

# Cognitive Enhancers

## Pharmacoepidemiology Report: FINAL CENSORED Report

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**Note**

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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website ([www.odprn.ca](http://www.odprn.ca)).

# Executive Summary

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## National and Provincial Trends in Cognitive Enhancer Prescribing

Quarterly dispensing of prescriptions for cognitive enhancers in Canada has increased by 17% over the past 4 years, from 752,465 prescriptions (3.9 prescriptions per 1,000 population) dispensed in the fourth quarter (Q4) of 2009 to 884,132 prescriptions (5.0 prescriptions per 1,000 population) dispensed by Q4 2014. Given the introduction of generic versions of cognitive enhancers in 2014, a nearly 50% reduction in costs were observed from just prior to the introduction of generics (\$55 million in the fourth quarter of 2013; \$60.24 per prescription dispensed) to the end of follow-up (\$28 million in the fourth quarter of 2014; \$31.45 per prescription dispensed). Between 2009 and 2014, donepezil was the most utilized cognitive enhancer (58%) in Canada, followed by galantamine (21%), rivastigmine (11%), and memantine (10%).

Ontario has the highest rate of publically-funded cognitive enhancer use in Canada, which increased almost 7-fold from 5 users per 1,000 elderly population in the first quarter of 2000 to 33 users per 1,000 elderly population in the fourth quarter of 2013. In 2013 Ontario had the highest annual rate of publicly-funded cognitive enhancer users with 41 users per 1,000 elderly population. This high rate of utilization in Ontario may be due to liberal listing for this class of medications relative to all other provinces in Canada. Among all other provinces, which all have more restrictive listings of cognitive enhancers, the annual rate of publically funded users ranged from 10 users per 1,000 elderly population in Saskatchewan to 33 users per 1,000 elderly population in New Brunswick in 2013. Donepezil was the most commonly used publically funded cognitive enhancer across all provinces in Canada (65% of all users). Galantamine was the second most commonly used publically funded cognitive enhancer drug across all provinces (26% of all users), except in British Columbia, where rivastigmine was the second most commonly used cognitive enhancer (20% of all users).

## Use of Cognitive Enhancers in Ontario

Overall, Ontario has seen a small increase in the use of cognitive enhancers over time, with the number of prescriptions dispensed, regardless of payer, having increased by 9.9%, from 396,552 prescriptions (27 prescriptions per 1,000 population) in the fourth quarter of 2009 to 435,982 prescriptions (28 prescriptions per 1,000 population) in the fourth quarter of 2014. Consequently, costs remained relatively stable between the fourth quarter of 2009 and the fourth quarter of 2013 at approximately \$28 million per quarter until the introduction of generic donepezil in 2014 after which costs dropped dramatically, decreasing by approximately 50% from \$26.6 million in the fourth quarter of 2013 to \$12.6 million in the fourth quarter of 2014.

Among publically-funded cognitive enhancers in Ontario, almost two-thirds of prescriptions (64.5%; 945,108) were for donepezil, followed by 28.2% (N=413,533) for galantamine in 2014. Conversely, among privately insured medications and those paid for in cash, the most popular cognitive enhancer

was memantine (69.6%; 71,417 prescriptions, and 68.7%; 97,392 prescriptions, respectively). This is likely because memantine is not publicly-covered in Ontario, thus patients wishing to access this medication must pay out of pocket or through a private insurer. There is little galantamine or rivastigmine use outside of the public drug program in Ontario.

### **Characteristics of Publically-funded Cognitive Enhancers Users within Ontario**

In 2013, there were 146,593 publically-funded cognitive enhancer users aged 65 and older in Ontario. The majority of users were prescribed donepezil (N=95,317; 65.0%), followed by galantamine (N=38,440; 26.2%), and rivastigmine (N=12,836; 8.8%). Users of cognitive enhancers in Ontario were found to be on average 82 years of age, approximately two-thirds were female (n=91,537), 21.2% (n=31,025) lived in LTC, and 77.6% (n=113,742) had a diagnosis of dementia. These individuals were found to be sicker than the general elderly population, with a median of 8 physician visits annually, almost half (47.5%) had visited the emergency room in the previous year, and almost a quarter of users (24.8%) were hospitalized in the previous year. Cognitive enhancer users were generally similar across drug groups, with the exception of rivastigmine users. Rivastigmine users are more likely to be male (42.8% vs. 37.6%), LTC residents (32.4% vs. 21.2%), have more comorbidities, and have a higher prevalence of dementia (83.6% vs. 77.6%) when compared to all cognitive enhancer users combined.

### **Patterns of Use and Discontinuation of Cognitive Enhancers in Ontario**

Between 2009 and 2012, we identified 73,609 elderly patients aged 66 years and older who newly initiated a cognitive enhancer in Ontario. The average age at time of initiation was 82 years. Most new users initiated donepezil (68.8%; n=45,802), with a majority of these medications prescribed by a general practitioner (63.1%; n=42,175). The vast majority of patients (90.8%; n=66,844) received at least 2 prescriptions in a 180 day period. One year after initiation of therapy, almost three-quarters of patients remained on therapy (70-75%). The time to discontinuation of cognitive enhancer treatment varied by drug therapy (censored data), with 65-70% of rivastigmine users remaining on therapy after 1 year compared to 70-75% of donepezil users and 70-75% of galantamine users.

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## Introduction

Cognitive enhancers are a drug class used in the treatment of dementia. Four cognitive enhancers are currently available in Canada (donepezil, galantamine, memantine, rivastigmine), but only 3 are available on the Ontario drug formulary (donepezil, galantamine, rivastigmine). Recent genericization and increased utilization of cognitive enhancers has generated interest in the undertaking of a drug class review.

The objectives of this report are to describe national and provincial trends in the use of cognitive enhancers and to identify patterns of use. Specifically, this report aims to:

1. Present national utilization trends of cognitive enhancers across Canada, including cross-provincial comparisons of population-adjusted rates of use
2. Present cross-provincial public drug program utilization comparisons of cognitive enhancers across Canada using population-adjusted rates of use
3. Examine trends in use of cognitive enhancers dispensed through the Ontario Drug Benefit program
4. Describe the characteristics of patients treated with cognitive enhancers in Ontario
5. Describe the course and length of cognitive enhancer therapy among those newly initiated on these drugs in Ontario

## Data Sources

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

IMS Geographic Prescription Monitor (GPM<sup>12</sup>) is a premium source of sales intelligence on retail prescription activity in Canada. Data is obtained from a representative sample of 65% of all Canadian pharmacies and is projected monthly by province or customized geography. Projections incorporate the number of pharmacies in a given area, the distance between IMS-captured and uncaptured pharmacies, and the size of the pharmacies. Projections are representative of provincial and national sales volumes. Data available through IMS Geographic Prescription Monitor (GPM<sup>12</sup>) includes prescription volumes and units (e.g. tablets, patches) dispensed, and are stratified by payer type (e.g. public drug plan, private drug plan, cash, Non-Insured Health Benefits). Data from IMS Geographic Prescription Monitor (GPM<sup>12</sup>) is available from the fourth quarter of 2009 to the fourth quarter of 2014.

### Canadian Institute for Health Information National Prescription Drug Utilization Information System

The National Prescription Drug Utilization Information System (NPDUIS) was developed by the Canadian Institute for Health Information 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 calendar year 2000 to 2013.

## Administrative Databases in Ontario

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

### Ontario Drug Benefit Database

The Ontario Drug Benefit (ODB) database contains individual-level claims data for all prescription drugs dispensed to Ontario residents eligible for public drug funding. Eligibility criteria include unemployment, disability, high prescription drug costs relative to net household income, receipt of home care services, residence in a long-term care facility, or age 65 years or older. This database is of high quality, with an error rate of <1% and can be linked to other health administrative databases to obtain patient demographic information.<sup>1</sup> We analyzed data from the ODB between January 2000 and December 2013.

### Other Health Administrative Databases

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

## Methods

All analyses using administrative databases in Ontario available through the Institute for Clinical Evaluative Sciences were approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

### National Trends in Utilization of Cognitive Enhancers

We used data from IMS Geographic Prescription Monitor (GPM<sup>12</sup>) to examine overall trends in the prescribing volumes of cognitive enhancers, at both national and provincial levels. We examined the number of prescriptions dispensed for cognitive enhancer products between October 2009 and December 2014. Analyses were stratified by payer of the prescription and by province. To conduct cross-provincial comparisons of publicly-funded cognitive enhancers, we leveraged the CIHI NPDUIS data. All cross-provincial analyses compared population-adjusted rates.

### Population Adjustment – Overall Utilization

For measures examining publicly-funded utilization of cognitive enhancers, we used the number of individuals eligible for provincial drug coverage in each year from 2000 to 2014 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 publicly 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. IMS analysis of number of prescriptions were adjusted for total populations as claims may have been used in those under the age of 65. Provincial population estimates were obtained from Statistics Canada for each year from 2009 to 2014 and used to adjust the overall utilization rates (per 1,000 population) across different provinces and nationally.

### **Characteristics of Publically-Funded Cognitive Enhancer Users in Ontario**

We used claims data from ODB to perform additional analyses of utilization of cognitive enhancers among patients in Ontario. These analyses included estimating the utilization and costs of publicly-funded cognitive enhancers. Users were defined in these analyses as individuals who received at least one prescription for a cognitive enhancer over the period of interest. We also examined baseline characteristics of patients dispensed a cognitive enhancer using linked administrative databases housed at the Institute for Clinical Evaluative Sciences, including the CIHI Discharge Abstract Database (to identify inpatient hospitalizations and Charlson comorbidity score), the CIHI National Ambulatory Care Reporting System (to identify emergency department visits), the Registered Persons Database (to determine demographic information such as age, gender, and income quintile), the Ontario Health Insurance Plan database (to identify outpatient physician visits), the ODB database (to identify past medication use), and the ICES Physician Database (to determine physician characteristics such as visits to specialists).

