Cognitive Enhancers for the Treatment of Alzheimer’s Disease
Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. The drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing.

Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.

Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.

Tara Gomes, Muhammad Mamdani and David Juurlink received grant funding from the Ministry of Health and Long-term Care.

No other study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the Cognitive Enhancer for Alzheimer’s Disease Drug Class Review.

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**Note**
Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final uncensored reports will be available on the ODPRN website within 6 months of posting of the final reports (www.odprn.ca).

**Update**

Please note that Appendix B was updated in February 2016
# List of Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AB</td>
<td>Alberta</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>Alzheimer’s Disease Assessment Scale-cognitive subscale</td>
</tr>
<tr>
<td>BC</td>
<td>British Columbia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIBIC-plus</td>
<td>Change Plus Caregiver Input</td>
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<tr>
<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
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<tr>
<td>EAP</td>
<td>Exceptional Access Program</td>
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<tr>
<td>GB</td>
<td>General Benefit</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICES</td>
<td>Institute for Clinical Evaluative Sciences</td>
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<tr>
<td>LU</td>
<td>Limited Use</td>
</tr>
<tr>
<td>MB</td>
<td>Manitoba</td>
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<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<tr>
<td>MOHLTC</td>
<td>Ministry of Health and Long-term Care</td>
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<tr>
<td>NB</td>
<td>New Brunswick</td>
</tr>
<tr>
<td>NIHB</td>
<td>Non-insured Health Benefits</td>
</tr>
<tr>
<td>NL</td>
<td>Newfoundland</td>
</tr>
<tr>
<td>NMA</td>
<td>Network meta-analyses</td>
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<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NNH</td>
<td>Number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NS</td>
<td>Nova Scotia</td>
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<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
</tr>
<tr>
<td>NT</td>
<td>Northwest Territories</td>
</tr>
<tr>
<td>NU</td>
<td>Nunavut</td>
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<td>ODB</td>
<td>Ontario Drug Benefit</td>
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<td>Ontario Drug Policy Research Network</td>
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<tr>
<td>ON</td>
<td>Ontario</td>
</tr>
<tr>
<td>OPDP</td>
<td>Ontario Public Drug Programs</td>
</tr>
<tr>
<td>PEI</td>
<td>Prince Edward Island</td>
</tr>
<tr>
<td>Q4</td>
<td>Fourth quarter</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
</tr>
<tr>
<td>QC</td>
<td>Quebec</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SK</td>
<td>Saskatchewan</td>
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<tr>
<td>SMH</td>
<td>St. Michael’s Hospital</td>
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<tr>
<td>YK</td>
<td>Yukon Territories</td>
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</table>
Executive Summary

In Canada, there are two types of cognitive enhancers available: cholinesterase inhibitors (i.e., donepezil, rivastigmine, galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonist (i.e., memantine). These drugs are available as oral formulations (e.g., tablet, rapidly disintegrating tablets, capsules, oral solution, extended release capsules). Additionally, rivastigmine is available as a transdermal patch but not as a generic. All oral formulations, with the exception of Exelon Oral Solution, are available generically. In Ontario, cholinesterase inhibitors are listed as Limited Use on the Ontario Drug Benefit (ODB) formulary. Exelon Oral Solution is available through the Exceptional Access Program (EAP); memantine is not listed on the ODB formulary nor is it available through EAP.

As part of the formulary modernization review, an evaluation of cognitive enhancers including the Limited Use criteria was undertaken, in order to provide policy recommendations for these products in Ontario.

Key Considerations for Reimbursement Options

Efficacy
Our analyses considered the following efficacy outcomes: cognition, global status, function and behavior, as well as mortality. For the outcome of cognition using Mini-Mental State Examination (MMSE), we found that donepezil and rivastigmine improved cognition in patients with all severities (mild, moderate and severe) of Alzheimer’s disease compared to placebo, although the differences were not considered clinically important. A statistical and clinically important difference on the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) was observed for donepezil compared to placebo. For patients with mild, moderate and moderate-to-severe Alzheimer’s disease, no statistically significant differences were found for cognition using MMSE as the measure. However, all cholinesterase inhibitors (but not memantine) improved cognition using MMSE compared to placebo in patients with mild-to-moderate Alzheimer’s disease, although the results are not considered clinically important. In patients with severe Alzheimer’s disease, donepezil improved cognition compared to placebo, although this difference was also not considered clinically important.

All cognitive enhancers improved global status compared to placebo. Galantamine demonstrated a clinically meaningful effect compared to placebo, donepezil, rivastigmine, and donepezil+memantine. For the other outcomes of function and behavior, there were no significant differences found between the cognitive enhancers. Rivastigmine decreased the risk of mortality compared to placebo and memantine.

Safety and tolerability
Our analyses considered the following safety outcomes: headache, gastrointestinal adverse effects, serious adverse effects, bradycardia and falls. All cholinesterase inhibitors caused more gastrointestinal adverse effects compared to placebo. However, rivastigmine patch decreased the risk of nausea compared to donepezil (Number Needed to Treat: NNT 30), galantamine (NNT 23) and rivastigmine oral (NNT 22). Overall, galantamine was most likely to cause
vomiting.

Rivastigmine increased the risk of headache compared to placebo. No differences were observed between agents for these safety outcomes of serious adverse effects, bradycardia or falls.

Accessibility and utilization
In Ontario, oral cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are available on the ODB formulary as Limited Use (LU) for patients with mild or moderate Alzheimer’s disease. However, since neither memantine nor rivastigmine patch is covered under the Ontario Public Drug Programs, these drugs are only accessible to individuals willing to pay cash or who have third party coverage.

In 2013, there were 146,593 publically-funded cognitive enhancer users aged 65 and older in Ontario. 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).

Pharmacoeconomics
*De novo economic analysis:* Based on the results of a de novo economic model, donepezil was the most cost-effective monotherapy across all patient subgroups. Memantine monotherapy and rivastigmine patch were not cost-effective.

*Budget impact analysis:* Listing donepezil as general benefit (with a generic pricing rule of 18%) would result in reduced expenditure ($5.4 million or 12% decrease) for cholinesterase inhibitors. However, strategies increasing access to patients with severe Alzheimer’s disease or allowing access to the rivastigmine patch would result in increased expenditure for cholinesterase inhibitors, ranging from $804,000 to $11 million (2-24% increase).

