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Utilization of Cholinesterase Inhibitors for Alzheimer Disease in Canada

CADTH

Authors: Ann Chang, Chris Vannabouathong, Christine Perras

Acknowledgments: Zahinoor Ismail, MD

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AD	Alzheimer disease
ChEI	cholinesterase inhibitor
FPT	federal, provincial, and territorial
MMSE	Mini-Mental State Exam
RDT	rapid dissolving tablet

Key Messages

- Due to upcoming Canadian market approvals of biologics for Alzheimer disease, a utilization study was conducted to assess the current utilization patterns and funding criteria for cholinesterase inhibitors (ChEIs) in selected Canadian jurisdictions from 2017 to 2020.
- Most jurisdictions list ChEIs as exception status, special authorization, or limited use drugs except Manitoba; as of 2018, Manitoba lists donepezil and galantamine as regular benefits and rivastigmine as an exception status drug. Additionally, British Columbia and New Brunswick fund galantamine and rivastigmine after a patient is deemed intolerant to donepezil.
- The following are insights from the utilization analysis.
  - Across Canada, there has been a decrease in the number of beneficiaries and claims for all ChEIs from 2017 to 2020 in all jurisdictions except Manitoba:
    - There was a 12% reduction in number of beneficiaries and a 17% reduction in the number of total claims from 2017 to 2020.
    - In Manitoba, there was an increase in the number of ChEI beneficiaries that peaked in 2018, which corresponds to the formulary changes for donepezil and galantamine during this period.
  - Across Canada, donepezil had the highest market share among all ChEIs each year from 2017 to 2020, which increased from 71.2% in 2017 to 75.8% in 2020. Galantamine had the second-highest market share each year. The market shares for both galantamine and rivastigmine decreased over time, indicating there is a preference for prescribing donepezil to patients with Alzheimer disease.
    - The greater use of donepezil may be explained by prescriber preferences or coverage criteria for ChEIs (e.g., donepezil is considered first line in British Columbia and New Brunswick).
  - The cumulative costs of all ChEIs paid for by public drug plans across Canada in 2020 was $20,659,136, a decrease of 43% from $36,325,781 in 2017, which corresponds with the decrease in the total number of ChEI beneficiaries.
    - Donepezil had the highest national total costs, followed by galantamine, then rivastigmine, which corresponds to the market share for each of these drugs. However, on a cost-per-beneficiary basis, donepezil was associated with the lowest cost estimates in each year from 2017 to 2020.

Background

Alzheimer disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide.[1] The prevalence of AD was 6.5% among Canadians 65 years and older as of 2017. This is expected to double in the next 10 years due to growth in the aging population, leading to a projected doubling of annual health care costs by 2031 from $8.3 billion to $16.6 billion.[1,2]

AD is characterized by the accumulation of amyloid beta plaques and neurofibrillary tau tangles in the brain, which are hypothesized to play a role in the decline of cognition, function, and behaviour.[3,4] The degeneration of cholinergic neurons and reduction in acetylcholine

transmission has been implicated in the pathophysiology of AD, contributing to symptoms such as memory loss, learning impairment, and behavioural changes.[5,6] First-line treatments for mild to moderate AD are the cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine, which increase concentrations of neuronal acetylcholine and improve symptoms such as memory loss and cognition.[7,8] In severe AD, memantine, an N-methyl-D-aspartate receptor antagonist, is used with or without ChEIs to reduce rates of cognitive decline.[9,10] ChEIs provide modest cognitive benefits that persist over time compared with untreated patients, but they do not modify disease progression.[11,12] ChEIs are also associated with a reduction in antipsychotic drug and anxiolytic drug use, and as a result may delay institutionalization.[13,14] All ChEIs have similar efficacy in maintaining Mini- Mental State Exam (MMSE) scores but vary in titration schedules and the frequency of side effects such as nausea, vomiting, dizziness, and headache, which may lead to discontinuation.[15,16] Currently, there is no cure for AD nor are there any disease-modifying therapies available in Canada.[3]

The oral originator products Aricept (donepezil), Exelon (rivastigmine), Reminyl (galantamine), and Ebixa (memantine) were marketed in Canada in 1997, 2000, 2001, and 2004, respectively.[17] Currently in Canada, donepezil is available as an oral tablet and oral rapid dissolving tablet (RDT), galantamine as a generic-only extended-release oral capsule, rivastigmine as an oral capsule, transdermal patch, and brand-only oral solution, and memantine as an oral tablet.[17] The overall cost-effectiveness of ChEIs in AD treatment is uncertain due to lack of functional status improvement despite MMSE score changes and limited long-term benefit of ChEIs due to the progressive nature of the disease.[16,18] However, in some studies, donepezil was found to be the more cost-effective drug as monotherapy with better tolerability, which may explain its role as first-line treatment compared with galantamine and rivastigmine despite the lack of preference for a specific ChEI in the Canadian guidelines for the treatment of dementia.[15,19,20]

Purpose of This Report

The aim of this project was to measure the utilization of ChEIs and memantine to determine prescribing patterns and expenditures in Canada. One component of the project was to compare reimbursement criteria for ChEIs and memantine across Canadian FPT federal, provincial, and territorial (FPT) jurisdictions. The current utilization of ChEIs and memantine in Canada may give an indication for the future use of drug products for the treatment of AD that are in clinical development.