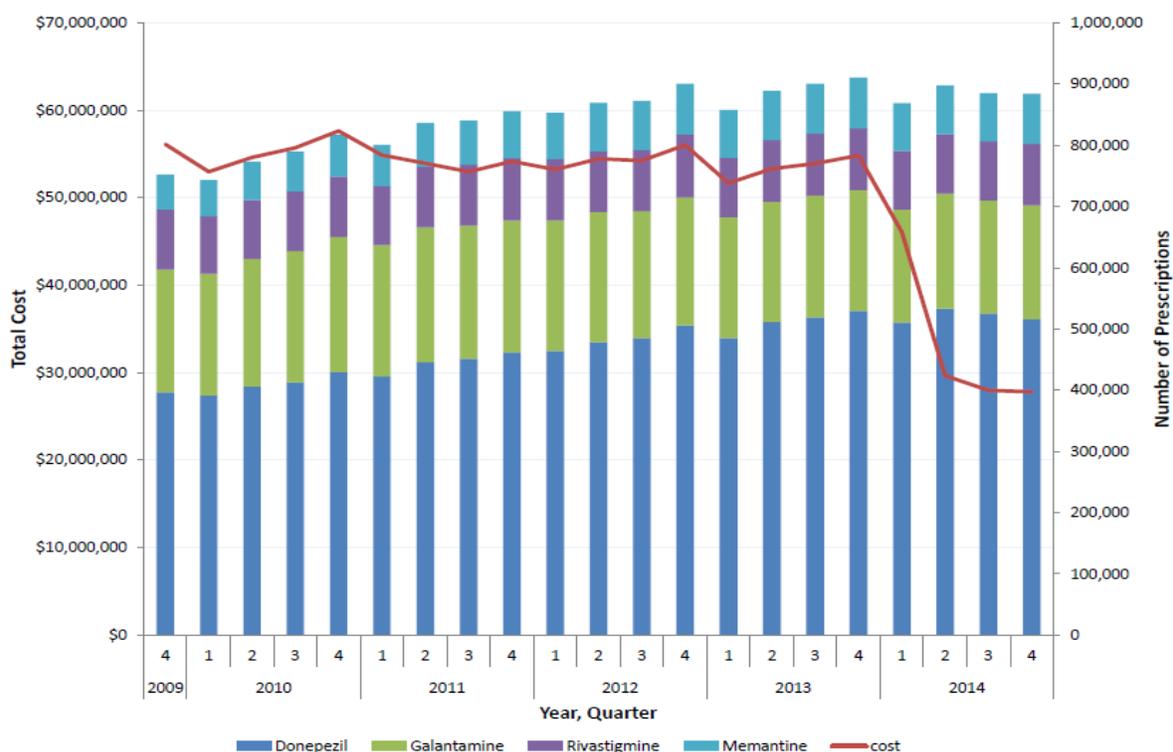
### **Adherence Among New Users of Cognitive Enhancers in Ontario**

We established a cohort of patients 66 years of age and older who were new users of cognitive enhancers between January 1, 2009 and December 31, 2013, to examine the duration of cognitive enhancer use in Ontario. Public drug coverage is universal for individuals aged over 65, and we do not have complete eligibility information for younger beneficiaries. Therefore, we restricted this analysis to individuals aged 66 and older in order to ensure complete medication records and accurate ascertainment of new use of cognitive enhancers. 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, 2014). Patients who switched between drugs within the drug class were still considered to be persistent. Discontinuation was defined on the basis of no subsequent prescription for a cognitive enhancer within 180 days of the previous prescription, which is consistent with previously published studies.<sup>2-4</sup> Differences in rates of discontinuation between cognitive enhancers were assessed using a Cox proportional hazards model adjusted for baseline characteristics. The proportional hazards assumption was violated and thus hazard ratios are reported as average hazard ratios over the follow-up.

## Exhibits and Findings

### National Trends in Utilization of Cognitive Enhancers

*Exhibit 1: Total utilization and cost of cognitive enhancers dispensed in Canada, by drug and quarter*



The number of prescriptions dispensed for cognitive enhancer products increased by 17% over the study period. Despite this increase in utilization, the cost of these products decreased considerably (49.3%) following the introduction of generic products in 2013.

#### Summary of Findings for Exhibit 1

1. The number of prescriptions dispensed for cognitive enhancer medications in Canada has increased 17.4% over the past 5 years, from 752,465 prescriptions dispensed in Q4 2009 to 884,132 prescriptions dispensed in Q4 2014.
2. Overall, there was a slight decrease in the number of prescriptions for galantamine (200,104 to 186,564 prescriptions between Q4 2009 and Q4 2014). Conversely, prescriptions for memantine increased 42% (from 57,531 prescriptions to 81,722 prescriptions between Q4 2009 and Q4 2014), prescriptions for donepezil increased 29.9% (from 396,885 to 515,572 prescriptions between Q4 2009 and Q2 2014) and prescriptions for rivastigmine increased 2.8% (from 97,945 to 100,274 prescriptions between Q4 2009 and Q4 2014, respectively).
3. Costs for cognitive enhancers remained relatively stable between Q4 2009 (\$56.1 million) and Q4 2013 (\$54.8 million). Following the introduction of generics in 2013, these costs dropped dramatically, falling 49.3% from \$54.8 million in Q4 of 2013 to \$27.8 million by Q4 of 2014.

## Population-adjusted Rates of Cognitive Enhancer Utilization, by Funding Type

**Methodological Note:**

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

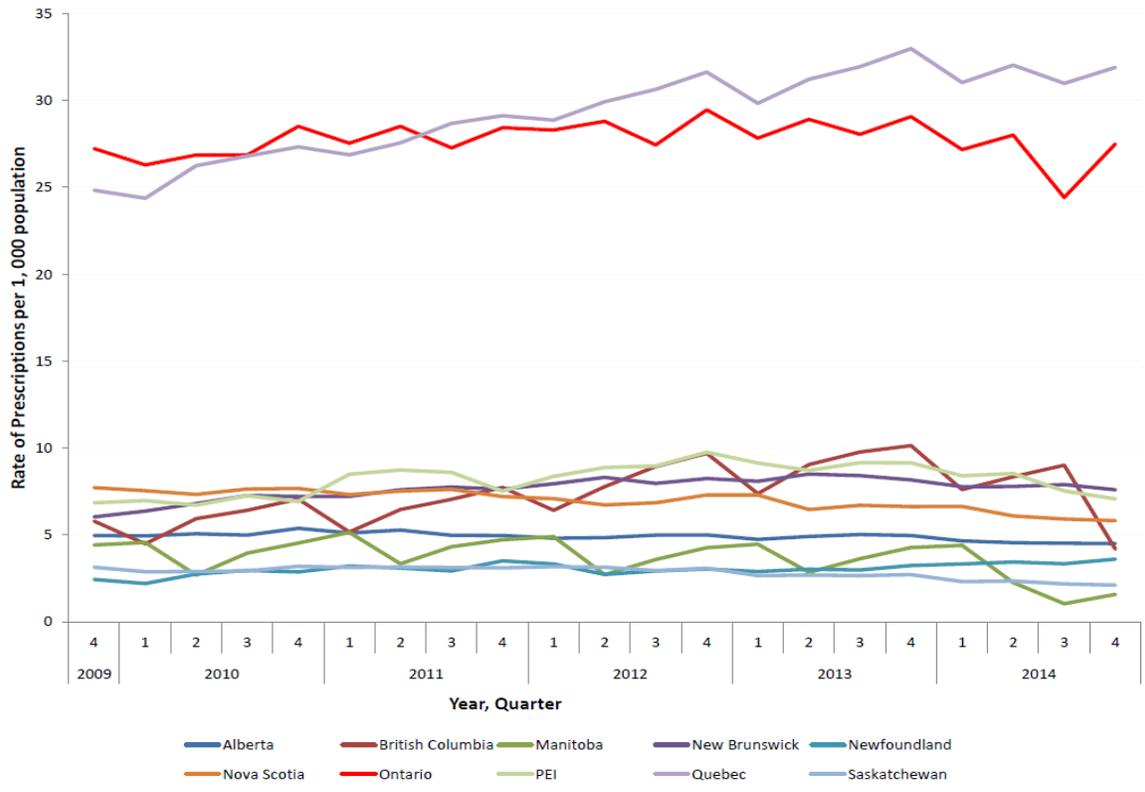
- Private drug insurance
- Cash
- Non-Insured Health Benefits

Public plan listings for cognitive enhancers across the provinces are as follows:

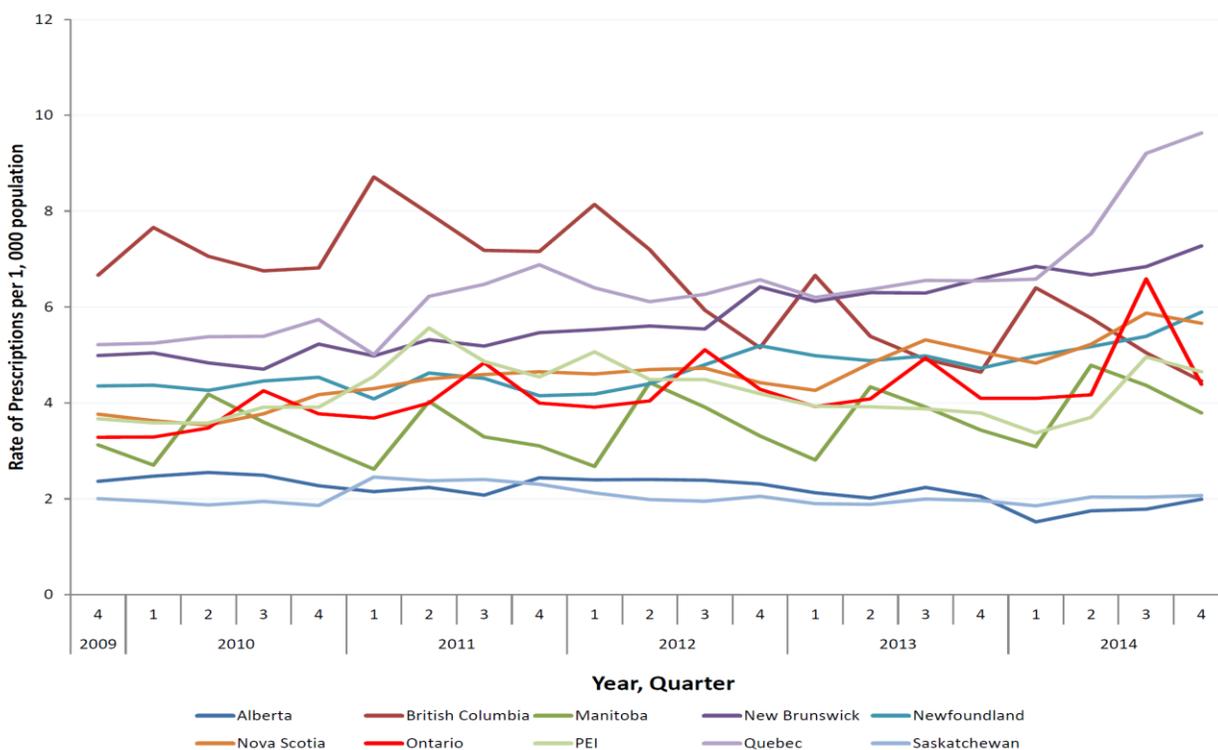
- Restricted (passive): Ontario
- Restricted (enforced): Alberta, British Columbia, Manitoba, Saskatchewan, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland

Public drug plan eligibility also differs by province which may impact the average age of beneficiaries. More detailed information on public plan listings is provided in [Appendix C](#).