Final Recommendation
Several factors were considered for the final recommendation:

- Across Canada, all public drug plans provide coverage for cholinesterase inhibitors as a restricted benefit (i.e., requiring authorization) for patients with mild to moderate Alzheimer’s disease.
- Ontario has the highest rate of publically-funded cognitive enhancer use in Canada, which may be reflective of the more liberal listing of these agents relative to other jurisdictions across Canada. However, accessibility to memantine and rivastigmine patch is limited, as these products are not covered in Ontario either on the ODB formulary or through the Exceptional Access Program.
- No coverage of cholinesterase inhibitors for the *initiation* of patients with severe disease is recommended. Although our analyses found that donepezil improved cognition compared to placebo in patients with severe disease, this difference was also not considered clinically important. It should be noted that the Citizen’s Panel preferred coverage of cholinesterase
inhibitors for all severities of Alzheimer’s disease, although concerns were raised regarding the potential increase in cost.

- It is not recommended that memantine be listed on the ODB formulary or available through EAP. Results from our rapid review/network meta-analyses (NMA) indicate that cholinesterase inhibitors, but not memantine, improve cognition and global status in patients with Alzheimer’s disease.

- All cholinesterase inhibitors cause more gastrointestinal adverse effects compared to placebo, although rivastigmine patch caused less gastrointestinal effects than oral cholinesterase inhibitors. The Citizen’s Panel noted that the rivastigmine patch provided an option for patients unable to tolerate the oral formulations.

- Donepezil was the most cost-effective monotherapy. At current prices, rivastigmine patch is not cost effective; however, with a price reduction of approximately 55% (ranging from 45-68% depending on disease severity and whether patient is community dwelling or institutionalized) rivastigmine patch becomes a cost-effective option. Strategies to allow access to the rivastigmine patch would result in increased expenditures ranging from $804,000 to $8 million (2-18% increase) based on 1-10% of patients currently on oral cholinesterase inhibitors switching to rivastigmine patch.

Based on the results of the review and feedback from the ODPHN Citizens’ Panel, the primary reimbursement option for cognitive enhancers recommended for the Ontario Public Drug Program is:

- Limited Use for oral cholinesterase inhibitors for initiation of patients with mild to moderate Alzheimer’s disease (with updated clinical criteria)

In addition, two additional reimbursement recommendations are made:

- Listing of rivastigmine patch on the Exceptional Access Program should be explored, provided a price reduction of approximately 55% is negotiated.

- No listing of memantine is recommended.
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**Rationale for Review**

In Canada, there are two types of cognitive enhancers available: cholinesterase inhibitors (i.e., donepezil, rivastigmine, galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonist (i.e., memantine). All cholinesterase inhibitors are Health Canada approved for the management of mild and moderate Alzheimer’s disease. In addition, donepezil is indicated for patients with severe Alzheimer’s disease and rivastigmine oral is indicated for patients with Parkinson’s disease dementia. Memantine is indicated for moderate to severe Alzheimer’s disease (either as monotherapy or in conjunction with a cholinesterase inhibitor). Cognitive enhancers are available as oral formulations (e.g., tablet, rapidly disintegrating tablets, capsules, oral solution, extended release capsules). Additionally, rivastigmine is available as a transdermal patch. All oral formulations, with the exception of Exelon Oral Solution, are available as generic formulations. In Ontario, the cholinesterase inhibitors are available as Limited Use on the Ontario Drug Benefit (ODB) formulary. Exelon Oral Solution is available through the Exceptional Access Program.

As part of the formulary modernization review, an evaluation of cognitive enhancers including the Limited Use criteria was undertaken, in order to provide policy recommendations for these products in Ontario.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: [http://www.odprn.ca](http://www.odprn.ca)

**Background Information**

Dementia causes progressive disability and affects functions such as memory, thinking, orientation, learning capacity, language and judgment.\(^1\)\(^2\) With the increase in the aging population, there are a growing number of patients affected by dementia. In Canada, approximately 6-15% of Canadians aged 65 years and older are living with dementia; this is expected to double by 2031, with more than one million Canadian living with dementia.\(^3\)

Alzheimer’s disease is the most common form of dementia, accounting for approximately 50% of new dementia diagnosis each year. Vascular dementia is the second most common type of dementia with an incidence of approximately 20% of all dementias.\(^4\) Approximately 27% of patients with Alzheimer’s disease have mild disease, 30% have moderate disease and 45% have severe disease.\(^5\) On average, an individual will live 7-10 years after diagnosis of Alzheimer’s disease. The burden of care for individuals with Alzheimer’s disease is significant: in Canada in 2008, the total economic burden for 480,000 individuals with dementia was estimated at approximately $15 billion.\(^4\)

There is no cure for Alzheimer’s disease. The pharmacological treatment of dementia focuses on improvement of cognitive deterioration with memory loss and the management of behavioural and psychological symptoms of dementia. The aims of treatment with the cognitive enhancers are to promote independence, maintain function and treat cognitive symptoms.\(^1\) This report focuses on
treatment of cognitive symptoms associated with Alzheimer’s disease.

**Public plan reimbursement of cognitive enhancers in Canada**

In Ontario, oral cholinesterase inhibitors are available on the ODB formulary as Limited Use for patients with mild to moderate Alzheimer’s disease. Memantine, rivastigmine patch and donepezil rapid disintegrating tablet are not listed on the ODB formulary nor are they available through the Exceptional Access Program. Rivastigmine oral solution is available through the Exceptional Access Program; criteria for coverage are for those patients meeting the LU criteria for cholinesterase inhibitors who are unable to swallow capsules.

The Limited Use criteria are as follows:

*Code 347: Initial Trial: For patients with mild to moderate Alzheimer's Disease (Mini-Mental State Exam [MMSE] 10-26). Patients will be reimbursed for a period of up to 3 months after which continued treatment must be reassessed.*

Network note: Maximum duration 3 months.

LU Authorization Period: 1 year.

*Code 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 MMSE score of 10-26.*

LU Authorization Period: 1 year.

In Canada, all public drug plans provide coverage for cholinesterase inhibitors as a restricted benefit for patients with mild to moderate Alzheimer’s disease. Memantine (for moderate to severe Alzheimer’s disease) is only available in Quebec.

**Exhibit 1: Public plan listings in Canada for cognitive enhancers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand/ generic</th>
<th>BC</th>
<th>AB</th>
<th>SK</th>
<th>MB</th>
<th>ON</th>
<th>QC</th>
<th>NB</th>
<th>NS</th>
<th>PEI</th>
<th>NL</th>
<th>YK</th>
<th>NIHB/NU/NW</th>
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</thead>
<tbody>
<tr>
<td>Aricept RDT, generic</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Res</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Exelon patch</td>
<td>Res</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Res</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Res</td>
<td>No</td>
</tr>
<tr>
<td>Memantine</td>
<td>Ebixa, generic</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Res</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

No=not listed
Pas=restricted listing – passive (e.g., Limited Use in Ontario)
Res=restricted listing – enforced
Current as of April 24, 2015
Objective

The objective of the drug class review of cognitive enhancers for Alzheimer’s disease is to provide evidence-informed policy recommendations for these drugs in Ontario.