Policy Issues

With the upcoming Health Canada reviews of several novel drugs for AD (e.g., donanemab, lecanemab, and aducanumab), an assessment of the current landscape of AD treatment is needed. The current iteration of the Canadian AD guidelines includes new recommendations on risk reduction and psychosocial and non-pharmacological interventions to current standard of care, leading to possible alternative treatment pathways for newly diagnosed patients.[20,21] Due to the prevalence of AD in Canada rising over the past few years, the

utilization of drugs for AD needed to be proactively examined because of these recent shifts in policies and treatment paradigms.

Policy Question

What is the current utilization of cholinesterase inhibitors and memantine in Canada for AD?

Research Questions

1. What are the funding criteria for cholinesterase inhibitors and memantine across the FPT jurisdictions?
2. How many claims and users of cholinesterase inhibitors and memantine were there from 2017 to 2020?
3. What were the expenditures on cholinesterase inhibitors and memantine from 2017 to 2020?

Methods

Data Sources

To determine coverage criteria across FPT drug plans, formulary websites and documents containing lists of regular benefit and restricted access drugs were searched. The reimbursed formulations, the coverage criteria, and any coverage restrictions and notes were summarized for all FPT drug plans except Quebec, Nunavut, and Northwest Territories (Appendix 1).

Claims data for ChEIs and memantine were extracted from the National Prescription Drug Utilization Information System (NPDUIS) database for all public drug plans with the exception of Quebec, Yukon Territories, Canadian Armed Forces, Non-Insured Health Benefits, and Veterans Affairs Canada, between January 1, 2017, and December 31, 2020 (Appendix 2). Drugs were included based on their Anatomical Therapeutic Chemical (ATC) code Level 5 (Table 1). Only claims where at least part of the claim was accepted by the public plan/program, either toward a deductible or for payment were included in the analysis. In accordance with the privacy policy of the Canadian Institute for Health Information, in cases where the number of active beneficiaries was less than 5 (but greater than 0), this number along with other associated values were suppressed to ensure confidentiality. The NPDUIS database does not include information regarding prescriptions that were written but never dispensed, nor does it include diagnoses or conditions for which prescriptions were written.

Table 1: Drugs Included in the NPDUIS Database Search

Drug	ATC Code	Product type
Memantine	N06DX01	5 mg and 10 mg oral tablets
Donepezil	N06DA02	5 mg and 10 mg oral tablets; 10 mg oral disintegrating tablet
Galantamine	N06DA04	8 mg, 16 mg, and 24 mg extended-release oral capsules
Rivastigmine	N06DA03	1.5 mg, 3 mg, 4.5 mg, and 6 mg oral capsules; 4.6 mg/day transdermal patch

ATC = Anatomical Therapeutic Chemical; NPDUIS = National Prescription Drug Utilization Information System.

Data Analysis

The utilization patterns were analyzed by calculating the market share of each drug as a proportion of all claimants who claimed a given drug from a public drug plan from 2017 to 2020. This calculation was performed within jurisdictions and at the national level. The total cost per beneficiary (amount paid by public drug plan) was calculated for each ChEI within jurisdictions and at the national level.

Findings

Funding Criteria for Cholinesterase Inhibitors Across Jurisdictions

Most jurisdictions reimburse all ChEIs under special authorization, limited use, or exception status criteria, except Manitoba (Table 2). In Manitoba, donepezil and galantamine are currently listed as regular benefit, whereas rivastigmine is listed under exception status (Appendix 1).[22,23] The reimbursement criteria in most jurisdictions include an MMSE score or similar psychometric questionnaire score submitted to the plan (Appendix 1).

Within Ontario, all ChEIs (except rivastigmine oral solution) are listed under regular benefits but require a limited use code corresponding to the initial or continuation treatment stage.[24] In Ontario, rivastigmine oral solution is reimbursed under the Exceptional Access Program for patients who are unable to swallow capsules. In British Columbia and New Brunswick, donepezil is listed as the first-line treatment option, and galantamine and rivastigmine are reimbursed if patients experience an intolerance to donepezil (Appendix 1). Most jurisdictions only reimburse rivastigmine oral capsules and the brand-only oral solution, with the exception of Yukon, which reimburses the transdermal patch formulation for patients who cannot use oral capsules (Appendix 1).

Memantine received a negative listing recommendation by CADTH in 2005 and is not reimbursed in any jurisdiction.[25] Given this, memantine is not discussed further in this report.

Table 2: Overview of Listing Status of Cholinesterase Inhibitors by Public Drug Plans

Province	Donepezil	Galantamine	Rivastigmine
British Columbia	Special authorization	Special authorization	Special authorization
Alberta	Special authorization	Special authorization	Special authorization
Saskatchewan	Exception status	Exception status	Exception status
Manitoba	Regular benefit	Regular benefit	Exception status
Ontario	Limited use	Limited use	Limited use[a]
New Brunswick	Special authorization	Special authorization	Special authorization
Nova Scotia	Exception status	Exception status	Exception status
Prince Edward Island	Special authorization	Special authorization	Special authorization
Newfoundland and Labrador	Special authorization	Special authorization	Special authorization
Yukon	Exception status	Exception status	Exception status

Province	Donepezil	Galantamine	Rivastigmine
Canadian Armed Forces	Not a benefit	Not a benefit	Not a benefit
Non-Insured Health Benefits	Limited use	Limited use	Limited use
Veterans Affairs Canada	Special authorization	Special authorization	Special authorization

[a]In Ontario, rivastigmine oral solution is reimbursed under the Exceptional Access Program for patients meeting the limited use criteria who are unable to swallow capsules.