Exhibit 2: Population-adjusted utilization of publically funded cognitive enhancers (prescriptions per 1,000 population) in Canada, by province and quarter



**Exhibit 3: Population-adjusted utilization of non-publically funded cognitive enhancers (prescriptions per 1,000 population) in Canada, by province and quarter**

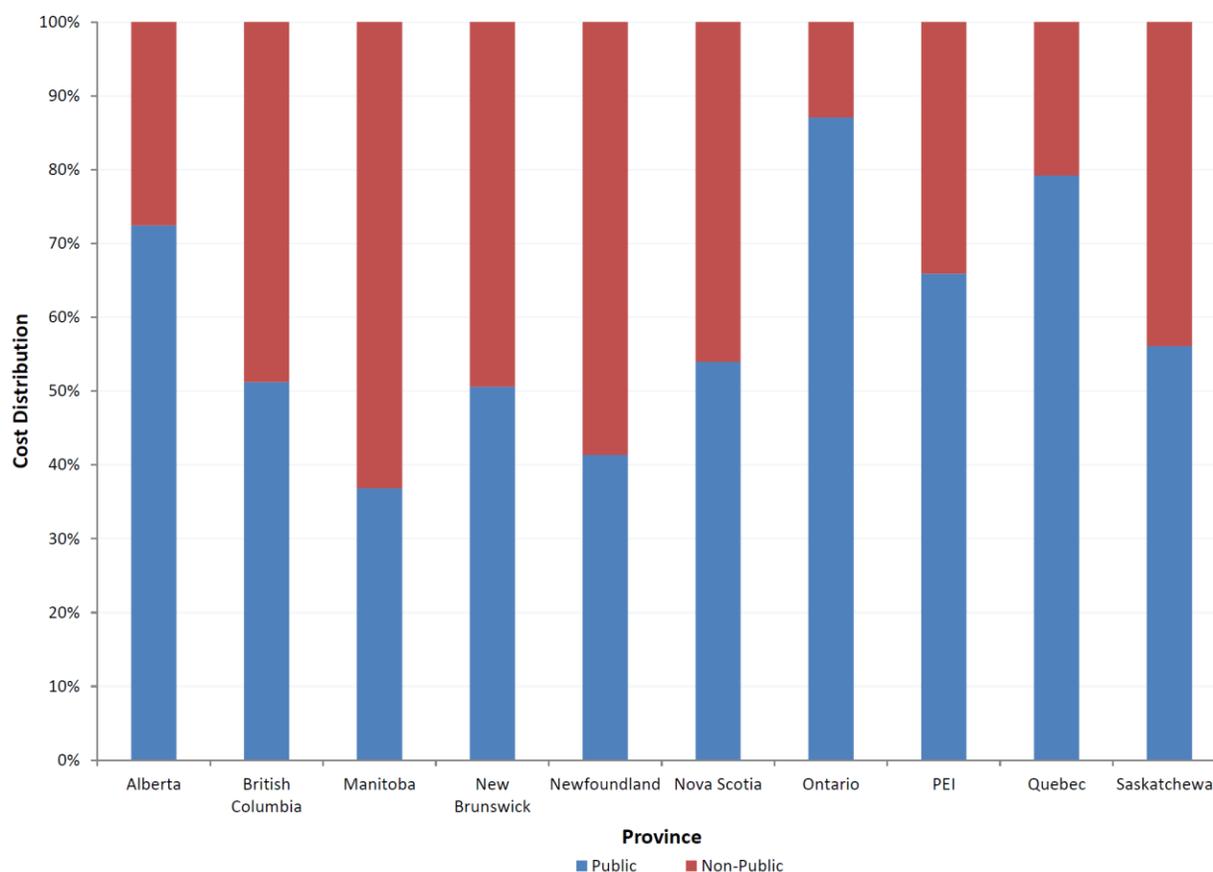


Ontario has the second highest rate of publically-funded cognitive enhancer products in Canada, while Quebec has the highest rate of cognitive enhancer use regardless of method of payment.

### Summary of Findings for Exhibit 2 and Exhibit 3

1. Quebec and Ontario exhibited much higher rates of publically-funded cognitive enhancer use (32 and 28 prescriptions per 1,000 population, respectively; national average of 10 prescriptions per 1,000 elderly population in Q4 2014) relative to other provinces. The remaining provinces exhibited much lower rates of use (range in Q4 2014: 2 [Manitoba] to 7 [Prince Edward Island] prescriptions per 1,000 elderly population).
2. In Q4 2014, Ontario had the second highest rate of publically-funded cognitive enhancer use (28 prescriptions per 1,000 elderly population).
3. Slight cross-provincial variations were noted in the rate of non-publically funded cognitive enhancer products (range in Q4 2014: 2 [Alberta] to 10 [Quebec] prescriptions per 1,000 elderly population)
4. By Q4 2014, non-publically funded cognitive enhancer use in Ontario was on par with the national average (4 prescriptions per 1,000 population; national average 5 prescriptions per 1,000 elderly population).

**Exhibit 4: Distribution of the costs for cognitive enhancers dispensed across Canada in 2014, by province**



The majority of cognitive enhancer products in Canada (76.8%) are paid for by provincial drug coverage, however this differs considerably by province.

#### Summary of Findings for Exhibit 4

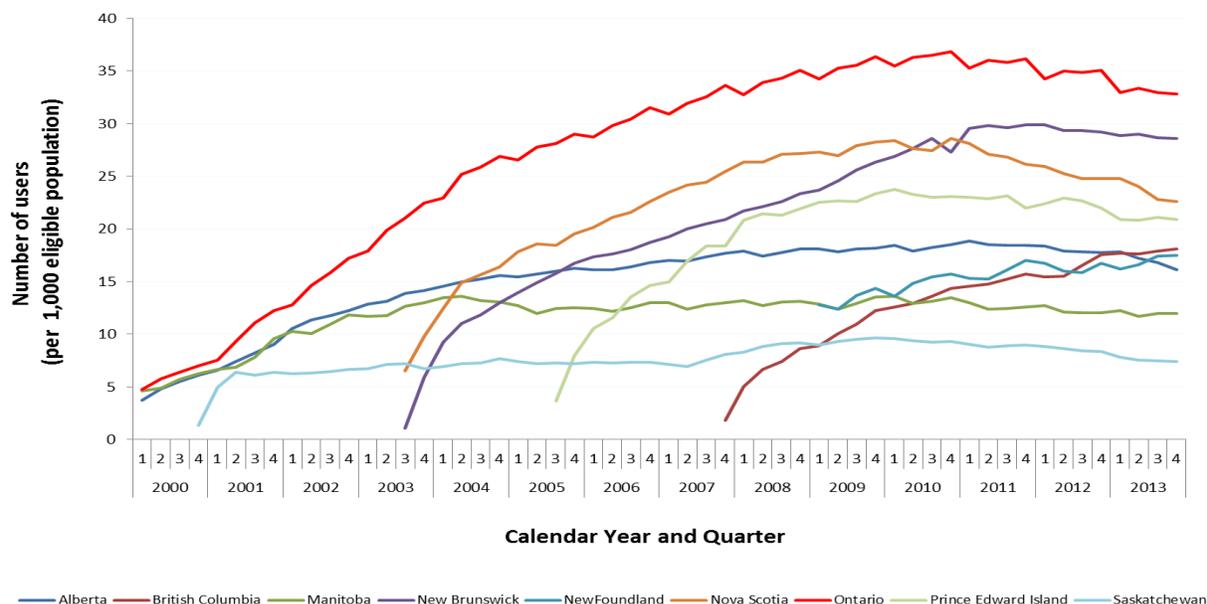
1. In 2014, a total of \$118 million was spent nationally on all cognitive enhancer products. The majority of these costs (76.8%; \$90.8 million) are paid for by provincial drug coverage (data not shown).
2. In Ontario, a total of \$52.4 million was spent on all cognitive enhancer products. The majority of these costs (87%; \$45.6 million) were paid by the provincial drug plan, which may be reflective of the unrestricted listing of these medications on the formulary.
3. Conversely, provinces such as Manitoba (total expenditures \$1.9 million) that have more restrictive access to these medications have a larger proportion of costs (63.2%, \$1.2 million) paid through non-publically funded drug program.

## Trends in Publicly-Funded Cognitive Enhancers across Canada

### 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 Quebec and the Canadian territories.

*Exhibit 5: Population-adjusted utilization of publicly funded cognitive enhancers (users per 1,000 elderly population) in Canada, by province and quarter, 2000 to 2013*

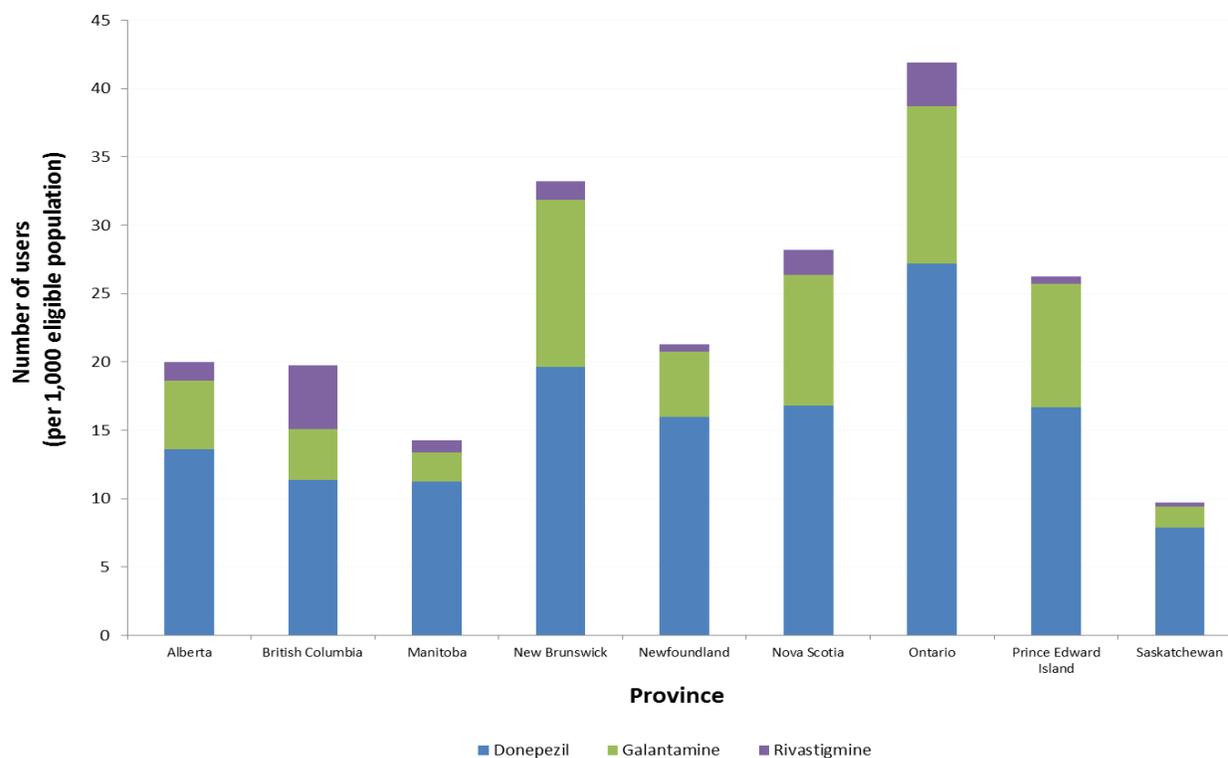


The rate of publicly-funded cognitive enhancer users has increased across all provinces since 2000. Ontario has the highest rate of publicly funded cognitive enhancer users. (Note: QC data not available)

### Summary of Findings for Exhibit 5

1. Ontario has the highest rate of cognitive enhancer users in provinces where data is available, which has increased almost 7-fold from 5 users per 1,000 elderly population in Q1 2000 to 33 users per 1,000 population in Q4 2013. This is expected since Ontario is the only province in Canada to have a passive listing of these drugs, compared to restricted listing in other provinces.
2. Beginning in 2011, the rate of cognitive enhancer users in Ontario, New Brunswick, Nova Scotia, PEI, and Saskatchewan decreased.
3. By the end of 2013, the eastern provinces in Canada (NB, NF, NS, PEI) had a higher rate of cognitive enhancer users compared to the western provinces (SK, MB, AB, BC).