Components of the Drug Class Review

The cognitive enhancers for Alzheimer’s disease drug class review is comprised of:

- qualitative analyses of perspectives of patients, pharmacists and prescribers
  - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for cognitive enhancers
- environmental scans of:
  - national and international drug policies
  - considerations relating to health equity
- analysis of real-world drug utilization using:
  - administrative claims data from Ontario and across Canada
  - summaries of relevant observational literature
- systematic review of the literature and network meta-analyses
- reimbursement-based economic analyses

Results from all of the above components were reviewed and consolidated into a set of policy recommendations.

Overview of Findings

Qualitative Research Team: Perspectives of Family Members and Healthcare Providers

Findings of the qualitative study represented common experiences and perceptions described across patient, physician, health navigator and pharmacist groups.

Perception of cognitive enhancers

Clinician and health navigator participants perceived that some family members of dementia patients may have a false expectation that the cognitive enhancer medication will improve the patient’s cognition, rather than slowing its decline. Clinician, health navigator and family member participants found it difficult to perceive the exact effectiveness of cognitive enhancers. Most did not perceive them to be extremely effective. Donepezil was perceived to be the most commonly used cognitive enhancer for patients with Alzheimer’s Disease. Other commonly prescribed products were galantamine and memantine.
“The families seem to take some solace in the fact that there is a medication that they feel is treating the dementia or, that’s usually their perception is that it’s treating the dementia and not so clearly communicated to them that it’s maybe helping to slow down the progression of the dementia” – Health Navigator Interviewee

**Prescription of cognitive enhancers**

Clinician participants reported that the severity of a patient’s dementia is one of the main factors that should influence a physician’s decision to prescribe a cognitive enhancer. They described that cognitive enhancers are not useful for patients with severe dementia; some participants suspected that many of these patients may be unnecessarily prescribed cognitive enhancers, particularly in long term care settings.

Clinician and health navigator participants were also asked to comment on their perception of cognitive assessment tools, since these are often used to gauge a patient’s need for cognitive enhancers. The majority of participants did not prefer to use the Mini Mental State Exam (MMSE) because it is privatized, and, they perceive that it is not a sensitive test and is not applicable for those from different cultural or linguistic backgrounds. Many physician participants preferred the Montreal Cognitive Assessment (MoCA) because they believe that it provides a better measure of executive domain function and is easier to administer and score. Clinician and health navigator participants also described concerns that many patients may not be monitored appropriately once they have been prescribed cognitive enhancers.

“If anyone ever audited my practice or audited the prescriptions I would fail because I don’t use the MMSE because it’s a test that is privatized now and can’t be used in you know in our setting unless you buy it and I have some but not enough, it’s also not as good a test as the MoCA” –Physician Interviewee

**Access to cognitive enhancers**

Clinician and family member interviewees said that patients over 65 years or those living in long term care do not have barriers to accessing commonly prescribed products on the ODB formulary such as donepezil and galantamine. Some participants did mention that there are a select few patients who may benefit from memantine, however if they don’t have private coverage they are not able to afford it. Clinician interviewees also mentioned the need for the rivastigmine patch formulation which is not on the formulary. In particular, they said that many patients tolerate the patch better than the pill formulation. Lastly, when asked about the ODB limited use criteria, some clinician and health navigator participants expressed that they wished for the criteria to be revised to include scores from alternative testing such as the MoCA.
Pharmacoepidemiology Team

Current Utilization across Canada
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%).

Exhibit 2: Total utilization and cost of cognitive enhancers dispensed in Canada, by drug and quarter
Trends in Provincially-Funded Cognitive Enhancers in Ontario
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 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 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.

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

Ontario has seen an 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. 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.

**Characteristics of Publically-funded Users of Cognitive Enhancers 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. 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, 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.

**Rapid Review Team**

**Efficacy**

We included randomized and non-randomized studies that examined cognitive enhancers (donepezil, rivastigmine, galantamine, and memantine) alone or in combination compared to each other or placebo. A total of 186 studies including 106 randomized controlled trials (RCTs) (number of patients=28269), 20 non-RCTs (n=2858), 8 cohort studies (n=1574) and 53 companion reports were included in the review. The number of patients included per trial ranged from 13 to 2,045. The age of included patients ranged from 61 to 86 years.

Network meta-analyses (NMA) and a pairwise meta-analyses were conducted for the following efficacy outcomes: cognition, function, behaviour, global status and mortality.

The results of the analysis are as follows (see Exhibit 4):

**Cognition:**

- Donepezil and rivastigmine improved cognition using MMSE in patients with all severities of Alzheimer’s disease compared to placebo; although these differences were statistically significant they are not considered clinically important. A statistical and clinically important difference on the ADAS-cog scale was observed for donepezil compared to placebo. According
to previous studies, an increase of 3 points is considered a minimal clinically important difference on the MMSE\(^7\), while a reduction of 4 points on the ADAS-cog considered a minimally clinically important difference\(^7\).

- For patients with mild, moderate and moderate-to-severe Alzheimer’s disease, no statistically significant differences were found for cognition using MMSE as the outcome. However, all cholinesterase inhibitors (but not memantine) improved cognition using MMSE compared to placebo in patients with mild-to-moderate Alzheimer’s disease, although the results are not considered clinically important. In patients with severe Alzheimer’s disease, donepezil improved cognition compared to placebo, although this difference was not considered clinically important.

**Global status**

- All cognitive enhancers improved global status compared to placebo. Galantamine demonstrated a clinically meaningful effect compared to placebo, donepezil, rivastigmine, and donepezil+memantine.

**Function, Behaviour**

- No differences were observed between the agents for outcomes of function or behavior.

**Mortality**

- Rivastigmine decreased the risk of mortality compared to placebo (Number needed to treat (NNT) 58) and memantine (NNT 56). However, the upper limit of the Credible Interval was close to 1 for both of these comparisons.

**Exhibit 4: Efficacy of cognitive enhancers for patients with Alzheimer’s disease**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
<th>Memantine</th>
<th>Rivastigmine + memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
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<tr>
<td><strong>Galantamine</strong></td>
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</tr>
<tr>
<td><strong>Rivastigmine</strong></td>
<td><img src="#" alt="Green" /></td>
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<td><img src="#" alt="Green" /></td>
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</tr>
<tr>
<td><strong>Memantine</strong></td>
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<td><img src="#" alt="Green" /></td>
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<td><img src="#" alt="Green" /></td>
</tr>
<tr>
<td><strong>Rivastigmine + memantine</strong></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
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<td><img src="#" alt="Green" /></td>
</tr>
<tr>
<td><strong>Donepezil + memantine</strong></td>
<td><img src="#" alt="Green" /></td>
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<td><img src="#" alt="Green" /></td>
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</tr>
</tbody>
</table>

The four contiguous circles correspond, from **LEFT** to **RIGHT** (respectively), to four efficacy outcomes: Cognition [MMSE (all levels of severity)], Function (ADCS-ADL), Behaviour (NPI), Global Status (CIBIC-plus)

- **A green circle** indicates that the “row” cognitive enhancer is **significantly (statistically) better** compared with the “column” cognitive enhancer.
- **A red circle** indicates that the “row” cognitive enhancer is **significantly (statistically) worse** compared with the “column” cognitive enhancer.
- **An open circle** indicates that there is **no statistically significant difference** between the “row” and “column” cognitive enhancers.
- **A missing circle** indicates that the outcome was **not available** for analysis.