Claims and Users of Cholinesterase Inhibitors From 2017 to 2020

Figure 1 provides the number of claims and beneficiaries nationally and all included drug products. There was a year-to-year decrease in the total number of beneficiaries for all ChEIs across Canada from 2017 to 2020 (Figure 1). Compared with 2017, the total number of beneficiaries decreased by 12% in 2020. There was also a year-to-year decrease in the number of claims for all ChEIs. Compared with 2017, the number of claims decreased by 17% in 2020.

Figure 2 presents the number of beneficiaries according to drug for each calendar year from 2017 to 2020. Across Canada, donepezil had the highest number of beneficiaries and rivastigmine had the lowest (Figure 2). Donepezil is the most commonly prescribed ChEI across Canada, which may be explained by factors such as formulary restrictions (e.g., as in British Columbia and New Brunswick) (Appendix 1) or physician preference due to ease of titration and lower risk of gastrointestinal side effects compared with galantamine and rivastigmine.[19,26,27] A year-to-year decrease in the number of beneficiaries occurred for all ChEIs. In 2020, there was a 7% decrease in the number of donepezil beneficiaries compared with 2017. There was a 16% decline in beneficiaries for galantamine; rivastigmine exhibited the largest degree of change, with an 18% decrease in beneficiaries in 2020 compared with 2017.

Figure 1: Number of Claims and Number of Beneficiaries for All Cholinesterase Inhibitors in Canada Between 2017 and 2020

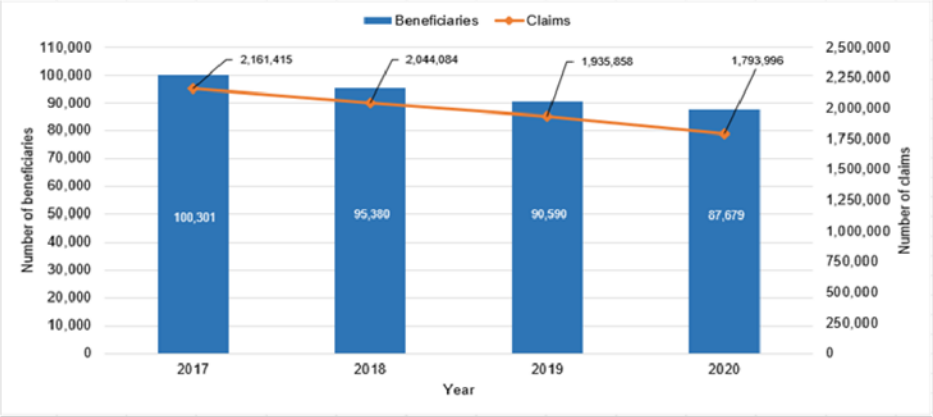
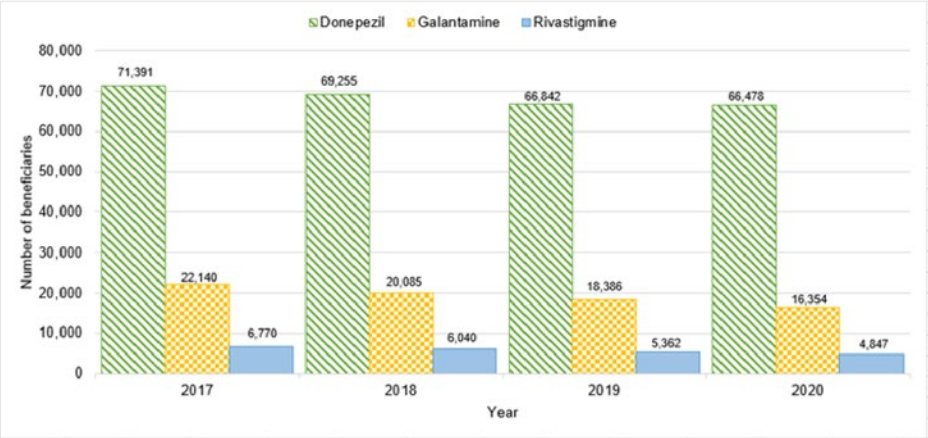


Figure 2: Number of Beneficiaries by Cholinesterase Inhibitors in Canada Between 2017 and 2020



Across jurisdictions, Manitoba was the only jurisdiction with an increase in the number of beneficiaries for AD drugs, mostly driven by the number of donepezil and galantamine beneficiaries (data not shown). This is likely due to changes to the reimbursement criteria in Manitoba in 2018 for donepezil and galantamine, which facilitated easier patient access to these drugs.[22] There was also a small yearly increase in the number of beneficiaries for donepezil in Prince Edward Island and Newfoundland and Labrador. However, the reimbursement criteria in both jurisdictions require MMSE scores to be within a certain range to be eligible for therapy, suggesting that there may be a higher population with AD or different prescribing patterns may be responsible for the rise in donepezil beneficiaries (Appendix 1).