**Exhibit 6: Population-adjusted utilization of publically funded cognitive enhancers in Canada in 2013, by province and drug**



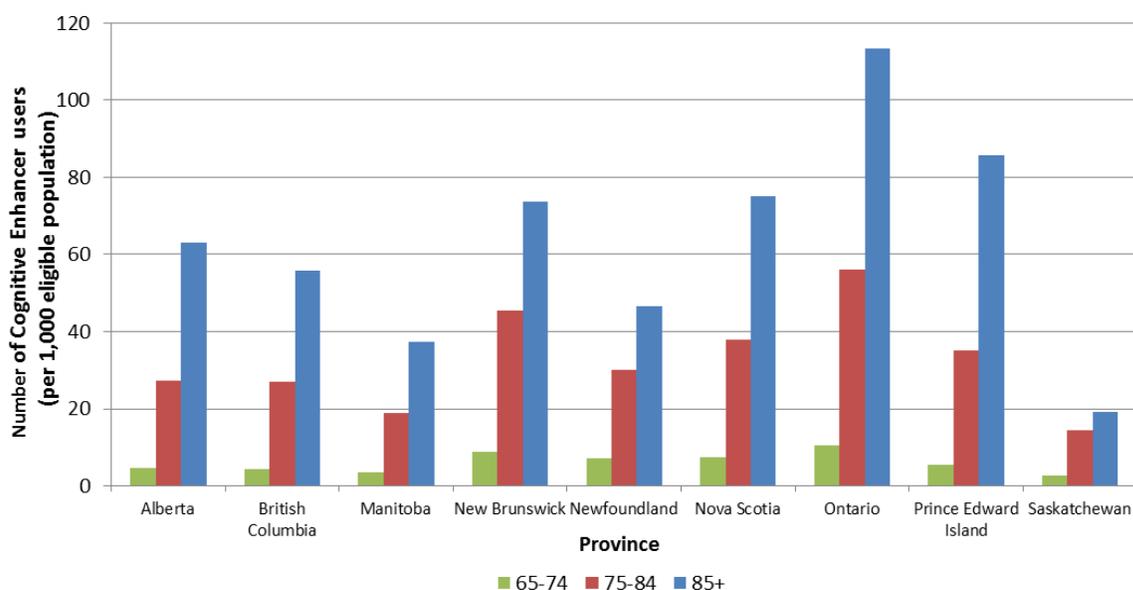
Donepezil is the most commonly used cognitive enhancer product by elderly patients eligible for public drug coverage, across all provinces in 2013.

### Summary of Findings for Exhibit 6

1. Ontario had the highest rate of publically-funded cognitive enhancer users (41 users per 1,000 elderly population) in 2013. Among the other provinces, with a restrictive listing of cognitive enhancers, the rate of users ranged from 10 users per 1,000 elderly population in Saskatchewan to 33 per 1,000 elderly population in New Brunswick in 2013.
2. Donepezil was the most commonly used cognitive enhancer across all provincial drug programs in Canada where data was available (from 8 users per 1,000 elderly population in Saskatchewan to 27 users per 1,000 elderly population in Ontario). Galantamine was the second most commonly used cognitive enhancer drug across all provinces (except British Columbia where rivastigmine was the second most commonly used cognitive enhancer).
3. New Brunswick had the highest rate of galantamine users (13 per 1,000 elderly population) and British Columbia had the highest rate of rivastigmine users (5 users per 1,000 elderly population).

NOTE: Between 2011 and 2013, there were less than 52 publically-funded users of memantine in Canada (46 in BC, 6 in MB and less than 5 in NS).

**Exhibit 7: Population-adjusted utilization of publically funded cognitive enhancers in Canada in 2013, by province and age-group**



The rate of cognitive enhancer use was lowest among users aged 65-74 and highest among users aged 85+ across all provinces in Canada, in 2013.

### Summary of Findings for Exhibit 7

1. Rates of cognitive enhancer use were found to be highest in those aged 85 years and older and lowest in those 65 to 74 years of age across all provinces in 2013.
2. In 2013, the rate of cognitive enhancer users in Ontario was higher than any other province in all 3 age groups (65-74: 10.6 users per 1,000 population; 75-84: 56.2 users per 1,000 population; 85+: 113.3 users per 1,000 population).
3. Saskatchewan had the lowest rate of users of all provinces studied for each age group in 2013 (65-74: 2.8 users per 1,000 population; 75-84: 14.3 users per 1,000 population; 85+: 19.24 users per 1,000 population).

**Exhibit 8: Population-adjusted utilization of publically funded cognitive enhancers in Canada in 2013, by province and drug and age-group**

Province	# of Cognitive Enhancer Users	Rate of users (per 1,000 elderly population)	Average Age of Cognitive Enhancer users	Rate of users (per elderly 1,000 population)			Rate of users (per elderly 1,000 population)		
				Donepezil	Galantamine	Rivastigmine	65-74	75-84	85+
<b>AB</b>	8,082	19.6	82.8	13.6	5.1	1.3	4.5	27.4	63.2
<b>BC</b>	12,754	19.0	82.8	11.4	3.7	4.6	4.3	27.0	55.9
<b>MB</b>	2,422	14.1	83.0	11.2	2.1	0.9	3.6	18.9	37.2
<b>SK</b>	1,442	9.6	82.0	7.9	1.5	0.3	2.8	14.3	19.2
<b>NS</b>	3,136	27.8	82.7	16.8	9.6	1.8	7.3	38.0	75.1
<b>NB</b>	2,406	32.7	82.6	19.6	12.2	1.4	8.8	45.4	73.7
<b>NL</b>	1,039	21.1	81.2	16.0	4.8	0.5	7.2	30.1	46.7
<b>PE</b>	587	25.5	83.1	16.7	9.0	0.5	5.6	35.2	85.7
<b>ON</b>	80,973	41.0	83.1	27.2	11.5	3.2	10.6	56.2	113.3

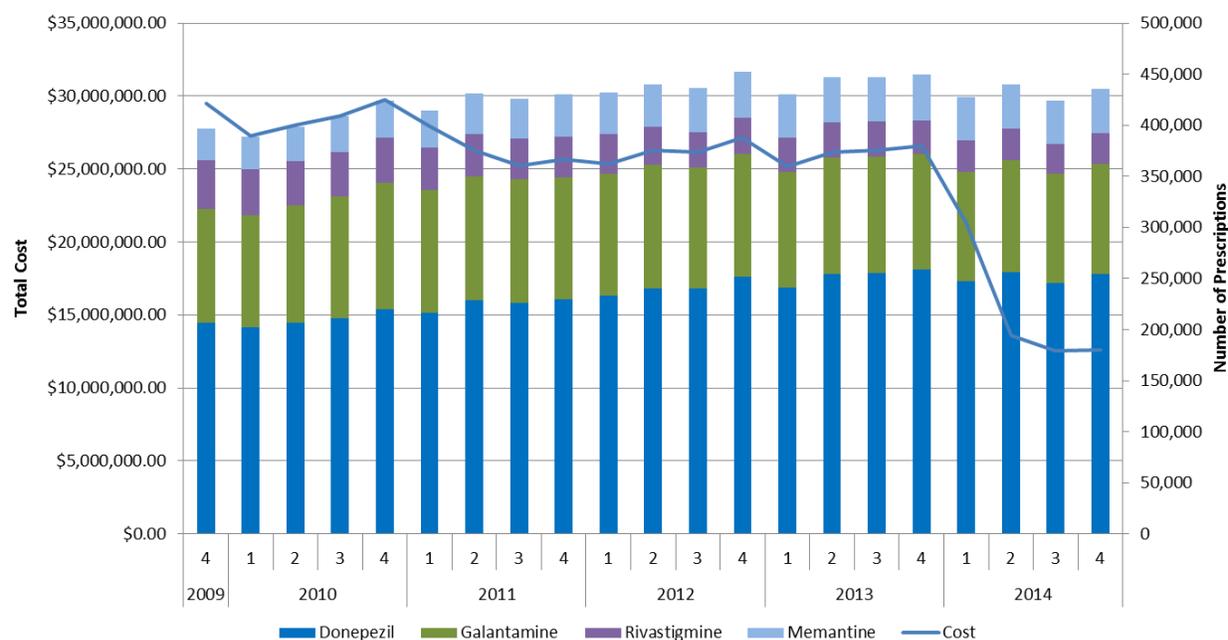
The rate of cognitive enhancer drug use in Canada varied by province, drug and age group. On average, cognitive enhancer users were 86 years of age and the majority used donepezil.

### Summary of Findings for Exhibit 8

1. In 2013, Ontario had the highest rate of cognitive enhancer users of all provinces studied, 41 users per 1,000 elderly populations (compared to between 9.6 to 32.7 users per 1,000 elderly population for all other provinces).
2. Despite having cognitive enhancer access restricted on the public drug formulary, New Brunswick had the second highest rate of users in 2013 (32.7 users per 1,000 elderly population). Conversely, Saskatchewan (another province that restricts access to cognitive enhancers) had the lowest rate of users (9.6 per 1,000 elderly population).
3. The average age of cognitive enhancer users was 82.6 across Canada in 2013 and was similar between provinces.

## Trends in Publically-Funded Cognitive Enhancers in Ontario

**Exhibit 9: Total utilization and cost of cognitive enhancers in Ontario, by drug and quarter**

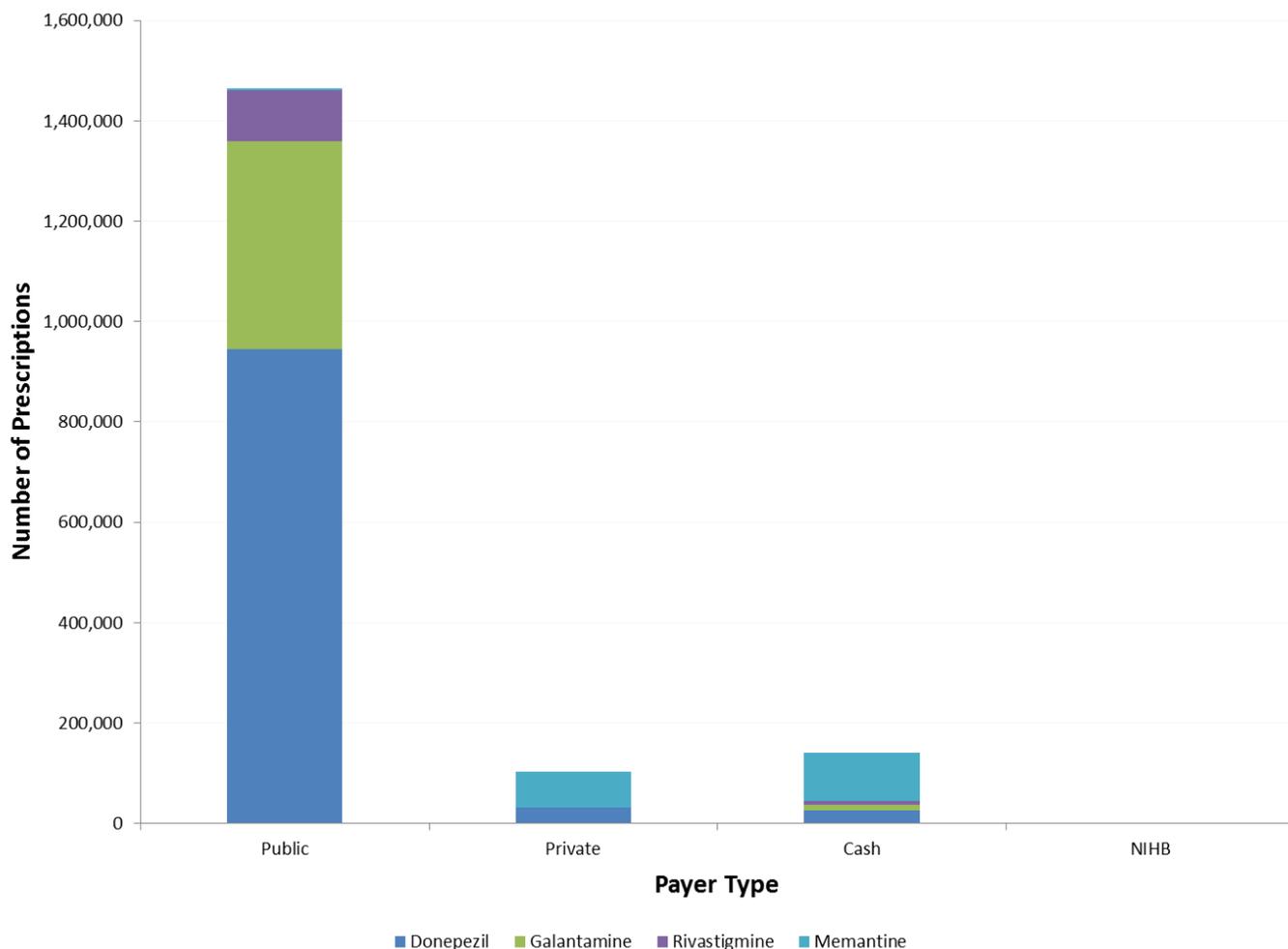


Trends in utilization and costs for cognitive enhancers in Ontario were similar to national trends. The number of prescriptions dispensed increased 9.9% and costs remained fairly stable before decreasing rapidly in 2013 upon the introduction of generic formulations.

