomized controlled trials and observational studies; this material is summarized in the report by the Systematic Review Team. A review of the observational literature reviewing the use of AP in the elderly specifically in Ontario will help provide real-world estimates of past utilization work of these products in this specific population. This review of evidence will give context to compare the findings of this report to previous published work.

Objectives

We conducted a rapid review of the observational literature to investigate the use, utilization, and treatments patterns of antipsychotics in the elderly ion Ontario since the year 2000.

Methods

Search Strategy

We performed a Medline search for all literature published between 2000 and April 2015. Search terms included "Antipsychotics" (including all specific generic names) and "Ontario". Overall, 191 abstracts were reviewed, and potentially relevant articles were obtained in full text. We excluded studies that only explored the safety of antipsychotics in this population.

Inclusion Criteria:

- English Language
- Published between 2000 and April 2015
- Elderly patient population
- Use, utilization or treatment patterns in Ontario
- Antipsychotics use assessed

Seven studies were included in the final review. 12 studies were excluded that assessed various safety outcomes in this population as their primary purpose. Of the 7 studies included, 6 utilized Ontario administrative databases and 1study utilized patient charts from a large mental-hospital in Ontario. The included studies all explored antipsychotic utilization in the elderly (Table 1). The located studies can be categorized into three major themes; 1) utilization of antipsychotics in nursing homes 2) Changes in utilization and costs of antipsychotics overtime in Ontario 3) Utilization of antipsychotics in elderly patients subgroups (Parkinson's disease and mental-illness).

Results

Use of antipsychotics in elderly patients living in long-term care

We identified 2 observational studies that explored patterns of use in patients in nursing homes. Both studies used retrospective cohort designs and leveraged Ontario's administrative claims data. One study[1] explored the patterns of use for those newly admitted to nursing homes with no past history of antipsychotics use. This study found that within 100 days, 17% of all users with no past history of antipsychotic use were exposed, this number rose to 24% by the end of the year. Those diagnosed with dementia (OR= 3.52; 95%CI 3.24 to 3.82) were found to be much more likely to be initiated on an antipsychotic. Rochon et al.[2] further explored the use of antipsychotics in elderly patients residing in nursing homes by exploring rates of use at a home level. Their work found that there was a large variation in prevalence of use between homes, ranging from 20.9% to 44.3%. Further exploration of the impact of clinical indication at home levels found that those in homes with high rates of prescribing were more likely to get antipsychotics regardless of indication (psychosis or dementia). (RR= 1.31; 95% CI = 1.26 to 1.35).

Utilization and costs of antipsychotics overtime

Three studies explored rates and costs of antipsychotics use in the elderly overtime. All 3 used a cross-section time-series analysis. Two of the studies explored the change in utilization and costs overtime from 1993 to 2002. Mamdani et al.[3] assessed all users of mental health related medications and found that among all mental health medication users antipsychotics grew from just 8.7% of all mental health users to 17.1% of all mental health users between 1993 and 2002. In that same time period the percent of costs of all mental health users attributable to antipsychotics grew from 8% to 20.9%. Rapoport et al.[4] further explored only antipsychotics use and found a 34.8% increase in the prevalence of use among all elderly patients. Prevalence of antipsychotics use was found to have increased from 2.2% in 1993 to 3.0% in 2002. This increase in use also aligned with a switch in antipsychotics of choice highlighted in both studies[3;4], with the introduction and preference of newer atypical antipsychotics. Utilization of typical antipsychotics decreased overtime, from 100% of antipsychotics in 1993 to 13% by the end of 2003. This switch from typical to atypical antipsychotics led to a 749% increase in costs for all antipsychotics, from $3.7 million in 1993 to $31.4 million in 2002. At the time of these studies no generic products were available for atypical antipsychotics.

The third study explored the impact of health Canada's safety warning on utilization of antipsychotics in the elderly across Ontario.[5] Between 2000 and 2007 health Canada released three separate warnings related to the safety of these medications in elderly patients. In that same time period only small decreases in the rate of growth were found to occur (5.0%, 4.9%, and 3.2%, respectively). In that same time period overall use of antipsychotics in the elderly increased 20% from 1,512 per 100,000 elderly in

September 2002 to 1,813 per 100,000 elderly in February 2007.