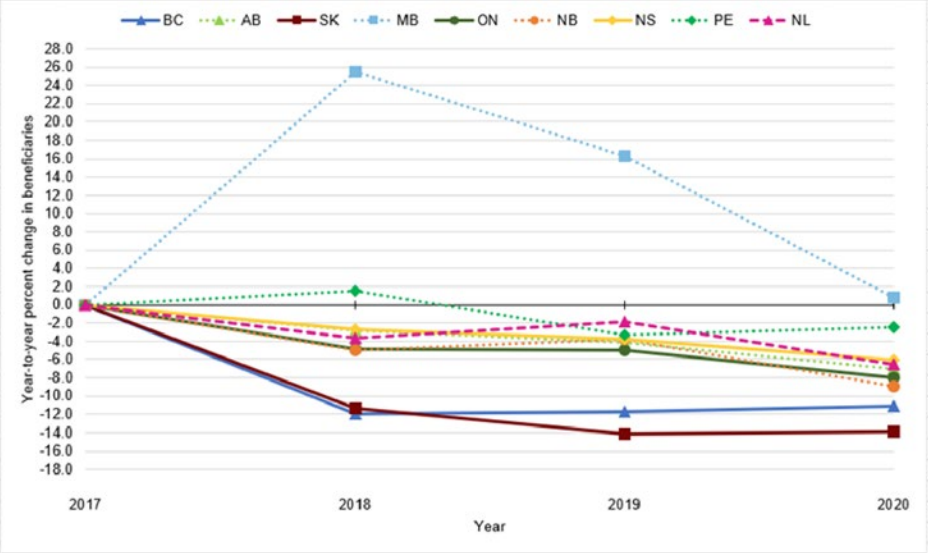
Figure 3 shows the yearly percentage changes in beneficiaries for all ChEIs by province from 2017 to 2020. Across Canada, all provinces showed year-to-year decreases in the total number of beneficiaries except Manitoba, which had an increase in beneficiaries (Figure 3). As mentioned previously, this was likely driven by the changes to the listing status for donepezil and galantamine in 2018, which resulted in the number of beneficiaries increasing by 25.5% compared with the number in 2017. A downward trend and plateau were observed for beneficiaries in Manitoba, leading to a 0.8% change in 2020, indicating that growth in the number of new and existing users for all ChEIs in this province has slowed over time. British Columbia and Saskatchewan had the greatest reduction in all ChEI beneficiaries in 2018, which plateaued in 2019 and 2020.

Market Share

Figure 4 presents the proportion of beneficiaries by drug from 2017 to 2020. Across Canada, donepezil had the highest market share from 2017 to 2020, followed by galantamine then rivastigmine. Over time, donepezil also increased its Canadian market share (71.2% in 2017 to 75.8% in 2020), while both galantamine and rivastigmine market shares decreased (22.1% in 2017 to 18.7% in 2020 and 6.7% in 2017 to 5.5% in 2020, respectively). Over the study period, the proportion of beneficiaries for donepezil in British Columbia, Manitoba, Ontario, New Brunswick, and Prince Edward Island grew, whereas this proportion declined in Alberta, Saskatchewan, Nova Scotia, and Newfoundland and Labrador (Appendix 3). Across jurisdictions, Manitoba had the highest proportion of donepezil beneficiaries in 2020 (88%),

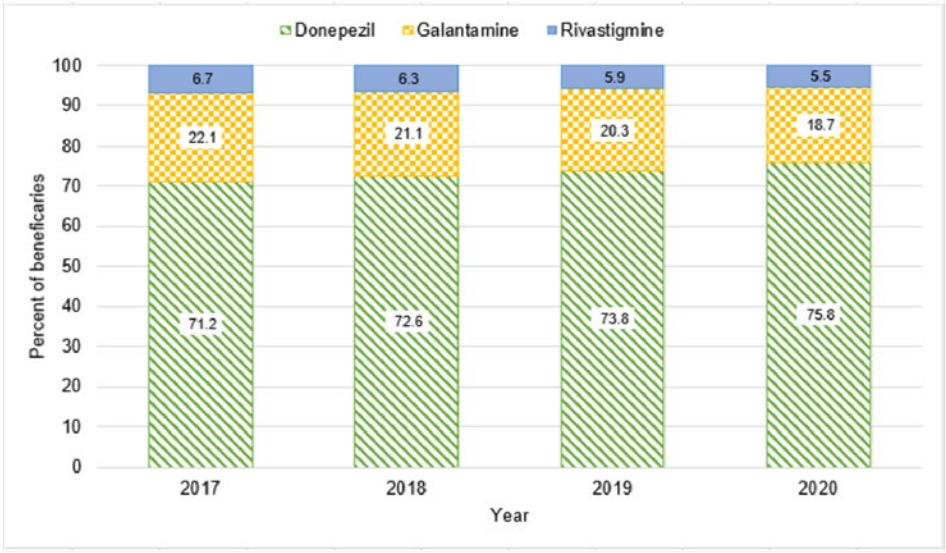
while Nova Scotia had the lowest (59%) (Appendix 3). For galantamine, Nova Scotia had the highest percentage of beneficiaries (33%), and Manitoba had the lowest in 2020 (9%). Rivastigmine had the lowest proportion of beneficiaries, ranging from 2% (Prince Edward Island) to 7% (British Columbia, Alberta, and Nova Scotia) in 2020 (data not shown).

Figure 3: Yearly Percent Change in Beneficiaries for All Cholinesterase Inhibitors by Province Between 2017 and 2020



AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan.

Figure 4: Proportion of Beneficiaries by Cholinesterase Inhibitors in Canada Between 2017 and 2020



Expenditures on Cholinesterase Inhibitors From 2017 to 2020

Figure 5 presents the cost paid by public drug plans by drug from 2017 to 2020. A year-to-year decrease in total costs paid for ChEIs was observed across Canada (Figure 5). The cumulative costs of all ChEIs paid for by public drug plans across Canada in 2020 totalled $20,659,136, a decrease of 43% from $36,325,781 in 2017. In 2020, there was a 49% decrease in donepezil costs, a 41% decrease in rivastigmine costs, and a 31% decrease in galantamine costs relative to 2017. For donepezil, total costs were driven by its high market share. Costs paid for rivastigmine were the lowest of all 3 ChEIs due to its low proportion of beneficiaries in Canada.