### Summary of Findings for Exhibit 9

1. The number of cognitive enhancer prescriptions dispensed in Ontario increased 9.9% from 396,552 prescriptions in Q4 2009 to 435,982 prescriptions in Q4 2014.
2. Overall, prescriptions for galantamine and rivastigmine decreased by 2.8% and 38.8%, respectively, over the study period. Conversely, prescriptions for donepezil increased 23.1% (from 206,543 to 254,350 prescriptions between Q4 2009 and Q2 2014) and memantine increased 44.2% (from 30,465 to 43,926 prescriptions between Q4 2009 and Q4 2014, respectively).
3. Costs remained relatively stable between Q4 2009 (\$29.5 million) and Q4 2013 (\$26.6 million). After the introduction of generics in 2013, these costs dropped dramatically in 2014, falling 52.6%, from \$26.6 million in Q4 2013 to \$12.6 million in Q4 2014.

**Exhibit 10: Distribution of the cognitive enhancer prescriptions dispensed in Ontario in 2014, by payer**



The vast majority of cognitive enhancer prescriptions are paid for through the public drug program in Ontario. Donepezil is the most commonly dispensed medication in the public drug program, compared to memantine among those prescriptions covered through private insurance or cash.

### Summary of Findings for Exhibit 10

1. The majority (85.7%; n=1,464,726) of prescriptions for cognitive enhancers are reimbursed by the public drug program. The remaining 6.0% (n=102,577) are paid for through private insurance, and 8.3% (n=141,754) are paid for with cash. Less than 0.1% (n=237) of prescriptions are paid through NIHB.
2. Among publicly funded cognitive enhancers, almost two-thirds of prescriptions (64.5%; 945,108) were for donepezil, followed by 28.2% (N=102,394) for galantamine in 2014. Conversely, among privately insured medications, and those paid for in cash, the most popular cognitive enhancer is memantine (69.6%; 71,417 prescriptions, and 68.7%; 97,392 prescriptions, respectively). There is very little galantamine or rivastigmine use outside of the public drug program.
3. Cognitive enhancers are rarely funded through NIHB. Only 237 prescriptions were identified in 2014.

## Characteristics of Publically-Funded Cognitive Enhancer Users in Ontario

Exhibit 11: Baseline characteristics of patients aged 65 and older treated with publically-funded cognitive enhancers in Ontario in 2013, by therapy

	Overall N=146,593	Donepezil N=95,317	Galantamine N=38,440	Rivastigmine N=12,836
<b>Age (Mean, SD)</b>	82.2 (6.8)	82.2 (6.8)	82.1 (6.8)	81.8 (7.0)
<b>Sex - Male (N, %)</b>	55,056 (37.6%)	35,203 (36.9%)	14,353 (37.3%)	5,500 (42.8%)
<b>LTC Residents (N, %)</b>	31,025 (21.2%)	18,572 (19.5%)	8,294 (21.6%)	4,159 (32.4%)
<b>Urban Location of residence</b>	128,484 (87.6%)	82,813 (86.9%)	34,085 (88.7%)	11,586 (90.3%)
<b>Income Quintile</b>				
missing	709 (0.5%)	469 (0.5%)	184 (0.5%)	56 (0.4%)
1	30,072 (20.5%)	19,344 (20.3%)	8,187 (21.3%)	2,541 (19.8%)
2	29,853 (20.4%)	19,352 (20.3%)	8,013 (20.8%)	2,488 (19.4%)
3	28,710 (19.6%)	18,683 (19.6%)	7,404 (19.3%)	2,623 (20.4%)
4	28,843 (19.7%)	18,786 (19.7%)	7,466 (19.4%)	2,591 (20.2%)
5	28,406 (19.4%)	18,683 (19.6%)	7,186 (18.7%)	2,537 (19.8%)
<b>Number of unique medications in last year (Median, IQR)</b>	9 (6-14)	9 (6-13)	9 (6-14)	10 (7-15)
<b>Charlson Morbidity Index</b>				
No hospitalization	83,128 (56.7%)	54,275 (56.9%)	21,951 (57.1%)	6,902 (53.8%)
0	18,527 (12.6%)	12,185 (12.8%)	4,749 (12.4%)	1,593 (12.4%)
1	19,199 (13.1%)	12,250 (12.9%)	5,019 (13.1%)	1,930 (15.0%)
2+	25,739 (17.6%)	16,607 (17.4%)	6,721 (17.5%)	2,411 (18.8%)
<b>Diagnosis of Dementia (N, %)</b>	113,742 (77.6%)	72,031 (75.6%)	30,976 (80.6%)	10,735 (83.6%)
<b>Hospitalizations within the last year (N, %)</b>	36,296 (24.8%)	23,839 (25.0%)	9,211 (24.0%)	3,246 (25.3%)
<b>Emergency visits within the last year (N, %)</b>	69,672 (47.5%)	45,424 (47.7%)	18,130 (47.2%)	6,118 (47.7%)
<b>Physician office visits within the last year (Median, IQR)</b>	8 (4-13)	8 (4-13)	8 (4-14)	8 (3-14)

Psychotropic use within 120 days of cohort entry (N, %)				
Antidepressants	53,296 (36.4%)	33,243 (34.9%)	14,567 (37.9%)	5,486 (42.7%)
Benzodiazepines	23,509 (16.0%)	14,999 (15.7%)	6,193 (16.1%)	2,317 (18.1%)
Mood Stabilizers	4,760 (3.2%)	3,050 (3.2%)	1,247 (3.2%)	463 (3.6%)
Stimulants	296 (0.2%)	170 (0.2%)	97 (0.3%)	29 (0.2%)
Antipsychotics	25,127 (17.1%)	14,628 (15.3%)	6,816 (17.7%)	3,683 (28.7%)

Cognitive enhancer users are generally older, female, and have high health service utilization (physician visits, ED visits and hospitalizations). There is a high degree of antipsychotic, antidepressant and benzodiazepine use among these individuals.

### Summary of Findings for Exhibit 11

1. In general, users of cognitive enhancers are 82 years of age, approximately two-thirds of users are female (62.4%), 21.2% live in LTC, and 77.6% have a diagnosis of dementia. These individuals are high users of the healthcare system, with a median 8 physician visits annually. Furthermore, almost half (47.5%) visited the ED, and almost one-quarter of users (24.8%) were hospitalized in 2013.
2. In general, users of cognitive enhancers are similar, with the exception of rivastigmine users. Rivastigmine users are more likely to be male (42.8%), LTC residents (32.4%), have more comorbidities (measured based on number of drugs dispensed and Charlson comorbidity index), and have a higher prevalence of dementia (83.6%).
3. Users of cognitive enhancers had recent use of antidepressants (36.4%), benzodiazepines (16.0%) and antipsychotics (17.1%). However, this differed based on the type of cognitive enhancer. Specifically, users of rivastigmine were more likely to have recently used antidepressants (42.7%) and antipsychotics (28.7%).

## Patterns of Cognitive Enhancer Use and Discontinuation Among New Users

Exhibit 12: Patterns of use among new users of publically-funded cognitive enhancers in Ontario, by therapy. January 2009-December 2013

	Overall	Donepezil	Galantamine	Rivastigmine
<b>Number of users</b>	<b>N=73,609</b>	<b>N=50,645</b>	<b>N=18,491</b>	<b>N=4,473</b>
<b>Number of users with more than 1 prescription during period of continuous use (N, %)</b>	66,844 (90.8%)	45,802 (90.4%)	16,995 (91.9%)	4,047 (90.5%)
<b>Among users with more than 1 prescription</b>				
<b>Age, Mean (SD)</b>	81.9 (6.6)	82.0 (6.6)	81.9 ( 6.6)	81.5 (6.8)
<b>LTC Residents (%)</b>	9,493 (14.2%)	6,008 (13.1%)	2,501 (14.7%)	984 (24.3%)
<b>Prescriber of Initial prescriptions</b>				
General Practitioner	42,175 (63.1%)	28,974 (63.3%)	10,649 (62.7%)	2,552 (63.1%)
Psychiatrists	2,287 (3.4%)	1,374 (3.0%)	787 (4.6%)	126 (3.1%)
Geriatricians	3,429 (5.1%)	2,309 (5.0%)	720 (4.2%)	400 (9.9%)
Neurologists	8,571 (12.8%)	5,562 (12.1%)	2,624 (15.4%)	385 (9.5%)
Other	3,398 (5.1%)	2,504 (5.5%)	685 (4.0%)	209 (5.2%)
Unknown	6,984 (10.4%)	5,079 (11.1%)	1,530 (9.0%)	375 (9.3%)
<b>Specialist visit in 3 months prior</b>				
Psychiatrists	7,287 (10.9%)	4,697 (10.3%)	1,973 (11.6%)	617 (15.2%)
Geriatricians	11,070 (16.6%)	7,396 (16.1%)	2,952 (17.4%)	722 (17.8%)
Neurologists	6,071 (9.1%)	4,029 (8.8%)	1,321 (7.8%)	721 (17.8%)
<b>% adherent to therapy after 1 year*</b>	70-75%	70-75%	70-75%	65-70%

*\*reported using Kaplan Meier estimate. Median time to discontinuation was not reached in any group within the 2 year follow-up. Information is censored to allow for publication*

### Summary of Findings for Exhibit 12

1. Between 2009 and 2012, 73,609 adults aged 66 and older initiated publically-funded cognitive enhancer medications in Ontario. More than 90% of these patients were prescribed at least two prescriptions within 180 days.
2. General practitioners made up the majority (63.1%; n=42,175) of physicians prescribing initial cognitive enhancer medications.
3. Rivastigmine users were more likely to receive their initial prescription from a geriatrician (9.9%; n=400) than donepezil users (5.0%; n=720) and galantamine users (4.2%). This may reflect that a higher proportion of rivastigmine users were long term care residents (24.3%; n=2,552), compared to 13.1% (n=6,008) of donepezil users and 14.7% (n=1,501) of galantamine users.
4. More rivastigmine patients visited a neurologist in the three months (17.8%; n=721) prior to cohort entry, compared to 8.8% (n=4,029) of donepezil users and 7.8% (n=1,321) of galantamine users.
5. The time to discontinuation of cognitive enhancer treatment varied by therapy (censored data), with 65-70% of rivastigmine users remaining on therapy after 1 year compared to 70-75% of donepezil users and 70-75% of galantamine users.

NOTE: Memantine was not captured during the study period since it is not on the Ontario public drug formulary.