Utilization of antipsychotics in special population

Two studies were found that explored use of antipsychotics in special elderly populations. Sproule et al explored use of antipsychotics in elderly patients who were admitted to a mental health hospital.[6] They compared differences in use of antipsychotics in elderly patients with younger patients also admitted to a mental health hospital. The study found that older patients received 30% lower initial doses at discharge and were more likely to receive olanzapine. The second study studied the use of antipsychotics in elderly patients with Parkinson's disease. Marras et al. found that 4.8% of elderly Parkinson's patients were dispensed an antipsychotics within a year and within 7 years that number rose to 35%.[7]

Conclusion and Key Findings

Studies in Ontario have specifically explored the utilization of antipsychotics in the elderly and changes over time; special attention was paid to those living in long-term care within this body of work. All studies found an increase in the use overtime, specifically with increased utilization of atypical antipsychotics. The increase of use was also found in populations of high risk (such as Parkinson's patients). The majority of the located studies were completed in the early part of the 2000s with much attention drawn with the rapid entry of brand-name atypical antipsychotics onto their market. No recent utilization studies have been completed to assess more recent changes and trends. Also no updated cost studies were found since the recent genericization of many of the original atypical antipsychotics.

Appendix A: Summary of Included Studies

Study Author	Study Design	Population	Outcomes of Interest (antipsychotic related)	Key Findings
Bronskill et al. (2004)[1]	Retrospective Cohort Study	>66 years and older and newly admitted to a nursing home with no past history of neuroleptics use (1998-2000)	1. Patters of initiations of neuroleptic drug use 2. Characteristics associated with higher likelihood of initiation 3. Type and dose of Initial neuroleptic 4. Contact with specialist	• Within 100 days 17% of patients were exposed to a neuroleptic • Within a year 24% of patients were exposed to a neuroleptic • Men and those with dementia were more likely to be initiated on a neuroleptic • 10% of initial doses exceeded recommended doses • Of those initiated on therapy only 14% had prior contact with a geriatrician of psychiatrist
Mamdani et al. (2005)[3]	Cross-sectional time-series	Community dwelling residents 65 years of age and older (1993-2002)	1. Estimate the prevalence of antipsychotics among older adults overtime that use mental health related medications 2. Estimate the cost of antipsychotics among older patients overtime that use mental health related medications	• Percent of all mental-health users that used antipsychotics rose from 8.7% in 1993 to 17.1% by 2002. • Total cost of all mental-health users that used antipsychotics rose from 8.0% in 1993 to 20.9% by 2002. • Utilization of typical antipsychotics decreased overtime, from 100% of antipsychotics in 1993 to 13% by the end of 2003.
Marras et al. (2006)[7]	Retrospective Cohort Study	>66 years and older with Parkinson's disease with no past history of antipsychotic use (1998-2003)	1. Patters of initiations of antipsychotics 2. Type and Initial antipsychotics	• Within a year 4.8% of patients were exposed to an antipsychotic • Within 7 years 35% of patients were initiated on an antipsychotic • Typical antipsychotics were used 56% of the time in 1998 and dropped to 9% by 2002
Rapoport et al. (2005)[4]	Cross-sectional time-series	Community dwelling residents 65 years of age and older	1. Estimate the prevalence of antipsychotics among older adults overtime	• Prevalence of antipsychotic use in the elderly increased 34.8% • Prevalence increased from 2.2% in 1993 to 3.0% in 2002. • Costs of antipsychotic use in the

		(1993-2002)	2. Estimate the cost of antipsychotics among older patients overtime	elderly increased 749%. • Total cost of antipsychotics increased from $3.7 million in 1993 to $31.4 million in 2002. • This is growth is due to the switch from typical antipsychotics which are largely generic to atypical antipsychotics which at the time were only available as brand name products
Rochon et al. (2007)[2]	Retrospective point-prevalence Cohort Study	>66 years and older living in a nursing home in 2003	1. Point prevalence rates of antipsychotic 2. Resident indications for antipsychotic therapy	• 32.4% of nursing home residents were dispensed an antipsychotic • Nursing homes ranged from 20.9% to 44.3%. • Homes that had higher rates of antipsychotic use were more likely to use antipsychotics regardless of clinical indications
Sproule et al. (2010)[6]	Retrospective Cohort Study	Patients discharged from a mental health centers and prescribed an antipsychotic	1. Comparison of older and younger patient prescription patterns	• Older patients received 30% lower initial doses • Older patients were more likely to receive Olanzapine
Valiyeva et al. (2008)[5]	Cross-sectional time-series	Community dwelling residents 65 years of age and older (2000-2007)	1. Assess the impact of health Canada warnings on prescription rates	• Small decrease after each of 3 warnings, 5.0%, 4.9%, and 3.2%, respectively. • Overall use of antipsychotics in the elderly increased 20% from 1,512 per 100,000 elderly in September 2002 to 1,813 per 100,000 elderly in February 2007