Figure 5: Costs Paid by Public Drug Plans for Cholinesterase Inhibitors in Canada Between 2017 and 2020

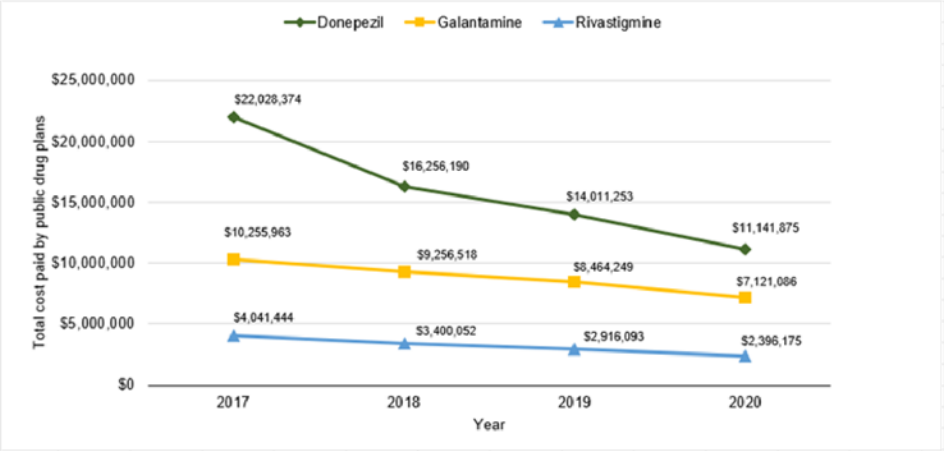
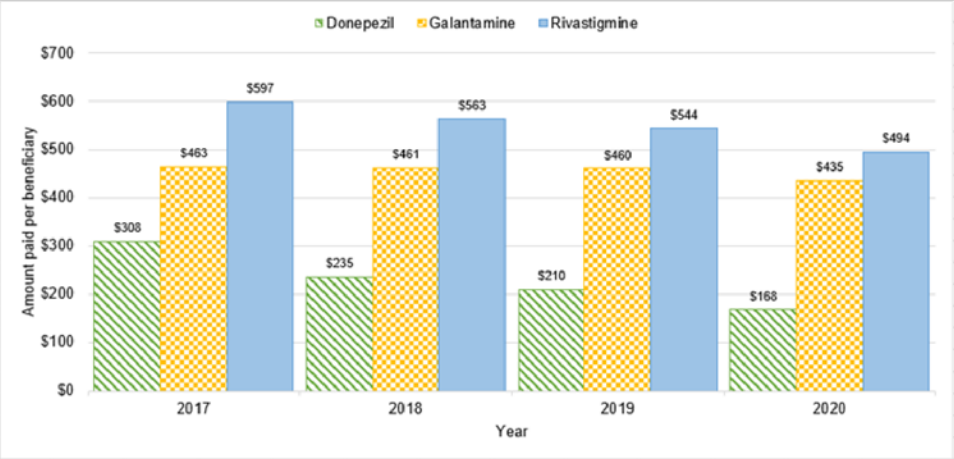


Figure 6 presents the average costs paid per individual beneficiary by drug from 2017 to 2020. Consistent with Figure 5, there was a year-to-year decline in the national cost per beneficiary for all ChEIs (Figure 6). Each year, donepezil had the lowest national cost per beneficiary, and rivastigmine had the highest. Across all jurisdictions, donepezil had the largest reduction in cost per beneficiary of all ChEIs (46% decrease in 2020 relative to 2017). Of all ChEIs, galantamine had the smallest reduction in costs per beneficiary (6% decrease in 2020 relative to 2017). Rivastigmine had a 17% decrease in costs per beneficiary in 2020 compared with 2017. Across jurisdictions in 2020, donepezil ranged from $71 per beneficiary (Saskatchewan) to $189 per beneficiary (Ontario), galantamine ranged from $176 per beneficiary (Manitoba) to $461 per beneficiary (Ontario), and rivastigmine ranged from $267 per beneficiary (Saskatchewan) to $891 per beneficiary (British Columbia) in 2020 (data not shown). Factors driving rivastigmine's higher cost per beneficiary may be its higher original list price and that the brand-only oral solution is reimbursed in most jurisdictions (Appendix 1).[17] Saskatchewan, Ontario, and Newfoundland and Labrador had a higher cost per beneficiary for galantamine compared with rivastigmine (data not shown).

Figure 6: Costs Paid by Public Drug Plans per Beneficiary by Cholinesterase Inhibitors in Canada Between 2017 and 2020



Discussion: Overall Utilization of Cholinesterase Inhibitors in Canada From 2017 to 2020

Although there was an overall increase in the Canadian elderly population between 2017 to 2020, the total number of ChEI users in Canada have declined over the same period. In 2020, the total amount paid by jurisdictions for all ChEIs was $20,659,136, a decrease of 43% since 2017. This was driven by the 12% decline in total ChEI beneficiaries since 2017. It is possible that more prescribers and patients were looking to alternative methods of AD management given the recent Canadian guideline updates on non-pharmacological strategies and psychosocial interventions, leading to reduced utilization of ChEIs across the country.[20] Across Canada, donepezil has the highest utilization rates throughout the study period, followed by galantamine then rivastigmine. The decline in total ChEI costs was driven by donepezil's large market share, as 71.2% to 75.8% of beneficiaries across the study period in Canada received donepezil. These results correspond to physician and formulary preference for donepezil as first-line treatment because of ease of titration and better tolerability.