**Safety and Tolerability**

Cholinesterase inhibitors are associated with a variety of adverse effects including gastrointestinal effects, headache, dizziness, tremor, insomnia, fatigue and vertigo. Gastrointestinal effects including abdominal pain, nausea, vomiting, diarrhea and anorexia, are commonly reported with cholinesterase
inhibitor treatment and are considered to be dose-dependent. (Buckley 2015) Nausea associated with these oral agents ranges from 3-47%, and 5-19% of patients may develop diarrhea. In contrast, nausea with rivastigmine patch occurs in 2-10% of patients and diarrhea in <7%.\(^8\)

In our analyses, the following safety outcomes were considered: nausea, vomiting, diarrhea, bradycardia, headache, falls, and all serious adverse events (see Exhibit 5).

**Headache**
- Rivastigmine increased the risk of headache compared to placebo (number needed to harm (NNH) 36).

**Gastrointestinal adverse effects**
- All cholinesterase inhibitors caused more gastrointestinal adverse effects compared to placebo.
- Rivastigmine patch decreased the risk of nausea compared to donepezil (NNT 30), galantamine (NNT 23) and rivastigmine oral (NNT 22).
- Overall, galantamine was most likely to cause nausea, and rivastigmine (oral) most likely to cause vomiting.

**Serious adverse effects, bradycardia, falls**
- No differences were observed between agents for these safety outcomes.

**Exhibit 5: Safety (nausea and vomiting) of cognitive enhancers for patients with Alzheimer’s disease**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
<th>Memantine</th>
<th>Rivastigmine + memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
</tr>
<tr>
<td><strong>Galantamine</strong></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
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<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
</tr>
<tr>
<td><strong>Rivastigmine</strong></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
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<tr>
<td><strong>Memantine</strong></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
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<td><img src="Green_Circle.png" alt="Green Circle" /></td>
</tr>
<tr>
<td><strong>Rivastigmine + memantine</strong></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
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<td><img src="Green_Circle.png" alt="Green Circle" /></td>
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<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
</tr>
<tr>
<td><strong>Donepezil + memantine</strong></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
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<td><img src="Green_Circle.png" alt="Green Circle" /></td>
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<td><img src="Green_Circle.png" alt="Green Circle" /></td>
<td><img src="Green_Circle.png" alt="Green Circle" /></td>
</tr>
</tbody>
</table>

The two contiguous circles correspond, from LEFT to RIGHT (respectively), to two safety outcomes: Nausea, vomiting

- **A green circle** indicates that the “row” cognitive enhancer is **significantly (statistically) better** compared with the “column” cognitive enhancer

- **A red circle** indicates that the “row” cognitive enhancer is **significantly (statistically) worse** compared with the “column” cognitive enhancer

- **An open circle** indicates that there is **no statistically significant difference** between the “row” and “column” cognitive enhancer

- **A missing circle** indicates that the **outcome was not available** for analysis

**Comparative safety, effectiveness and adherence of cognitive enhancers: review of observational literature**

A rapid review of the observational literature was conducted to investigate the comparative safety, effectiveness, and adherence of galantamine, rivastigmine, donepezil and memantine. A total of 15 studies met the inclusion criteria.
Comparative effectiveness: Five studies\textsuperscript{9-13} compared effectiveness between cognitive enhancers. All studies reported the MMSE and found no differences in effectiveness between drugs using this outcome. 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.

Comparative safety and adherence: Thirteen studies compared the safety and/or adherence of cognitive enhancers.\textsuperscript{9,12-23} 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. As well, none of the adherence studies controlled for severity of disease, which may have also significantly affected the findings. For safety-related adherence, limited research suggested that donepezil and galantamine may be superior to rivastigmine in terms of adherence, although further research to control for confounding variables, is required to confirm these findings.

Health Canada alerts and warnings

- Health Canada issued an advisory in 2015 for donepezil warning of the risk of two potentially serious conditions: rhabdomyolysis and neuroleptic malignant syndrome.\textsuperscript{24}
- Health Canada issued an “Important Safety Information” advisory in 2010 regarding symptoms associated with overdose related to medication error/incorrect use of Exelon Patch (rivastigmine transdermal patch).\textsuperscript{25}
- An advisory was issued in 2014 by Health Canada regarding the risk of serious skin reactions associated with the use of Reminyl ER (galantamine).\textsuperscript{26} Very rare cases of serious skin reactions including Stevens-Johnson syndrome, acute generalized exanthematous pustulosis and erythema multiforme have been reported in patients receiving Reminyl ER.
- In 2005, Health Canada issued an advisory regarding safety information in association with galantamine (Reminyl) in patients with mild cognitive impairment.\textsuperscript{27} Galantamine was not shown to be effective in patients with mild cognitive impairment. As well, an increase in death was observed in patients treated with galantamine.

Pharmacoeconomics Team

Cost-Effectiveness Literature Review
The two previous reviews cognitive enhancers for treating AD were conducted by the National Health Service Health Technology Assessment programme and served as the basis for evaluating the cost-effectiveness evidence prior to this update.\textsuperscript{28,29} Findings from both reviews were generally supportive of the cost-effectiveness of cholinesterase inhibitors and memantine, with some evidence suggesting that treatment may only be cost-effective within certain patient subgroups.

Six Canadian economic evaluations examined the cost-effectiveness of cholinesterase inhibitors and memantine in AD patients; however, five of these studies were published more than 8 to 15 years ago and their findings may not accurately reflect current clinical evidence or cost data. The most recent Canadian study published in 2011 found that the concomitant use of memantine and a cholinesterase
inhibitor was dominant over cholinesterase inhibitor alone from the health care payer and societal perspective. Factors limiting the applicability of this study for our review include a lack of transparency in the economic model and clarity surrounding the modeled patient population, not accounting for the effects of treatment waning, as well as the adoption of a seemingly narrow research question and reliance on a single observational study to provide estimates of disease progression. In addition, assumptions regarding the impact of treatment on delay to institutionalization remain unsupported by clinical data. This study is also susceptible to bias due to industry sponsorship.