## Key Findings

### National and Provincial Trends in Cognitive Enhancer Prescribing

Quarterly dispensing of prescriptions for cognitive enhancers in Canada has increased by 17% over the past 4 years, from 752,465 prescriptions (3.9 prescriptions per 1,000 population) dispensed in the fourth quarter (Q4) of 2009 to 884,132 prescriptions (5.0 prescriptions per 1,000 population) dispensed by Q4 2014. Given the introduction of generic versions of cognitive enhancers in 2013, a nearly 50% reduction in costs were observed from just prior to the introduction of generics (\$55 million in the fourth quarter of 2013; \$60.24 per prescription dispensed) to the end of follow-up (\$28 million in the fourth quarter of 2014; \$31.45 per prescription dispensed). Between 2009 and 2014, donepezil was the most utilized cognitive enhancer (58%) in Canada, followed by galantamine (21%), rivastigmine (11%), and memantine (10%).

In 2014, a total of \$118 million was spent nationally on all cognitive enhancer products. The majority of these costs (76.8%) were paid for by provincial drug programs. In Ontario, the highest proportions of cognitive enhancer costs are paid for by the provincial drug program (87%). Quebec was found to have the highest rate of cognitive enhancer prescribing compared to all other provinces (32 prescriptions dispensed per 1,000 population). Ontario had the second-highest rate of publically-funded prescriptions for cognitive enhancers (28 prescriptions dispensed per 1,000 population) in Canada. This high rate of utilization in Ontario may be due to liberal listing for this class of medications relative to all other provinces in Canada. Non-publically funded cognitive enhancer use in Ontario was on par with the national average (4 prescriptions per 1,000 population vs. national average of 5 prescriptions per 1,000 population).

Ontario has the highest rate of publically-funded cognitive enhancer use in Canada, which increased almost 7-fold from 5 users per 1,000 elderly population in the first quarter of 2000 to 33 users per 1,000 elderly population in the fourth quarter of 2013. In 2013, Ontario had the highest annual rate of publicly-funded cognitive enhancer users with 41 users per 1,000 elderly population. This high rate of utilization in Ontario may be due to liberal listing for this class of medications relative to all other provinces in Canada. Among all other provinces, which all have more restrictive listings of cognitive enhancers, the annual rate of publically funded users ranged from 10 users per 1,000 elderly population in Saskatchewan to 33 users per 1,000 elderly population in New Brunswick in 2013. Donepezil was the most commonly used publically funded cognitive enhancer across all provinces in Canada (65% of all users). Galantamine was the second most commonly used publically funded cognitive enhancer drug across all provinces (26% of all users), except in British Columbia, where rivastigmine was the second most commonly used cognitive enhancer (20% of all users).

### Use of Cognitive Enhancers in Ontario

Overall, Ontario has seen a small increase in the use of cognitive enhancers over time, with the number of prescriptions dispensed, regardless of payer, having increased by 9.9%, from 396,552 prescriptions (27 prescriptions per 1,000 population) in the fourth quarter of 2009 to 435,982 prescriptions (28

prescriptions per 1,000 population) in the fourth quarter of 2014. Consequently, costs remained relatively stable between the fourth quarter of 2009 and the fourth quarter of 2013 at approximately \$28 million per quarter until the introduction of generic donepezil in 2014 after which costs dropped dramatically, decreasing by approximately 50% from \$26.6 million in the fourth quarter of 2013 to \$12.6 million in the fourth quarter of 2014. The majority (85.7%) of prescriptions for cognitive enhancers are reimbursed by the public drug program. The remaining 6.0% are paid for through private insurance, and 8.3% are paid for with cash. Less than 0.1% of prescriptions are paid through NIHB.

Among publicly-funded cognitive enhancers in Ontario, almost two-thirds of prescriptions (64.5%; 945,108) were for donepezil, followed by 28.2% (N=413,533) for galantamine in 2014. Conversely, among privately insured medications and those paid for in cash, the most popular cognitive enhancer was memantine (69.6%; 71,417 prescriptions, and 68.7%; 97,392 prescriptions, respectively). This is likely because memantine is not publicly-covered in Ontario, thus patients wishing to access this medication must pay out of pocket or through a private insurer. There is little galantamine or rivastigmine use outside of the public drug program in Ontario. In 2013, as expected, the rate of cognitive enhancer users increased as age increased (65-74: 10.6 users per 1,000 population; 75-84: 56.2 users per 1,000 population; 85+: 113.3 users per 1,000 population).

### **Characteristics of Cognitive Enhancers Users with in Ontario**

In 2013, there were 146,593 publically-funded cognitive enhancer users aged 65 and older in Ontario. The majority of users were prescribed donepezil (N=95,317; 65.0%), followed by galantamine (N=38,440; 26.2%), and rivastigmine (N=12,836; 8.8%). Users of cognitive enhancers in Ontario were found to be on average 82 years of age, approximately two-thirds were female (n=91,537), 21.2% (n=31,025) lived in LTC, and 77.6% (n=113,742) had a diagnosis of dementia. These individuals were found to be sicker than the general elderly population, with a median of 8 physician visits annually, almost half (47.5%) had visited the emergency room in the previous year, and almost a quarter of users (24.8%) were hospitalized in the previous year. Cognitive enhancer users were generally similar across drug groups, with the exception of rivastigmine users. Rivastigmine users are more likely to be male (42.8% vs. 37.6%), LTC residents (32.4% vs. 21.2%), have more comorbidities, and have a higher prevalence of dementia (83.6% vs. 77.6%) when compared to all cognitive enhancer users combined.

### **Patterns of Use and Discontinuation of Cognitive Enhancers in Ontario**

Between 2009 and 2012, we identified 73,609 elderly patients aged 66 years and older who newly initiated a cognitive enhancer in Ontario. The average age at time of initiation was 82 years. Most new users initiated donepezil (68.8%; n=45,802), with a majority of these medications prescribed by a general practitioner (63.1%; n=42,175). The vast majority of patients (90.8%; n=66,844) received at least 2 prescriptions in a 180 day period. One year after initiation of therapy, almost three-quarters of patients remained on therapy (70-75%). The time to discontinuation of cognitive enhancer treatment varied by drug therapy (censored data), with 65-70% of rivastigmine users remaining on therapy after 1

year compared to 70-75% of donepezil users and 70-75% of galantamine users.

## Health Equity

Stratified analyses suggest that there is not a major equity issue in access to cognitive enhancers by sex. Given the passive nature of the restricted listing of these products on the Ontario public drug formulary, rates of use among those eligible for drug coverage in Ontario are among the highest in Canada. This suggests that there are no considerable barriers to access of these products. There is some evidence to suggest that patients unable to access memantine through the public drug programs are having to rely on private drug programs or out of pocket costs (Memantine accounted for about 70% of all privately and cash covered cognitive enhancer products).

## Limitations

### Data Availability

Several limitations to the availability of data warrant discussion:

1. No data is available for the Territories, and therefore all analyses are restricted to inter-provincial comparisons.
2. IMS Geographic Prescription Monitor (GPM<sup>12</sup>) does not collect patient-level data, and therefore information on privately funded prescriptions is only available at the prescription and unit (e.g. tablet) level.
3. There is no data available for publically paid prescriptions in Quebec from CIHI 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 prescriptions in each quarter and annually. Therefore, these may slightly underestimate the true size of the public beneficiary population; however, this does reflect the number of active beneficiaries (e.g. those filling at least one prescription over a given year) each year.
5. All data presented are based on prescriptions filled. We are unable to confirm whether a patient actually took the medication.

### Generalizability

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

### Adherence

All data used in these analyses are based on dispensing patterns, and we do not know whether subjects

actually took the medications. This is particularly questionable among the population of individuals who only received one prescription for a cognitive enhancer. 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 cognitive enhancer users who were dispensed more than one prescription.

## Overall Conclusion

Ontario was found to have the highest rates of publically-funded cognitive enhancer use in Canada, which is likely due to having the most open criteria for reimbursement for the drug class. Utilization of cognitive enhancers continues to grow both nationally and in Ontario, although costs have actually decreased since 2013 due to the introduction of generics. With a growing elderly population, extended life-expectancy, and lack of alternate treatment options we do not expect this trend to change in the future.

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## Review of the Observational Literature

### Objectives

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

### Methods

#### Search Strategy

We conducted a rapid review of the observational literature to investigate the comparative safety, effectiveness, and adherence of galantamine, rivastigmine, donepezil and memantine. The exact search strategy performed can be found in Appendix A. The inclusion criteria for text screening are as below:

#### Inclusion Criteria:

- English language
- Published between 1996 and 2014
- Dementia population
- Safety, effectiveness or adherence outcome reported
- Comparison between two or more cognitive enhancers

### Results

Overall, 875 abstracts were reviewed, and 17 potentially relevant articles were obtained in full text. 15 of these studies were identified for the final review by meeting our inclusion criteria. Five studies examined effectiveness, eight studies examined adherence, three studies examined safety, and two studies examined adherence related to safety (Appendix B).

#### Comparative Effectiveness

Five of the identified studies compared effectiveness between cognitive enhancers. Overall, these studies were small (41-242 subjects), with the exception of Santoro et al. which included 938 subjects. The identified studies found mixed results using a variety of measures as outcomes, with four of the five studies reporting on more than one measure in their results.<sup>1,2,3,5</sup> All five studies reported the Mini Mental State Examination (MMSE) and found no differences in effectiveness between drugs using this outcome. Similarly, two studies reported the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and found no differences.<sup>2,5</sup> Three studies reported the Activities of Daily Living scale (ADL) – one of which found that the donepezil-treated patients declined marginally less than the rivastigmine group (-0.3 +/- 0.1 vs. -0.7 +/- 0.1,  $p = 0.02$ )<sup>1</sup>, while another study found the inverse, an improvement in the rivastigmine group compared to donepezil at the 3-month follow-up (0.12 +/- 0.43 vs. -0.25 +/- 0.46,  $p < 0.05$ ), this same finding was not found at the 6-month follow-up.<sup>2</sup> The third and largest study reporting ADL found no differences based on the ADL outcome.<sup>5</sup> Three studies reported the Instrumental Activities of Daily Living scale (IADL), two of which found no differences<sup>1,2</sup>, however, the third, larger study by Santoro et al., found that galantamine caused a marginally larger functional decline

than donepezil (-0.88 +/- 0.13 vs. -0.40 +/-0.06,  $p = 0.002$ ).<sup>5</sup>

Overall, although some studies did find marginal differences between the cholinesterase inhibitors on functional scales, any differences in effectiveness are difficult to conclude. Many of the studies are limited by small samples sizes and limited clinical generalizability. Additionally, these studies are limited by selection bias due to the fact that galantamine and rivastigmine are often prescribed to patients who have failed or are unable to tolerate donepezil. This leads to galantamine and rivastigmine users being sicker and, in turn, possibly introducing bias to the findings.<sup>1</sup> Only one of the identified effectiveness studies used a new-user design which would allow for a less biased comparison, and this was the only study to find that rivastigmine was superior to donepezil.<sup>2</sup> Additionally, this study was also the only study to control for severity of disease in patients, by stratifying the subjects using propensity scores.<sup>2</sup> Moreover, two studies did not include galantamine in their effectiveness analysis at all, and only compare donepezil and rivastigmine.<sup>1,3</sup> As such, the evidence for comparative effectiveness of cognitive enhancers is insufficient to make a conclusive statement about the superiority of any one cholinesterase inhibitor.

### **Adherence and Safety**

Thirteen of the studies identified compared the safety and/or adherence of cognitive enhancers. Eight studies examined adherence only, three studies examined safety only, and two studies examined safety-related adherence.