On a per beneficiary basis, donepezil is the lowest priced ChEI, and its national costs paid per beneficiary decreased the most, followed by rivastigmine then galantamine. These findings are consistent with the length of time that donepezil generics have been available on the Canadian market, physician preference because of ease of titration, and high rates of use in Canada which drove down costs.[26,27] The cost per beneficiary for rivastigmine is the highest of all ChEIs in Canada, but when compared between jurisdictions, galantamine costs in 2020 surpassed rivastigmine costs in Saskatchewan, Ontario, and Newfoundland and Labrador. However, these costs did not follow a trend from year-to-year and costs were still comparable between the 2 drugs in these jurisdictions in 2020. Because reimbursement criteria for these drugs were similar across jurisdictions, this may reflect increased utilization of galantamine due to prescriber and patient preferences, especially considering the gastrointestinal burden of rivastigmine formulations.[15,27]

Limitations

One of the limitations of this study was that the claims data used were not indication-specific because ChEIs may also be used as treatment for Lewy body dementia. Rivastigmine is also approved for use in Parkinson disease, which may overestimate its utilization for the AD indication.[28] Second, off-formulary products, such as memantine, donepezil RDT, and rivastigmine transdermal patch, were not included, thus these utilization trends were not reviewed in this report. Because tolerance and adherence may be an issue with these products, the transdermal patch or RDT formulations may be prescribed to patients in some provinces and purchased out-of-pocket by the patient or caregiver, which would be a gap in our data, especially if there is a large population using these off-formulary formulations.[19,27] A third limitation is related to the cost-per-beneficiary estimates, which are a function of utilization, dosing, and list prices. Interjurisdictional and interpatient variations in these factors limit the comparability of the cost-per-beneficiary estimates between jurisdictions.

Information on patients' history of previously trialled ChEIs were not included and, because some provinces require patients to trial donepezil first before receiving other ChEIs, the market share for existing donepezil users may be underestimated. Differences in drug plan product listing prices, coverage criteria and access, and patient and caregiver preferences all play a role in treatment decisions, and it is unclear to what degree each of these factors influences ChEI utilization.

Conclusions and Implications for Decision- or Policy-Making

Utilization of ChEIs within the past 5 years has been declining across Canada despite the increasing size of the elderly population. Provincial reimbursement criteria, clinical evidence, and physician preference drove widespread use of donepezil as first-line treatment in AD, contributing to its large market share and decreasing costs per beneficiary in the past 5 years. Manitoba recently revised the reimbursement criteria for ChEIs, listing both donepezil and galantamine as a regular benefit, which explains the increase in the number of ChEI users in 2018. This important finding demonstrates how formulary policy changes can have a direct influence on uptake and utilization of drugs within a jurisdiction. Overall costs for ChEIs have also been declining, possibly due to the increasing availability of generics and provincial price negotiations. The relative cost per beneficiary for ChEIs in Saskatchewan, Ontario, and Newfoundland and Labrador do not align with national patterns and could be an area of further investigation for payers. Because ChEI use has been declining across Canada, ongoing assessment of the clinical value and cost-effectiveness of ChEIs should be conducted, especially in light of new AD therapies coming onto the Canadian market.

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Appendix 1: Funding Criteria for All Cholinesterase Inhibitors by Jurisdiction

Table 3: Funding Criteria of Cholinesterase Inhibitors by Jurisdiction (Current as of April 27, 2022)

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
British Columbia	**Oral tablets** For the treatment of mild to moderate Alzheimer disease, Alzheimer disease with a vascular component, Alzheimer disease with Parkinsonian features (Lewy bodies), or mixed dementia with Alzheimer disease, in patients with: • A Standardized Mini-Mental State Exam score of ≥ 10 to ≤ 26 AND • A Global Deterioration Scale stage of ≥ 4 to ≤ 6	For the treatment of mild to moderate Alzheimer disease, Alzheimer disease with a vascular component, Alzheimer disease with Parkinsonian features (Lewy bodies), or mixed dementia with Alzheimer disease, in patients with: • A Standardized Mini-Mental State Exam score of ≥ 10 to ≤ 26 AND • A Global Deterioration Scale stage of ≥ 4 to ≤ 6 AND • An intolerance to donepezil.	Oral capsules: Same criteria as galantamine	Coverage is not available for patients switching from 1 cholinesterase inhibitor to another due to ineffectiveness (clinical failure). Patients must be assessed on a regular basis (every 6 months) to ensure continued therapeutic benefit.
Alberta	**Oral tablets** For the treatment of Alzheimer disease in patients who meet the following criteria: • a Mini-Mental State Exam score between 10-26, or • a St. Louis University Mental Status Exam score between 6-26, or • a Rowland Universal Dementia Assessment Scale score between 9-22, or • an InterRAI-Cognitive	Same criteria as donepezil	Oral capsules, oral solution: Same criteria as donepezil	Coverage cannot be provided for 2 or more medications used in the treatment of Alzheimer disease (donepezil, galantamine, rivastigmine) when these medications are intended for use in combination.