Sources

(1) Bronskill SE, Anderson GM, Sykora K, Wodchis WP, Gill S, Shulman KI et al. Neuroleptic Drug Therapy in Older Adults Newly Admitted to Nursing Homes: Incidence, Dose, and Specialist Contact. 2004; 52:749-755.

(2) Rochon PA, Stukel TA, Bronskill SE, Gomes T, Sykora K, Wodchis WP et al. Variation in nursing home antipsychotic prescribing rates. 2007; 167:676-683.

(3) Mamdani M, Rapoport M, Shulman KI, Herrmann N, Rochon PA. Mental health-related drug utilization among older adults: prevalence, trends, and costs. 2005; 13:892-900.

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(6) Sproule BA, Lake J, Mamo DC, Uchida H, Mulsant BH. Are antipsychotic prescribing patterns different in older and younger adults?: a survey of 1357 psychiatric inpatients in Toronto. 55:248-254.

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Appendix B: Available Antipsychotic Products in Canada by Class

	Typicals			Atypicals	
Drug	**Generic**	**Formulations**	**Drug**	**Generic**	**Formulations**
Chlorpromazine	Generic	Injection, tablet	Aripiprazole	No	Tablet, Depot injection
Flupentixol	Yes (depot injection)	Tablet, depot injection	Asenapine	NO	Sublingual Tablet
Fluphenazine	Yes	Tablet, depot injection	Clozapine	Yes	Tablet
Haloperidol	Yes	Tablet, depot injection, injection, oral liquid	Lurasidone	No	Tablet
Loxapine	Yes	Tablet, oral concentrate, IM injection	Olanzapine	Yes	Tablet, Sublingual Tablet,
Methotrimeprazine	Yes (tablet)	Injection, tablet	Paliperidone	No	Tablet, Depot injection
Periciazine	No	Capsules, oral drops	Quetiapine	Yes	Tablet, Extended-Release tablet
Perphenazine	Yes	Tablet, oral liquid	Risperidone	Yes	Tablet, Sublingual Tablet, Extended-Release Injection, Oral Liquid
Pimozide	Yes	Tablet	Ziprasidone	No	Tablet
Pipotiazine	No	Injection			
Prochlorperazine	Yes	Tablet, injection			
Thioproperazine	No	Tablet			
Thiothixene	No	Capsules			
Trifluoperazine	Yes	Tablet, syrup			
Zuclopenthixol	No	Tablet, depot injection, injection			

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

Drug	Brand/ generic	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NW
Aripiprazole	Abilify	Res	Ben	Res	Ben	Ben	Ben	Res	Res	Res	Res	Res	Res
	Abilify Maintena	No	No	No	No	No	No	No	No	No	No	No	No
Asenapine	Saphris	Res	Res	Res	No	Ben	No	Res	Res	Res	Res	Res	Res
Clozapine	Generic	Ben	Ben	Res	Ben	Ben	Ben	Ben	Res	Res	Res	Ben	Ben
Lurasidone	Latuda	No	Ben	No	Ben	Ben	Res	Res	Res	No	Res	Res	No
Olanzapine	Zyprexa, Generic	Res	Ben	Res	Ben	Ben	Ben	Res	Res	Res	Res	Ben	Ben
	Zyprexa IM	No	No	No	No	No	No	No	No	No	No	No	No
Paliperidone	Invega	Ben	Ben	No	No	Ben	No	No	No	No	No	No	No
	Invega Sustenna	Res	Res	Res	No	Ben	Res	Res	Res	No	Res	No	Res
Quetiapine	Seroquel XR, Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	No	No	No	Ben
	Seroquel, Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Res	Ben	Ben	Ben
Risperidone	Risperdal Consta	Res	Res	Res	No	Ben	Res	Res	Res	Res	Res	Res	Res
	Risperdal, Generic	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Ben	Res	Ben	Ben	Ben
Ziprasidone	Zeldox	Res	Ben	Ben	Ben	Ben	Ben	Ben	Res	Res	Res	Ben	Res