#### *Comparative Safety*

The safety studies identified in the review all employed a new-user design to compare the frequency of adverse events (AE) related to gastrointestinal side effects, psychiatric disturbances, and cardiac issues between agents. Hughes et al. (n=8,267) found that there were no significant differences between groups for stomach pain, vomiting and insomnia. Differences between drugs were found, with the galantamine users being significantly more likely to experience diarrhea compared to rivastigmine or donepezil users (8.9% vs. 6.8% vs. 6.4%, respectively,  $p = 0.035$ ), and less likely to experience weight loss (15.6% vs. 20.0% vs. 20.3%, respectively,  $p = 0.010$ ).<sup>6</sup> Raschetti et al. (n=5,462) also found some significant differences between drugs and their associations with a variety of adverse events, finding that rivastigmine and galantamine- treated patients were more likely to experience any AE (19% and 24%, respectively) compared with donepezil-treated patients (13%) ( $p < 0.001$ ).<sup>7</sup>

Only one large study compared rates of mortality between cognitive enhancers. This large cohort study compared AEs associated with new prescriptions of cognitive enhancers, including memantine, in US and Danish cohorts.<sup>8</sup> The study found a difference across both large cohorts; in the US cohort, galantamine was found to be associated with reduced overall mortality compared to donepezil (Hazard Ratio (HR) = 0.76, 95% CI = 0.63–0.92).<sup>8</sup> In the Danish cohort, memantine was associated with greater risk of fatal or nonfatal MI (HR = 1.33, 95% CI = 1.08–1.63) and cardiac death (HR = 1.31, 95% CI = 1.12–1.53), compared to donepezil. In both the US and Danish cohort, memantine was associated with a higher risk of all-cause mortality relative to donepezil (HR = 1.20, 95% CI = 1.13–1.28; HR = 1.83, 95% CI = 1.73–1.94, respectively). Caution must be taken when interpreting these results in the context of memantine's safety profile due to possible selection bias in the Danish cohort, where physicians may be channeling patients with more severe disease to memantine. Moreover, two of the three safety studies

report differences in baseline characteristics between treatment groups, introducing bias to the results.

### *Adherence*

Eight included studies compared rates of adherence and were found to provide varying evidence, with each drug having one study proclaiming superior adherence to other cognitive enhancers. This is likely due to the high level of heterogeneity in study design and adherence definitions across studies.

Four large studies compared donepezil, rivastigmine, and galantamine, with each drug demonstrating superiority in at least one study. The first of these studies was a four-year long Finnish study ( $n=6,858$ ,  $M_{age} = 79.3$ ,  $SD=6.7$ ) which found that subjects were more likely to discontinue treatment at 1 year if treated with galantamine or rivastigmine, in comparison to donepezil (25%, 26% vs. 18%,  $\chi^2$ ,  $p < 0.0001$ ).<sup>10</sup> In contrast, a large Canadian study by Blais et al. ( $n=28,405$ ) found that the mean difference in the percentage of time patients were adherent was 2.7% (95% CI=1.3–4.1) and 0.6% (95% CI=-0.2–1.3) with rivastigmine and galantamine, respectively, compared to donepezil, signifying that rivastigmine exhibits better adherence than donepezil.<sup>12</sup> Two studies concluded the superiority of galantamine over other drugs for adherence. The first of these two studies was a one-year long Canadian study ( $n=7,255$ ) that uniquely included two different formulations of galantamine, galantamine-ER and -IR, and demonstrated galantamine-ER's superior one-year persistence rate (54%, CI = 51-57%) over both rivastigmine (40%, CI = 37-43%) and donepezil (46%, CI = 43-49%).<sup>13</sup> This paralleled the work by Kroger et al. who conducted a three-year study in the Netherlands ( $n=3,369$ ) and concluded that rivastigmine users were more likely to discontinue from 6-36 months compared to galantamine users (54.0% and 38.0%, respectively,  $p < 0.01$ ). This study did not include any donepezil users.<sup>14</sup>

A few small studies were also found that explored the comparative adherence of these agents. Two of these smaller studies showed no statistically significant difference between groups in terms of adherence.<sup>5,9</sup> A third study concluded that rivastigmine was associated with higher discontinuation compared to donepezil, with a number needed to harm of 8 ( $\chi^2 4.02$ ,  $p=0.03$ )<sup>11</sup>. Lastly, the fourth study was the only one study to include memantine users; this year-long study found that memantine had lower discontinuation rates (45.0%, CI = 43.1-46.8%) than galantamine (54.7%, CI = 52.7-56.7%), donepezil (60.0%, CI = 58.8-61.2%), and rivastigmine (67.3%, CI = 65.8-68.7%).<sup>15</sup>

The evidence for comparisons of cognitive enhancer adherence was found to be heterogeneous, which may be due to differences in populations, study designs and methods used across studies. Two of the eight adherence studies reported differences between treatment populations in terms of demographics, which may have confounded results.<sup>5,13</sup> Inclusion criteria varied across studies, with some studies using diagnosis, such as Alzheimer's Disease, as a criterion, while other studies only required individuals to be on prescribed cognitive enhancers. The latter inclusion criteria may produce inaccurate results, since it does not account for off-label use, where cognitive enhancers may be less effective or may exhibit lower adherence. Moreover, there is considerable heterogeneity in definitions of adherence as well. Examples of adherence definitions included discontinuation after < 4 weeks, one-year persistence and medication possession ratios (defined as the sum of drug supply days between the first and last filled prescriptions divided by the number of days between these fill dates). Six of the eight adherence studies utilized a new user design. However, none of the adherence studies controlled for severity of disease, which may have also significantly affected the findings.

### Comparative Safety-related Adherence

The evidence regarding safety-related adherence is likely most clinically useful, as it provides information for only the discontinuations which are due to drug-induced AEs, the most common of which are gastrointestinal side effects, such as diarrhea. Only two small studies reported safety-related adherence and both of them did not employ a new user design or control for severity of disease states. The first study by Mossello et al. (n=212) found that donepezil was associated with significantly fewer withdrawals due to AE (3%) than rivastigmine (17%,  $p < 0.01$ ) and galantamine (21%,  $p < 0.01$ ) at 9 months.<sup>1</sup> In contrast, the second study by Sobow & Kloszewska (n=183), which only compared rivastigmine and donepezil, found no differences between agents.<sup>3</sup> The percentage of patients who did not tolerate a minimum effective dose was found not to be statistically significantly different between donepezil and rivastigmine. There was also no difference in percentage of patients tolerating low (5 mg for donepezil and 3-6 mg of rivastigmine; 87 vs. 85%) or high (10 mg for donepezil and 9-12 mg for rivastigmine; 60 vs. 58%) doses of either drug. The only significant finding was that the donepezil-treated group was more likely to achieve the maximum recommended dose (10 mg for donepezil and 12 mg for rivastigmine) compared to the rivastigmine group (60 vs. 21%). The study did not report its follow-up period.<sup>3</sup>

Overall, some research suggests that donepezil and galantamine may be superior to rivastigmine in terms of adherence, although further research, which controls for confounding variables, is required to confirm these findings. In terms of galantamine, specifically, although five of the identified studies concluded that galantamine was superior to other cognitive enhancers, all of these studies were sponsored by a pharmaceutical companies, which may have influenced the findings.<sup>6,8,13,14,15</sup> As well, further research must establish standardized definitions of adherence, in order to allow study results to be more easily compared. Moreover, studying populations in which cholinesterase inhibitors are indicated only, as opposed to studying all individuals taking cholinesterase inhibitors, may provide results that are more relevant to subjects with dementia. Lastly, evidence related to memantine use was limited and inconclusive.

### Conclusions

Comparative observational studies of cognitive enhancers were found to have a large amount of heterogeneity. The evidence available on comparisons of cognitive enhancers is mixed, and dependent on the population, outcome selection, sponsorship of study, and methods applied. Overall, due to the low quality, and heterogeneous nature of the evidence available, no conclusive statements can be made regarding differences in effectiveness, safety or adherence between cognitive enhancers.

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## Appendix A: Medline Search Strategy

1. donepezil.mp (2546)
2. rivastigmine.mp (1286)
3. galantamine.mp (1611)
4. memantine.mp (2339)
5. cholinesterase inhibitor.mp (1724)
6. acetylcholinesterase inhibitor.mp (1276)
7. 1 or 2 or 3 or 4 or 5 or 6 (8297)
8. safety.mp (316602)
9. tolerability.mp (30967)
10. adverse event.mp 13197
11. adherence.mp 90093
12. effectiveness.mp (265029)
13. efficacy.mp (487003)
14. 8 or 9 or 10 or 11 or 12 or 13 (1012144)
15. 7 and 14 (1687)
16. Limit 15 to (English language and humans and yr="1996-Current") (1238)
17. Limit 16 to Randomized Controlled Trial (363)
18. 16 not 17 (875)

## Appendix B: Summary of Included Studies

Author	Study Design	Study period	Population (Sample Size)	New User Design (Y/N)	Country	Drugs Included	Age in years (mean (SD))	Duration of Follow-up	Outcomes	Key Findings
Pakrasi et al. (2003) <sup>11</sup>	Survey	1998-2001	<ul style="list-style-type: none"> <li>Dementia patients starting cholinesterase inhibitors (ChEI)</li> <li>From old age community and hospital psychiatric services (N=160)</li> </ul>	Y	England	Don, Riv, Gal	75.9 (7.1)	Not reported	<u>Adherence</u>	<ul style="list-style-type: none"> <li>Number needed to harm of 8 for Riv, compared to Don (<math>\chi^2</math> 4.02, p=0.03)</li> <li><b>Donepezil associated with less discontinuation than rivastigmine</b></li> </ul>
*Mossello et al. (2004) <sup>1</sup>	Cohort	2000-2002	<ul style="list-style-type: none"> <li>Elderly patients with mild to moderate AD</li> <li>From outpatient clinics (N=212)</li> </ul>	N	Italy	Don, Riv, Gal	78 (6)	9 months	<u>Efficacy:</u> MMSE, ADL, IADL, <u>Adherence-related safety:</u> withdrawals due to adverse events (AE)	<ul style="list-style-type: none"> <li>Don associated with fewer withdrawals due to AE (3%), compared to Riv (17 %, p &lt; 0.01) and Gal (21 %, p &lt; 0.01)</li> <li>No significant difference in MMSE and IADL score changes over time between Don and Riv</li> <li>ADL score declined less at 9 months in Don group compared with Riv (-0.3 +/- 0.1 vs. -0.7 +/- 0.1, p = 0.02) (not enough people taking Gal to include in results)</li> <li><b>Donepezil associated with less discontinuation compared to rivastigmine and galantamine, donepezil may be more efficacious than rivastigmine (on functional scale, not cognitive)</b></li> </ul>
*Aguglia et al. (2004) <sup>2</sup>	Propensity matched cohort	2000-2002	<ul style="list-style-type: none"> <li>Mild to moderate AD patients with dementia</li> <li>From Alzheimer's specialized university-based clinic (N=242)</li> </ul>	Y	Italy	Don, Riv, Gal	77.16 (8.18)	6 months	<u>Efficacy:</u> MMSE, ADAS-cog, IADL, ADL	<ul style="list-style-type: none"> <li>At 3 months, Riv had a higher change in ADL scores compared to Don (0.12 +/- 0.43 vs. -0.25 +/- 0.46, p &lt; 0.05)</li> <li>No statistically significant differences were reported at 6 months</li> <li><b>Rivastigmine may be more efficacious than donepezil (on functional scale)</b></li> </ul>
*Hughes et al. (2004) <sup>6</sup>	Cohort	2000-2002	<ul style="list-style-type: none"> <li>ChEI users</li> <li>From several nursing homes</li> <li>Residents could not have previous history of the GI outcomes evaluated in the study 60 days before initiating therapy (N=8,267)</li> </ul>	Y	US	Don, Riv, Gal	Not reported	1 year	<u>Safety:</u> GI AEs	<ul style="list-style-type: none"> <li>Residents taking Gal more likely to experience diarrhea compared to Riv or Don groups (8.9% vs. 6.8% vs. 6.4%, p = 0.035), and less likely to lose weight (15.6% vs. 20.0% vs. 20.3%, p = 0.010)</li> <li><b>Galantamine less likely to be associated with weight loss and more likely to be associated with diarrhea</b></li> </ul>
Raschetti et al. (2005) <sup>7</sup>	Cohort	2000-2001	<ul style="list-style-type: none"> <li>Mild to moderate AD patients with cognitive deficits for more than 6 months</li> <li>From outpatient clinics (N=5,462)</li> </ul>	Y	Italy	Don, Riv, Gal	76 (7)	Average of 10.5 months	<u>Safety:</u> AE related to treatment	<ul style="list-style-type: none"> <li>Higher proportion of patients receiving Riv and Gal (19% and 24%) compared with Don (13%) experienced AEs (p &lt; 0.001)</li> <li><b>Donepezil less likely to be associated with AEs compared to rivastigmine and galantamine</b></li> </ul>