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
	Performance Scale score between 1-4			
Saskatchewan	**Oral tablets:** • A diagnosis of probable Alzheimer disease as per DSM-V criteria. • A mild to moderate stage of the disease with a Mini-Mental State Exam score of 10-26 established within 60-days prior to application. • A Functional Activities Questionnaire must be completed within 60-days prior to initial application. • Patients must discontinue all drugs with anticholinergic activity at least 14 days before the Mini-Mental State Exam and Functional Activities Questionnaire are administered. Drugs with anticholinergic activity are not to be used concurrently with donepezil therapy. • Patients' intolerant to 1 drug may be switched to another drug in this class. Intolerance should be observed within the first month of treatment.	Same criteria as donepezil	Oral capsules, oral solution: Same criteria as donepezil	• Eligible patients currently taking donepezil would require assessment at 6-month intervals. To continue receiving donepezil, patients must not have both a greater than 2-point reduction in Mini-Mental State Exam and a 1-point increase in Functional Activities Questionnaire in a 6-month evaluation period. Scores are compared to the most recent test results. • Eligible new patients will enter a 3-month treatment period with donepezil. During the 3-month trial, patients must exhibit an improvement from the initial Mini-Mental State Exam or Functional Activities Questionnaire to continue treatment with donepezil. The improvement must be at least 2 Mini-Mental State Exam points or -1 Functional Activities Questionnaire. Patients who meet these requirements will be re-evaluated at 6-month intervals. To continue receiving donepezil, patients must not have both a greater than 2-point reduction in Mini-Mental State Exam and a 1-point increase in Functional Activities Questionnaire in a 6-month evaluation period. Scores are compared to the most recent test results. • The Mini-Mental State Exam score must remain at 10 or greater at all times to be eligible for coverage.

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
				• Patients who do not meet criteria to continue donepezil can be re-evaluated within 3 months to confirm deterioration before coverage is discontinued. • Donepezil does not need to be discontinued prior to Mini-Mental State Exam or Functional Activities Questionnaire testing. • A patient intolerant of 1 drug and switching to a second will be considered a "new" patient and will be assessed as such. • Coverage will not be considered for patients who have failed on other drugs in this class.
Manitoba	Oral tablets: regular benefit	Regular benefit	Oral capsules, tablets, oral solution - Confirmed diagnosis of Alzheimer Disease with DSMIV criteria with: • Memory impairment (impaired ability to learn new information or to recall previously learned information); plus at least 1 of the following: ◦ Aphasia; problems with language (receptive and expressive) ◦ Apraxia: impaired ability to carry out motor activities despite intact motor function ◦ Agnosia; failure of recognition - especially	

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
			people ◦ Disturbance in executive functioning • The above deficits must have: ◦ Caused significant decline in previous levels; and ◦ A gradual onset and continued cognitive decline; and ◦ The absence of other causative conditions; and ◦ The deficits do not occur exclusively during the course of delirium; and ◦ Normal test results for all of the following values: complete blood count, thyroid-stimulating hormone, electrolytes, vitamin B12, and glucose; and ◦ The initial Mini-Mental State Exam score must be between 10 and 26 and measured within 30 days of the application.	
Ontario	**Oral tablets** Limited Use code: • 347- Initial Trial: For patients with mild to moderate Alzheimer Disease (Mini-Mental	Same criteria as donepezil	Oral capsules: Same criteria as donepezil	

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
	State Exam 10-26). Patients will be reimbursed for a period of up to 3 months after which continued treatment must be reassessed. • 348- Continuation: Further reimbursement will be made available to those patients whose disease has not progressed/deteriorated while on this drug. Patients must continue to have a Mini-Mental State Exam score of 10-26.			
New Brunswick	**Oral tablets** For the treatment of patients with mild to moderate dementia who meet the following criteria: • Mini-Mental State Exam score of 10 to 30 • Functional Assessment Staging Test score of 4 to 5 Clinical Note: • Requests must contain an updated Mini-Mental State Exam and Functional Assessment Staging Test score completed within 6 months of the request.	For the treatment of patients with mild to moderate dementia who have had an intolerance to donepezil and who meet the following criteria: • Mini-Mental State Exam score of 10 to 30 • Functional Assessment Staging Test score of 4 to 5 Clinical Notes: • Requests must contain an updated Mini-Mental State Exam and Functional Assessment Staging Test score completed within 6 months of the request. • The nature of the intolerance must be described.	Oral capsules: Same criteria as galantamine **Oral solution** • For the treatment of patients with mild to moderate dementia for whom oral tablets or capsules are not an option and who meet the following criteria: • Mini-Mental State Exam score of 10 to 30 • Functional Assessment Staging Test score of 4 to 5 Clinical Note: • Requests must contain an updated Mini-Mental State Exam and Functional Assessment Staging Test	

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
			score completed within 6 months of the request.	
Nova Scotia	Oral tablets For the treatment of patients with mild to moderate dementia who meet the following criteria: • A Mini-Mental Statement Exam score of 10 to 30; AND • A Functional Assessment Staging Test) score of 4 to 5.	Same criteria as donepezil	Oral capsules, oral solution: Same criteria as donepezil	
Prince Edward Island	**Oral tablets** For the treatment of patients with a diagnosis of mild to moderate probable Alzheimer Disease or possible Alzheimer Disease with a vascular component, with Lewy bodies, or other factors (as specified) and who meet the following criteria: • An initial 90-day trial using an available cholinesterase inhibitor is available to patients who: ◦ Have a diagnosis of probable or possible Alzheimer Disease, AND ◦ Are 65 years of age or older (Coverage for patients less than 65 years of age will be considered upon receipt of a written consultation from	Same criteria as donepezil	Oral capsules: same criteria as donepezil	All Mini-Mental State Exam must be completed within 90-days of the request for coverage. Patients unable to tolerate the first cholinesterase inhibitor or where their Mini-Mental State Exam score remained between 10 and 24, but declined significantly during the trial, may also qualify for a second 90-day trial using a different cholinesterase inhibitor. Patients must stop the first cholinesterase inhibitor before coverage for the second 90-day trial of a cholinesterase inhibitor will be approved. Continued Coverage: • Continued coverage of cholinesterase inhibitors may be available to patients who: ◦ Participated in a 90-day trial of a cholinesterase inhibitor during which their Mini-Mental State Exam score remained between 10 and 24 and either stabilized or improved, OR