**De novo Economic Evaluation**

The objectives of the de novo economic evaluation were to assess the cost-effectiveness of various treatment options for AD compared to each other or no pharmacologic treatment. Costs and quality-adjusted life years (QALYs) of cholinesterase inhibitor monotherapy or memantine monotherapy and the concomitant use of cholinesterase inhibitor with memantine compared with no treatment among elderly patients with AD were assessed using a Markov model. The patient groups that were considered included mild, moderate, and severe AD patients in the community or in institutional care.

Based on the results of a de novo economic model, at a willingness to pay of less than $12,000 per QALY, no pharmacologic treatment is optimal. If a payer’s willingness to pay per QALY is between $12,000 and $29,000, a strategy of initiating donepezil monotherapy is optimal. At a willingness to pay value greater than $29,000 per QALY, a strategy of initiating combination therapy with donepezil and memantine is optimal, although there is great degree of uncertainty around this specific finding.

**Budget Impact Analysis**

Total OPDP expenditure for cholinesterase inhibitors used to treat AD has increased from $14 million in 2000 to almost $120 million in 2010. Recently, there has been a reduction in the expenditure for this drug class to $49 million in 2014 with the introduction of generic products. In 2014, donepezil had the largest market share at 85%, while galantamine had 12% and rivastigmine had 3%.

Without any changes to current reimbursement for cholinesterase inhibitor, expenditure is expected to be $45.4 million in 2017. Listing generic donepezil as general benefit (at a reduced price of 18% of brand name) may result in a 12% reduction in expenditure for cholinesterase inhibitors by 2017, assuming between 1% and 10% of users on galantamine or rivastigmine will switch to donepezil. All other alternative reimbursement strategies would result in an increased expenditure for cholinesterase inhibitors by 2017.
Exhibit 5: Estimated budget impact (2017) for alternative reimbursement options for cholinesterase inhibitors

<table>
<thead>
<tr>
<th>Option</th>
<th>Reimbursement strategy</th>
<th>% users switch</th>
<th>Total cost (2017)</th>
<th>Net budget impact</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>LU for ChEI (status quo)</td>
<td>NA</td>
<td>$45,379,630</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>B</td>
<td>EAP for Exelon patch AND LU for ChEI</td>
<td>1% to Exelon patch</td>
<td>$46,183,483</td>
<td>$803,853</td>
<td>2%↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% to Exelon patch</td>
<td>$53,418,164</td>
<td>$8,038,534</td>
<td>18%↑</td>
</tr>
<tr>
<td>C</td>
<td>LU for ChEI for all severities of AD</td>
<td>No change in usage</td>
<td>$45,379,630</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5%↑ in usage</td>
<td>$47,648,611</td>
<td>$2,268,981</td>
<td>5%↑</td>
</tr>
<tr>
<td>D</td>
<td>LU for ChEI for all severities AND EAP for Exelon patch</td>
<td>No change in usage, 5% to Exelon patch</td>
<td>$49,369,897</td>
<td>$4,019,267</td>
<td>9%↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5%↑ in usage, 10% to Exelon patch</td>
<td>$56,089,071</td>
<td>$10,709,442</td>
<td>24%↑</td>
</tr>
<tr>
<td>E</td>
<td>GB for donepezil (18% generic pricing rule) AND LU rivastigmine (oral) and galantamine</td>
<td>1% to donepezil</td>
<td>$40,090,974</td>
<td>-$5,288,656</td>
<td>12%↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% to donepezil</td>
<td>$39,751,370</td>
<td>-$5,628,259</td>
<td>12%↓</td>
</tr>
</tbody>
</table>

EAP: Exceptional Access Program; LU: Limited Use; ChEI: cholinesterase inhibitor; AD: Alzheimer’s disease; NA: not applicable

Based on the results of the de novo modeling, Option E is considered cost-effective. Strategies relating to the reimbursement of rivastigmine patch (Option B and Option D) were not cost-effective. A price reduction ranging from 45-68% for rivastigmine patch would be needed for rivastigmine patch to become cost-effective; the price reduction varies by the severity of disease and location of the patient (i.e., institutionalized or community-dwelling).

Health Equity Issues

No major health equity issues were identified in this review. See Appendix A for Health Equity Considerations.

Accessibility of Cognitive Enhancers

No accessibility issues were identified in Ontario in our review for cholinesterase inhibitors in patients eligible for coverage through ODB, including those 65 years and older. Specifically, no accessibility concerns for donepezil and galantamine were identified, although barriers for memantine and rivastigmine patch were noted, as these two products are not covered under OPDP.

Reimbursement Options for Consideration

Key Considerations

Efficacy

- For the outcome of cognition using MMSE, our analyses found that donepezil and rivastigmine improved cognition in patients with all severities of Alzheimer’s disease compared to placebo,
although the differences were not considered clinically important. A statistical and clinically important difference on the ADAS-cog scale was observed for donepezil compared to placebo.

- For patients with mild, moderate and moderate-to-severe Alzheimer’s disease, no statistically significant differences were found for cognition using MMSE as the outcome. However, all cholinesterase inhibitors (but not memantine) improved cognition using MMSE compared to placebo in patients with mild-to-moderate Alzheimer’s disease, although the results are not considered clinically important. In patients with severe Alzheimer’s disease, donepezil improved cognition compared to placebo, although this difference was not considered clinically important.
- All cognitive enhancers improved global status compared to placebo. Galantamine demonstrated a clinically meaningful effect compared to placebo, donepezil, rivastigmine, and donepezil+memantine
- There were no significant differences found between the cognitive enhancers for outcomes of function or behavior.
- Rivastigmine decreased the risk of mortality compared to placebo (NNT 58) and memantine (NNT 56). However, the upper limit of the Credible Interval was close to 1 for both of these comparisons.

Safety and tolerability

- Our analyses considered the following safety outcomes: mortality, headache, gastrointestinal adverse effects, serious adverse effects, bradycardia and falls.
- All cholinesterase inhibitors caused more gastrointestinal adverse effects compared to placebo. However, rivastigmine patch decreased the risk of nausea compared to donepezil (NNT 30), galantamine (NNT 23) and rivastigmine oral (NNT 22). Overall, galantamine was most likely to cause nausea, and rivastigmine (oral) most likely to cause vomiting.
- Rivastigmine increased the risk of headache compared to placebo (Number Needed to Harm: 36).
- No differences were observed between agents for these safety outcomes of serious adverse effects, bradycardia or falls.

Accessibility

- In Ontario, oral cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are available on the ODB formulary as Limited Use for patients with mild or moderate Alzheimer’s disease. However, neither memantine nor rivastigmine patch are covered under the Ontario Public Drug Programs.
- In 2013, there were 146,593 publically-funded cognitive enhancer users aged 65 and older in Ontario. 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).