No=not listed (red)
Res=restricted listing – enforced (yellow)
Ben=unrestricted listing (green)

Appendix D: Chlorpromazine (CPZ) equivalents

Class	Drug	Dose Equivalent Factor (CZDeq)
Atypical	Aripiprazole	20
	Asenapine	20
	Clozapine	1.50
	Olanzapine	30
	Lurasidone	5
	Paliperidone	66.6
	Quetiapine	0.8
	Risperidone	100
	Ziprasidone	3.75
Typicals	Chlorpromazine	1
	Flupenthixol	60
	Fluphenazine	50 (Long-acting inj = 17.8 or 14.2)
	Haloperidol	60 (long-acting inj = 35.7)
	Loxapine	10
	Methotrimeprazine	2
	Molindone	6
	Periciazine	12
	Perphenazine	20
	Pimozide	75
	Pipotiazine	2

Class	Drug	Dose Equivalent Factor (CZDeq)
	Prochlorperazine	6.86
	Thioridazine	1.20
	Thiothixene	20
	Trifluperazine	30
	Zuclopenthixol	12 (long-acting inj = 4.3)

Sources:

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2. Woods S. Chlorpromazine Equivalent doses for atypical antipsychotics.

Appendix E: Dementia Definition

Data Sources and Codes used to define Dementia	
Databases Used: OHIP or DAD and ODB	**Definition** One code during 5 year look back of the following in CIHI-DAD dementia related codes: **ICD-10 Code:** F00.0, F00.1, F00.2, F00.9, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03.0, F05.1, F06.5, F06.6, F06.8, F06.9, F09, G30.0, G30.1, G30.8, G30.9, G31.0, G31.1, R54 **OR** **OHIP Dementia Diagnosis DXCODE –** 290, 331, 797 **OR** **One year look back for cognitive enhancers (donepezil, galantamine, rivastigmine)**

Appendix F: Baseline Characteristics of antipsychotic therapy among elderly patients with dementia who are new users of provincially-funded antipsychotics in Ontario, by setting and class. January 2009 – December 2013

	Setting					
	Community			Long-Term Care		
	Overall	Atypical	Typical	Overall	Atypical	Typical
Number of users	**N=34,195**	**N=28,048**	**N=6,147**	**N=24,804**	**N=20,188**	**N=4,616**
Number of users with only 1 prescription date during period of continuous use (N, %)	**8,560 (25.0%)**	**5,182 (18.5%)**	**3,378 (55.0%)**	**4,995 (20.1%)**	**2,485 (12.3%)**	**2,510 (54.4%)**
Age Mean (SD)	82.0 (7.0)	82.1 (7.0)	81.3 (7.4)	85 (7.0)	85.0 (7.0)	85.0 (7.3)
Sex - Male (%)	10,171 (39.7%)	9,025 (39.5%)	1,146 (41.4%)	6,833 (34.5%)	6,141 (34.7%)	692 (32.9%)
Location of residence Urban	22,604 (88.2%)	20,192 (88.3%)	2,412 (87.1%)	16,666 (84.1%)	14,989 (84.7%)	1,677 (79.6%)
Income Quintile						
1	5,091 (19.9%)	4,526 (19.8%)	565 (20.4%)	4,791 (24.2%)	4,268 (24.1%)	523 (24.8%)
2	5,228 (20.4%)	4,641 (20.3%)	587 (21.2%)	3,927 (19.8%)	3,496 (19.7%)	431 (20.5%)
3	5,099 (19.9%)	4,596 (20.1%)	503 (18.2%)	3,788 (19.1%)	3,413 (19.3%)	375 (17.8%)
4	4,991 (19.5%)	4,455 (19.5%)	536 (19.4%)	3,705 (18.7%)	3,286 (18.6%)	419 (19.9%)
5	5,135 (20.0%)	4,568 (20.0%)	567 (20.5%)	3,448 (17.4%)	3,099 (17.5%)	349 (16.6%)
Number of unique medications (based on drug name) in last year Median (IQR)	10 (6-14)	10 (6-14)	13 (8-18)	11 (7-16)	11 (7-16)	13 (8-19)
Number with 1 or more hospitalizations	8,962 (35.0%)	7,512 (32.9%)	1,450 (52.4%)	8,000 (40.4%)	7,002 (39.6%)	998 (47.4%)
Physician office visits within the last year Median (IQR)	4 (2-6)	3 (2-5)	5 (3-8)	2 (1-4)	2 (1-4)	2 (1-4)
Specialist visits within 3 months						