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
	a neurologist, psychiatrist or geriatrician supporting the diagnosis and treatment), AND ◦ Have not previously used a cholinesterase inhibitor, AND ◦ Have a Mini-Mental State Exam score of between 10 and 24. A Mini-Mental State Exam score of 25 or 26 will be considered upon receipt of a written consultation from a neurologist, psychiatrist or geriatrician supporting the diagnosis and treatment.			◦ Have been previously approved for 12-months of coverage, during which their Mini-Mental State Exam score remained above 10 and either stabilized or improved. All Mini-Mental State Exam must be completed within 90-days of the request for coverage. Continued coverage will not be approved for patients where their latest Mini-Mental State Exam score is less than 10 or has dramatically decreased during the previous trial or monitoring period.
Newfoundland and Labrador	**Oral tablets** For the treatment of patients with mild to moderate dementia who meet the following criteria: • A Mini-Mental State Exam score of 10 to 30 AND; • A Functional Assessment Staging Test) score of 4 to 5.	Same criteria as donepezil	Oral capsules, oral solution: Same criteria as donepezil	
Yukon	Oral tablets: For mild or moderate Alzheimer (with Mini-Mental State Exam score 10-26 within previous 3 months). Reviewed on a case-by-case basis. Reapply with updated MMSE score each time. Only 1 drug approved at any time; no combination therapy.	Same criteria as donepezil	Oral capsules: Same criteria as donepezil Transdermal Patch: For patients who cannot use the oral form.	

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
Non-insured Health Benefits	• Initial 12-month coverage for cholinesterase inhibitors: ◦ diagnosis of mild to moderate Alzheimer disease; and ◦ Mini-Mental State Exam score of 10-26, established within the last 60 days; or ◦ Montreal Cognitive Assessment score of 10-26, established within the last 60 days; or ◦ Global Deterioration Scale score between 4 to 6, established within the last 60 days. Continued coverage beyond 12 months will be based on improvement or stabilization of cognition, function, or behaviour. • Criteria for coverage at every 12-month interval: ◦ clinically meaningful response as determined by stabilization or improvement while on therapy; and ◦ Alzheimer disease has not progressed to Global Deterioration Scale stage 7 or Mini-Mental State Exam or MoCA less than 10.	Same criteria as donepezil	Oral capsules, oral solution: same criteria as donepezil	

Jurisdiction	Donepezil	Galantamine	Rivastigmine	Notes
Veterans Affairs Canada	• Special Authorization benefits require pre-authorization from VAC.	Same criteria as donepezil	Oral capsules: Same criteria as donepezil	

DSM = Diagnostic and Statistical Manual of Mental Disorders

Note that this table has not been copy-edited.

Appendix 2: List of Public Drug Plans and Programs Within the NPDUIS Database

Table 4: Public Drug Plans and Programs Within the NPDUIS Database

Jurisdiction	Plan or program code- description
Alberta	• Non-Group • Seniors • Palliative Care
British Columbia	• Fair Pharma Care • Permanent Residents of Licensed Residential Care Facilities • Recipients of British Columbia Income Assistance • Cystic Fibrosis • Children in the At Home Program • No-Charge Psychiatric Medication Program • Palliative Care Drug Plan • Smoking Cessation
Saskatchewan	Universal Program
Manitoba	• Employment and Income Assistance Program • Palliative Care • Pharmacare • Personal Home Care/Nursing Homes
Ontario	Ontario Drug Benefit Program
New Brunswick	Prescription Drug Program, including: • Seniors • Nursing Home Residents • Social Development Clients • Individuals in Licensed Residential Facilities • Children in Care of the Minister Social Development and Children With Disabilities • Multiple Sclerosis • HIV/AIDS • Cystic Fibrosis • Organ Transplant Recipients • Growth Hormone Deficiency • Drug Plan
Nova Scotia	• Diabetic Assistance Pharmacare Program • Palliative Drug Care Program • Pharmacare Long-Term Care (Under 65) • Drug Assistance for Cancer Patients • Seniors' Pharmacare Program • Family Pharmacare Program

Jurisdiction	Plan or program code- description
Prince Edward Island	• Diabetes Control Program • Generic Drug Program • Opioid Replacement Therapy Drug Program • Immunization Program • Family Health Benefit Program • High-Cost Drug Program • Nursing Home • Seniors' Drug Cost Assistance Program • Catastrophic Drug Program • Children in Care Financial Assistance • Sexually Transmitted Diseases • Quit Smoking Program
Newfoundland and Labrador	• Foundation Plan • 65 Plus Plan • Access Plan • Select Needs/Cystic Fibrosis Plan • Select Needs/Growth Hormone Plan • Assurance Plan
Yukon	• Chronic Disease Program • Children's Drug and Optical Plan • Pharmacare

NPDUIS = National Prescription Drug Utilization Information System.