Pharmacoeconomics

- *De novo economic analysis:* Based on the results of a de novo economic model, donepezil was
the most cost-effective monotherapy across all patient subgroups. Memantine monotherapy and rivastigmine-patch were not cost-effective. Combination therapy involving memantine and a cholinesterase inhibitor (specifically donepezil) may be cost-effective although there is a great degree of uncertainty around this finding.

- **Budget impact analysis**: Listing donepezil as general benefit (with a generic pricing rule of 18%) would result in reduced expenditure ($5.4 million or 12% decrease) for cholinesterase inhibitors. However, strategies increasing access to patients with severe AD or allowing access to the rivastigmine patch would result in increased expenditure for cholinesterase inhibitors, ranging from $804,000 to $10.7 million (2-24% increase).

**Reimbursement Options**

Based on the review of the cognitive enhancers in patients with Alzheimer’s disease, five reimbursement options were considered.

**Option A: Limited Use for cholinesterase inhibitors (status quo) for initiation in patients with mild to moderate Alzheimer’s disease**

- Limited Use for all formulations currently listed on ODB formulary: donepezil oral, rivastigmine oral, galantamine oral
- For patients with mild to moderate Alzheimer’s disease
- Clinical criteria: to be developed (see Appendix B)

**Pros:**
- Our analyses found that cholinesterase inhibitors (but not memantine) improved cognition in patients with mild to moderate Alzheimer’s disease. Although donepezil improved cognition in patients with severe Alzheimer’s disease, this was based on limited number of studies.
- Rivastigmine patch was not found to be cost-effective for the treatment of Alzheimer’s disease.
- No change in expenditures is expected with this option.

**Cons:**
- This option does not increase accessibility to patients for the use of the rivastigmine patch nor memantine. Rivastigmine patch was found to be as efficacious as oral rivastigmine but associated with less gastrointestinal adverse effects.

**Option B: Limited Use for cholinesterase inhibitors and Exceptional Access Program for rivastigmine patch for initiation in patients with mild to moderate Alzheimer’s disease**

- Limited Use for all formulations currently listed on ODB formulary: donepezil oral, rivastigmine oral, galantamine oral
- Exceptional Access Program for rivastigmine patch
- For patients with mild to moderate Alzheimer’s disease
- Clinical criteria: to be developed (see Appendix B)
**Pros:**

- Our analyses found that cholinesterase inhibitors (but not memantine) improved cognition in patients with mild to moderate Alzheimer’s disease. Although donepezil improved cognition in patients with severe Alzheimer’s disease, this was based on limited number of studies.
- Rivastigmine patch was found to be as efficacious as oral rivastigmine but associated with less gastrointestinal adverse effects; however in the pharmacoeconomic analyses it was found not to be cost-effective. Rivastigmine patch is an option for patients who have had a trial of at least two oral cholinesterase inhibitors and have been unable to tolerate the gastrointestinal adverse effects associated with these oral agents, or for those patients who are unable to swallow oral medications.

**Cons:**

- This option does not increase accessibility to patients for the use of the memantine.
- An increase in expenditure of $804,000 to $8 million dollars (2-18% increase) can be expected.

**Option C: Limited Use for cholinesterase inhibitors for initiation in all severities of Alzheimer’s disease**

- Limited Use for all formulations currently listed on ODB formulary: donepezil oral, rivastigmine oral, galantamine oral
- For patients with all severities of Alzheimer’s disease (mild, moderate and severe)
- Clinical criteria: to be developed (see Appendix B)

**Pros:**

- Our analyses found that cholinesterase inhibitors (but not memantine) improved cognition in patients with mild to moderate Alzheimer’s disease. Donepezil also improved cognition in patients with severe Alzheimer’s disease, although this was based on limited number of studies.
- Donepezil is approved by Health Canada for all severities of Alzheimer’s disease.
- Rivastigmine patch was not found to be cost-effective for the treatment of Alzheimer’s disease.

**Cons:**

- This option does not increase accessibility to patients for the use of the memantine or rivastigmine patch.
- A possible 5% increase in expenditures ($2.3 million) may result if more patients with severe Alzheimer’s disease are initiated on cholinesterase inhibitors.

**Option D: Limited Use for cholinesterase inhibitors and Exceptional Access Program for rivastigmine patch for initiation in all severities of Alzheimer’s disease**

- Limited Use for all formulations currently listed on ODB formulary: donepezil oral, rivastigmine oral, galantamine oral
- Exceptional Access Program for rivastigmine patch
- For patients with all severities of Alzheimer’s disease (mild, moderate and severe)
- Clinical criteria: to be developed (see Appendix B)
Pros:
- Our analyses found that cholinesterase inhibitors (but not memantine) improved cognition in patients with mild to moderate Alzheimer’s disease. Donepezil also improved cognition in patients with severe Alzheimer’s disease, although this was based on limited number of studies.
- Donepezil is approved by Health Canada for all severities of Alzheimer’s disease.
- Rivastigmine patch was found to be as efficacious as oral rivastigmine but associated with less gastrointestinal adverse effects; however in the pharmacoeconomic analyses it was found not to be cost-effective. Rivastigmine patch is an option for patients who have had a trial of at least two oral cholinesterase inhibitors and have been unable to tolerate the gastrointestinal adverse effects associated with these oral agents, or for those patients who are unable to swallow oral medications.

Cons:
- This option does not increase accessibility to patients for the use of the memantine.
- A 9-24% increase in expenditures ($4-10.7 million) may result if more patients with severe Alzheimer’s disease are initiated on cholinesterase inhibitors and rivastigmine patch is funded under EAP.

Option E: General Benefit for donepezil and Limited Use for rivastigmine and galantamine for initiation in patients with mild to moderate Alzheimer’s disease

- General Benefit for donepezil (based on 18% generic pricing agreement)
- Limited Use for oral rivastigmine and oral galantamine
- For patients with mild to moderate Alzheimer’s disease
- Clinical criteria: to be developed (see Appendix B)

Pros:
- Our analyses found that cholinesterase inhibitors (but not memantine) improved cognition in patients with mild to moderate Alzheimer’s disease. Although donepezil improved cognition in patients with severe Alzheimer’s disease, this was based on limited number of studies.
- Overall, donepezil was at least as efficacious as other cholinesterase inhibitors and may be better tolerated in terms of gastrointestinal effects than rivastigmine or galantamine.
- Although cholinesterase inhibitors currently are approximately 25% of the brand name cost, further reduction to 18% for donepezil would result in decrease in expenditure ($5.6 million or 12%).
- Rivastigmine patch was not found to be cost-effective for the treatment of Alzheimer’s disease.