	Setting					
	Community			Long-Term Care		
	Overall	Atypical	Typical	Overall	Atypical	Typical
Number of users	**N=34,195**	**N=28,048**	**N=6,147**	**N=24,804**	**N=20,188**	**N=4,616**
Psychiatrists	4,597 (17.9%)	4,305 (18.8%)	292 (10.5%)	3,230 (16.3%)	2,967 (16.8%)	263 (12.5%)
Geriatricians	5,007 (19.5%)	4,617 (20.2%)	390 (14.1%)	2,043 (10.3%)	1,793 (10.1%)	250 (11.9%)
Neurologists	2,457 (9.6%)	2,236 (9.8%)	221 (8.0%)	984 (5.0%)	889 (5.0%)	95 (4.5%)
Charlson Morbidity Index						
No hospitalization	12,420 (48.4%)	11,531 (50.4%)	889 (32.1%)	7,754 (39.1%)	7,060 (39.9%)	694 (33.0%)
0	3,249 (12.7%)	2,966 (13.0%)	283 (10.2%)	2,382 (12.0%)	2,118 (12.0%)	264 (12.5%)
1	3,709 (14.5%)	3,381 (14.8%)	328 (11.8%)	3,875 (19.6%)	3,495 (19.7%)	380 (18.0%)
2	2,441 (9.5%)	2,079 (9.1%)	362 (13.1%)	2,234 (11.3%)	1,974 (11.2%)	260 (12.3%)
3+	3,816 (14.9%)	2,909 (12.7%)	907 (32.8%)	3,564 (18.0%)	3,056 (17.3%)	508 (24.1%)
Concomitant psychotropic use during continuous use of AP						
Antidepressants	15,952 (62.2%)	14,726 (64.4%)	1,226 (44.3%)	14,415 (72.8%)	12,986 (73.4%)	1,429 (67.9%)
Benzodiazepine	9,485 (37.0%)	8,245 (36.1%)	1,240 (44.8%)	8,579 (43.3%)	7,613 (43.0%)	966 (45.9%)
Mood Stabilizer	2,053 (8.0%)	1,844 (8.1%)	209 (7.5%)	1,701 (8.6%)	1,509 (8.5%)	192 (9.1%)
Stimulants	132 (0.5%)	111 (0.5%)	21 (0.8%)	40 (0.2%)	39 (0.2%)	<=5
Cognitive enhancers	13,560 (52.9%)	12,895 (56.4%)	665 (24.0%)	8,763 (44.2%)	8,127 (45.9%)	636 (30.2%)
Antipsychotic Use						
Prescriber of Initial Prescription						
General Practitioner	17,342 (67.6%)	15,582 (68.1%)	1,760 (63.6%)	18,962 (95.7%)	16,956 (95.8%)	2,006 (95.3%)
Specialist	4,831 (18.8%)	4,698 (20.5%)	133 (4.8%)	118 (0.6%)	110 (0.6%)	8 (0.4%)
Other	2,424 (9.5%)	1,750 (7.7%)	674 (24.3%)	581 (2.9%)	511 (2.9%)	70 (3.3%)

**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, another record has been suppressed as well in order to avoid residual disclosure issues.*

Appendix G: Most common initial antipsychotics dispensed to new users by drug name

Atypicals		
Drug name	**Frequency**	**Percent**
Quetiapine	22100	47.3 %
Risperidone	18479	39.6 %
Olanzapine	5845	12.5 %
Aripiprazole	201	0.4 %
Paliperidone	56	0.1 %
Ziprasidone	16	0.03 %
Typicals		
Haloperidol	3238	56.0 %
Prochlorperazine	1693	29.3 %
Methotrimeprazine	503	8.6 %
Chlorpromazine	130	2.3 %
Loxapine	127	2.2 %
Perphenazine	26	0.5 %
Trifluoperazine	22	0.4 %
Flupentixol	17	0.3 %
Fluphenazine	15	0.3 %
Pimozide	12	0.2 %
Other	10	0.2 %

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