Author	Study Design	Study period	Population (Sample Size)	New User Design (Y/N)	Country	Drugs Included	Age in years (mean (SD))	Duration of Follow-up	Outcomes	Key Findings
Kapaki & Paraskevass (2006) <sup>4</sup>	Cohort		<ul style="list-style-type: none"> <li>Patients with diagnosis of 'pure' AD or AD with cerebrovascular lesions, fulfilling the NINCDS-ADRDA or the NINDS-AIREN criteria respectively</li> <li>From neurology outpatient department of university</li> <li>Patients receiving vitamin E, nootropics or other cognition-enhancing drugs excluded (N=41)</li> </ul>	N	Greece	Don, Riv, Gal	70 (7.8)	24-72 months	<u>Efficacy:</u> MMSE	<ul style="list-style-type: none"> <li>No significant differences (Gal vs riv <math>p = 0.08</math>)</li> </ul>
*Sobow & Kloszewsk a (2006) <sup>3</sup>	Cohort	1998-2000	<ul style="list-style-type: none"> <li>ChEI users who were seen for at least 6 months after prescription were included</li> <li>NINCSD-ADRDA used to establish diagnosis of either probable or possible AD (N=183)</li> </ul>	N	Poland	Don, Riv	77 (6.6)	Not reported	<u>Efficacy:</u> MMSE, CGI-C,  <u>Adherence-related safety</u>	<ul style="list-style-type: none"> <li>Clinical non-tolerance rate not statistically significant between Don and Riv (11.9% vs 14.6%, <math>p=0.59</math>)</li> <li>Maximum recommended dose achieved by more patients on Don than Riv (60 vs 21%, <math>p&lt;0.001</math>)</li> <li>No statistically significant difference in: frequency of side effects (71.3% on Don and 78% on Riv, <math>p=0.3</math>) and drop-out due to AE (14.6% on Don and 22.8% on Riv (<math>p=0.4</math>))</li> <li>No statistically significant difference in: MMSE (mean change for donepezil <math>0.8\pm 0.4</math>; <math>p=0.3</math> and for Riv <math>0.6\pm 0.6</math>; <math>p=0.5</math>) and CGI (74% of patients on Don and 68.6% on Riv were responders (<math>p=0.4</math>))</li> <li><b>Donepezil slightly better than rivastigmine in achieving maximum tolerated dose</b></li> </ul>
*Blais et al. (2009) <sup>12</sup>	Cohort	1997-2006	<ul style="list-style-type: none"> <li>ChEI users (aged 50+) on provincial administrative database</li> <li>Must have been insured by the Quebec drug plan for at least 1 year before the first prescription (N=28,405)</li> </ul>	Y	Canada	Don, Riv, Gal	Not reported	Not reported	<u>Adherence:</u> Medication Possession Ratio	<ul style="list-style-type: none"> <li>The mean differences in percentage of time patients were adherent were 2.7% (95% CI=1.3–4.1) and 0.6% (95% CI= -0.2–1.3) with Riv and Gal, respectively, compared with Don</li> <li><b>Galantamine has better adherence than donepezil, rivastigmine same as donepezil</b></li> </ul>
*Herrman n et al. (2009) <sup>13</sup>	Cohort	2006-2007	<ul style="list-style-type: none"> <li>ChEI users on Ontario Drug Benefit Plan</li> <li>Aged 65+ years</li> <li>Mild to moderate AD (N=7,255)</li> </ul>	Y	Canada	Don, Riv, Gal (immediate and extended release)	Not reported	1 year	<u>Adherence</u>	<ul style="list-style-type: none"> <li>Statistically significant difference in 1-year clinical persistence rate between Gal-ER=53.6% (95% CI 50.7, 56.5) and Don=45.9% (95% CI 43, 48.8) or Riv=40.2% (95% CI 37.3, 43.1), but no difference between Don and Riv</li> <li><b>Galantamine-ER has better adherence than donepezil and rivastigmine</b></li> </ul>

Author	Study Design	Study period	Population (Sample Size)	New User Design (Y/N)	Country	Drugs Included	Age in years (mean (SD))	Duration of Follow-up	Outcomes	Key Findings
*Santoro et al. (2010) <sup>5</sup>	Cohort	2000-2001	<ul style="list-style-type: none"> <li>Mild to moderate AD patients</li> <li>From Alzheimer's specialized university-based clinic and to have experienced typical AD disturbances for at least 6 months (N=938)</li> </ul>	N	Italy	Don, Gal, Riv	Not reported	36 weeks	<u>Efficacy:</u> ADAS-cog, MMSE, IADL, ADL, CDR, NPI  <u>Adherence</u>	<ul style="list-style-type: none"> <li>Gal group lost mean of 0.88 on IADL compared to Don group (p = 0.002)</li> <li><b>Galantamine less efficacious than donepezil</b></li> </ul>
Kinnair et al. (2011)	Cohort		<ul style="list-style-type: none"> <li>ChEI users from psychiatric services for elderly in a small region (N=134)</li> </ul>	Y	UK	Don, Riv, Gal	Not reported	Not reported	<u>Adherence</u>	<ul style="list-style-type: none"> <li>Riv users were not enough to be included in analysis</li> <li><b>No differences between drugs</b></li> </ul>
*Kroger et al. (2012) <sup>14</sup>	Cohort	1998-2008	<ul style="list-style-type: none"> <li>ChEI users on PHARMO RLS database</li> <li>Had 1+ years of exposure history in PHARMO RLS and had at least one subsequent medication dispensing after first dispensing (N=3,369)</li> </ul>	Y	Netherlands	Riv, Gal	76.3 (7.7)	3 years	<u>Adherence</u>	<ul style="list-style-type: none"> <li>Between 6-36 months, Riv users more likely to discontinue compared to Gal users (54.0% and 38.0%, respectively, p &lt; 0.01)</li> <li><b>Galantamine has better adherence compared to rivastigmine</b></li> </ul>
*Fosbol et al. (2012) <sup>8</sup>	Cohort	Danish – 1997-2007, US – 2006-2009	<ul style="list-style-type: none"> <li>US cohort: ChEI users, 65+ years, had 12 months of continuous enrollment in Medicare Parts A and B and 6 months of continuous enrollment in Medicare Part D before the index date (N=46,737)</li> <li>Danish cohort: ChEI users, 65+ years, and had at least 12 months of data before the index date (N=29,496)</li> </ul>	Y	US & Denmark	Don, Riv, Gal, Memantine	Not reported	US cohort: median of 489 days, IQR 226-814 Danish cohort: median of 935 days, IQR 444-1,566	<u>Safety:</u> Hospitalization for MI, heart failure, syncope, atrioventricular block	<ul style="list-style-type: none"> <li>Danish cohort: greater risk of cardiac death associated with memantine (HR = 1.31, 95% CI = 1.12–1.53)</li> <li>US cohort: HR of mortality was 0.76 (95% CI = 0.63–0.92) for Gal, 1.05 (95% CI = 0.96–1.16) for Riv, 1.20 (95% CI = 1.13–1.28) for memantine</li> <li>Danish cohort: HR of mortality was 0.98 (95% CI = 0.93–1.07) for Gal, 1.22 (95% CI = 1.12–1.32) for Riv, 1.83 (95% CI = 1.73–1.94) for memantine</li> <li><b>In US cohort, galantamine associated with less mortality than donepezil</b></li> <li><b>In Danish cohort, memantine associated with greater risk of MI and cardiac death than donepezil</b></li> </ul>
*Taipale et al. (2014) <sup>10</sup>	Cohort with matching	2005-2009	<ul style="list-style-type: none"> <li>Community-dwelling individuals with verified diagnoses of AD (according to NINCDS-ADRDA and DSM-IV)</li> <li>For each individual with AD, a comparison individual matched with age (<math>\pm 1</math> year), sex, and region of residence, without AD was identified (N=6,858)</li> </ul>	Y	Finland	Don, Riv, Gal	79.3 (6.7)	4 years	<u>Adherence</u>	<ul style="list-style-type: none"> <li>Compared with donepezil users, Riv [HR= 1.34 (CI 1.22–1.48)] and Gal [HR= 1.23 (CI 1.15–1.37)] users more likely to discontinue</li> <li><b>Donepezil has better adherence than rivastigmine and galantamine</b></li> </ul>

Author	Study Design	Study period	Population (Sample Size)	New User Design (Y/N)	Country	Drugs Included	Age in years (mean (SD))	Duration of Follow-up	Outcomes	Key Findings
*Haider et al. (2014) <sup>15</sup>	Cohort	2008-2010	<ul style="list-style-type: none"> <li>ChEI users with at least 1 medical claim for dementia</li> <li>Aged 50+ years (N=15,809)</li> </ul>	Y	Austria	Don, Riv, Gal, memantine	79.9 (7.7)	1 year	<u>Adherence</u>	<ul style="list-style-type: none"> <li>Compliance statistically significant for Gal (35.3%) and memantine (50.8%), not for Don (29.7%), and Riv (28.3%)</li> <li><b>Galantamine and memantine have better adherence than rivastigmine and donepezil</b></li> </ul>

\*Studies whose primary objective is comparative analyses between drugs.

Don=Donepezil, Riv=Rivastigmine, Gal=Galantamine, ChEI = cholinesterase inhibitor, MI = myocardial infarction, HR = Hazard Ratio, ADL=Activities of Daily Living Scale, IADL =Instrumental Activities of Daily Living, CGI=The Clinical Global Impressions Scale, MMSE =Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, ADAS-cog=Alzheimer's Disease Assessment Scale-cognitive subscale

## Appendix C: Public Plan Listings for Cognitive Enhancers in Canada, by Province

Drug	Brand/ generic	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NW
<b>Donepezil</b>	Aricept, generic	Res	Res	Res	Res	Pas	Res						
	Aricept RDT, generic	No	No	No	No	No	Res	No	No	No	No	No	No
<b>Rivastigmine</b>	Exelon, generic	Res	Res	Res	Res	Pas	Res						
	Exelon oral solution	Res	Res	Res	No	No	Res	Res	Res	No	Res	No	Res
	Exelon patch	Res	No	No	No	No	Res	No	No	No	No	Res	No
<b>Galantamine</b>	Reminyl, generic	Res	Res	Res	Res	Pas	Res						
<b>Memantine</b>	Ebixa, generic	No	No	No	No	No	Res	No	No	No	No	No	No

No=not listed, Pas=restricted listing – passive (e.g., Limited Use in Ontario), Res=restricted listing – enforced, FB=full benefit