Cons:
- This option does not increase accessibility to patients for the use of the memantine or rivastigmine patch.
Other Issues for Consideration

Use of cholinesterase inhibitors in patients with Parkinson’s disease

Rivastigmine is approved by Health Canada for symptomatic treatment of patients with idiopathic Parkinson’s disease and mild to moderate dementia. There have been two recent meta-analyses that showed benefit, albeit modest improvement, for cholinesterase inhibitors in the treatment of this patient population.\(^{31,32}\) Although the risk of falls was not increased in patients with Parkinson’s disease treated with cholinesterase inhibitors, adverse reactions such as nausea, vomiting, diarrhea and worsening psychosis and agitation were reported.

Recommendation: Although cholinesterase inhibitors for the treatment of Parkinson’s disease dementia were not part of the ODPRN drug class review, additional review of these agents (in particular rivastigmine) is warranted for consideration for funding by MOHLTC.

ODPRN Citizens’ Panel

Findings from the Citizens’ Panel contributed to selection of final policy recommendations. Citizens’ Panel (CP) members rated each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. Through one teleconference meeting and two rounds of an online survey, CP members voiced the following perceptions:

Option A (LU for oral cholinesterase inhibitors, mild to moderate Alzheimer’s disease):
- Felt it restricted accessibility to individuals with severe dementia
- “Status quo does not improve access to any helpful treatments. Patients suffer the most with this plan.”

Option B (LU for oral cholinesterase inhibitors, EAP for rivastigmine patch, mild to moderate Alzheimer’s disease)
- The panel had similar concerns to option A in terms of restricting access to those with severe dementia, but they were glad that the patch is listed for those that need it.
- “While greater access is helped with this option at the end of the day the high cost of the patch makes this option not viable.”

Option C (LU for cholinesterase inhibitors for all severities)
- Members still thought the patch should be available and listed.
- Expanding access for all severities was perceived to be reasonable given the benefits of the drugs.
- They agreed that there was no need to increase access to memantine if it is not as effective.

Option D (LU for cholinesterase inhibitors, EAP for rivastigmine patch, all severities)
- Perceived as most the favourable option as it covered all severities and included the patch.
• There were some concerns regarding the cost and how much it would increase for this option.

Option E (GB for donepezil, LU oral rivastigmine and galantamine)
• Some concerns that the general benefit listing may allow for misuse.
• Others still had concerns that rivastigmine patch was not covered.

Exhibit 7: Overall option ranking

<table>
<thead>
<tr>
<th>Option</th>
<th>Mean Ranking (1 = Most Acceptable 5 = Least Acceptable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option A: LU for cholinesterase inhibitors (mild to moderate severity) (status quo)</td>
<td>4.6</td>
</tr>
<tr>
<td>Option B: LU for cholinesterase inhibitors and EAP for rivastigmine patch (mild to moderate severity)</td>
<td>3.0</td>
</tr>
<tr>
<td>Option C: LU for cholinesterase inhibitors (all severities)</td>
<td>3.0</td>
</tr>
<tr>
<td>Option D: LU for cholinesterase inhibitors and EAP for rivastigmine patch (all severities)</td>
<td>1.4</td>
</tr>
<tr>
<td>Option E: GB for donepezil and LU for oral rivastigmine and galantamine</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Final Policy Recommendations
Cholinesterase inhibitors are currently listed as Limited Use in Ontario for the management of patients with mild and moderate Alzheimer’s disease. Several factors were considered in the final recommendations:

• Across Canada, all public drug plans provide coverage for cholinesterase inhibitors as a restricted benefit (i.e., requiring authorization) for patients with mild to moderate Alzheimer’s disease.
• Ontario has the highest rate of publically-funded cognitive enhancer use in Canada, which may be reflective of the more liberal listing of these agents relative to other jurisdictions across Canada. However, accessibility to memantine and rivastigmine patch is limited, as these products are not covered in Ontario either on the ODB formulary or through the Exceptional Access Program.
• No coverage of cholinesterase inhibitors for the initiation of patients with severe disease is recommended. Although our analyses found that donepezil improved cognition compared to
placebo in patients with severe disease, this difference was also not considered clinically important. It should be noted that the Citizen’s Panel preferred coverage of cholinesterase inhibitors for all severities of Alzheimer’s disease, although concerns were raised regarding the potential increase in cost.

- It is not recommended that memantine be listed on the ODB formulary or available through EAP. Results from our rapid review/network meta-analyses (NMA) indicate that cholinesterase inhibitors, but not memantine, improve cognition and global status in patients with Alzheimer’s disease.
- All cholinesterase inhibitors cause more gastrointestinal adverse effects compared to placebo, although rivastigmine patch caused less gastrointestinal effects than oral cholinesterase inhibitors. The Citizen’s Panel noted that the rivastigmine patch provided an option for patients unable to tolerate the oral formulations.
- Donepezil was the most cost-effective monotherapy. At current prices, rivastigmine patch is not cost effective; however, with a price reduction of approximately 55% (ranging from 45-68% depending on disease severity and whether patient is community dwelling or institutionalized) rivastigmine patch becomes a cost-effective option. Strategies to allow access to the rivastigmine patch would result in increased expenditures ranging from $804,000 to $8 million (2-18% increase) based on 1-10% of patients currently on oral cholinesterase inhibitors switching to rivastigmine patch.

Based on the results of the review and feedback from the ODPRN Citizens’ Panel, the primary reimbursement option for cognitive enhancers recommended for the Ontario Public Drug Program is:
- Limited Use for oral cholinesterase inhibitors for initiation of patients with mild to moderate Alzheimer’s disease (with updated clinical criteria)

In addition, two additional reimbursement recommendations are made:
- Listing of rivastigmine patch on the Exceptional Access Program should be explored, provided a price reduction of approximately 55% is negotiated.
- No listing of memantine is recommended.
### Exhibit 8: Assessment of Reimbursement Options

<table>
<thead>
<tr>
<th></th>
<th>Option A*: LU for oral ChEI</th>
<th>Option B*: LU for oral ChEI + EAP rivastigmine patch</th>
<th>Option C: LU for oral ChEI for all severities</th>
<th>Option D: LU for oral ChEI, EAP for rivastigmine patch, all severities</th>
<th>Option E*: GB donepezil (18% generic pricing), LU oral rivastigmine, galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>All ChEI (but not memantine) improve cognition in patients with mild-to-moderate AD</td>
<td>All ChEI improved global status compared to placebo (for all severities)</td>
<td>Donepezil improved cognition in severe AD compared to placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety concerns</strong></td>
<td>All ChEI cause GI effects</td>
<td>Rivastigmine patch is better tolerated than oral products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accessibility</strong></td>
<td>No change in number of patients</td>
<td>No change in number of patients</td>
<td>↑ in pts (estimate 5% in in number of patients)</td>
<td>↑ in pts (estimate 5% in in number of patients)</td>
<td>No change in number of patients</td>
</tr>
<tr>
<td><strong># of users potentially eligible for EAP (quarterly)</strong></td>
<td>Not applicable</td>
<td>700-7000 users (1-10% of users switch to rivastigmine patch)</td>
<td>Not applicable</td>
<td>700-7000 users (1-10% of users switch to rivastigmine patch)</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Budget impact</strong></td>
<td>No change</td>
<td>Cost increases of $804,000-$88M (2-18%↑)</td>
<td>No change to cost increases of $2.3 M (0-5%↑)</td>
<td>Cost increases of $804,000 - $10.7 M (2-24%↑)</td>
<td>Cost savings of $5.3 M (↓12%)</td>
</tr>
<tr>
<td><strong>Alignment with other jurisdictions</strong></td>
<td>Restricted listing in all jurisdictions. All jurisdictions cover mild and moderate AD.</td>
<td>Patch covered in BC, QC, YK</td>
<td>ChEI only covered in mild and moderate AD across all jurisdictions</td>
<td>Patch covered in BC, QC, YK</td>
<td>ChEI only covered in mild and moderate AD across all jurisdictions</td>
</tr>
<tr>
<td><strong>Indication creep</strong></td>
<td>Unenforced restriction criteria via LU listing may result in continued use of ChEI for patients who do not meet LU criteria.</td>
<td>Indication creep unlikely for rivastigmine patch due to individual clinical review</td>
<td>Unenforced restriction criteria via LU listing may result in continued use of ChEI for patients who do not meet LU criteria.</td>
<td>Indication creep unlikely for rivastigmine patch due to individual clinical review</td>
<td>Unenforced restriction criteria via LU listing may result in continued use of ChEI for patients who do not meet LU criteria.</td>
</tr>
</tbody>
</table>

* for mild and moderate Alzheimer’s disease  
**In 2013 there were 146,593 publically-funded cognitive enhancer users aged 65 and older in Ontario
Reference List


(8) Lexi-Comp Inc. Lexicomp Online. 2015.


(12) Santoro A, Siviero P, Minicuci N, Bellavista E, Mishto M, Olivieri F et al. Effects of donepezil,


Ontario Drug Policy Research Network
examens/aricept-eng.php . 2015.


### Appendix A: Health Equity Considerations for Cognitive Enhancers

<table>
<thead>
<tr>
<th>Populations</th>
<th>Proposed Cognitive Enhancer recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)</td>
<td>No accessibility issues identified. Coverage of medications, including cognitive enhancers, for Aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.</td>
</tr>
<tr>
<td>Age-related groups (e.g., children, youth, seniors, etc.)</td>
<td>Elderly: No restrictions for cognitive enhancer use in the elderly were identified.</td>
</tr>
<tr>
<td>Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual,</td>
<td>No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage through ODB.</td>
</tr>
<tr>
<td>intellectual/developmental, learning, mental illness, addictions/substance</td>
<td></td>
</tr>
<tr>
<td>use, etc.)</td>
<td></td>
</tr>
<tr>
<td>Ethno-racial communities (e.g., racial/racialized or cultural minorities,</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>immigrants and refugees, etc.)</td>
<td></td>
</tr>
<tr>
<td>Francophone (including new immigrant francophones, deaf communities using</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>LSQ/LSF, etc.)</td>
<td></td>
</tr>
<tr>
<td>Homeless (including marginally or under-housed, etc.)</td>
<td>Not eligible for ODB coverage.</td>
</tr>
<tr>
<td>Linguistic communities (e.g., uncomfortable using English or French, literacy</td>
<td>The MMSE, which is currently used as a cognitive evaluation tool, is not routinely available in languages other than English. This may bias use of cholinesterase inhibitors.</td>
</tr>
<tr>
<td>affects communication, etc.)</td>
<td></td>
</tr>
<tr>
<td>Low income (e.g., unemployed, underemployed, etc.)</td>
<td>No accessibility issues identified; low income individuals who receive public drug coverage will have access to cognitive enhancers through ODB.</td>
</tr>
<tr>
<td>Religious/faith communities</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Rural/remote or inner-urban populations (e.g., geographic or social</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>isolation, under-serviced areas, etc.)</td>
<td></td>
</tr>
<tr>
<td>Sex/gender (e.g., male, female, women, men, trans, transsexual,</td>
<td>No accessibility issues identified for sex/gender in the review.</td>
</tr>
<tr>
<td>transgendered, two-spirited, etc.)</td>
<td></td>
</tr>
<tr>
<td>Sexual orientation, (e.g., lesbian, gay, bisexual, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td>Other: please describe the population here.</td>
<td>None identified.</td>
</tr>
</tbody>
</table>

Appendix B: Proposed LU Criteria for Initiation of Cholinesterase Inhibitors (Please note that Appendix B was updated in February 2016)

Criteria for Coverage (for Initiation of Therapy)
1. Patient with a diagnosis of Alzheimer's Disease
   AND
2. Patient has mild to moderate stage of disease based on cognitive testing [e.g., MMSE (10-26) OR MoCA (10-18)] OR global assessment [e.g., Global Deterioration Scale (GDS) stage 4, 5 or 6]

LU Authorization Period
1 year

Criteria for Continued Coverage
1. Patient has a clinically meaningful response as determined by stabilization or improvement while on therapy
   AND
2. Patient has not progressed to Global Deterioration Scale (GDS) stage 7

Duration of Approval (for continued coverage)
1 year

Therapeutic Notes:
- Cholinesterase inhibitors are not recommended for patients with mild cognitive impairment, as these agents are ineffective and potentially harmful in this population.
- Discontinuation of cholinesterase inhibitors may be considered in the following situations:
  o Patient’s rate of cognitive, functional and/or behavioural decline is greater on treatment compared to no treatment
  o Patient’s dementia progresses to a stage where there is no longer a meaningful benefit (i.e., GDS stage 7)
  o Patient experiences adverse effects that are intolerable and likely related to the cholinesterase inhibitor
  o Patient is non-adherent
  o Patient has comorbidities that make continued use of the agent either unacceptably risky or futile (e.g., terminally ill)
- If patients are on higher doses of a cholinesterase inhibitor, tapered withdrawal has been suggested to avoid withdrawal effects.
### Explanation of Criteria

<table>
<thead>
<tr>
<th>Current criteria</th>
<th>Proposed criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with mild to moderate Alzheimer’s Disease</td>
<td>For patients with mild to moderate Alzheimer’s Disease</td>
<td>• Our results indicated that in patients with severe Alzheimer’s disease, only donepezil improved cognition compared to placebo, although this difference was not considered clinically important.</td>
</tr>
</tbody>
</table>
| **Mini-Mental State Exam [MMSE] 10-26** | MMSE 10-26 or MoCA 10-18 or Global Deterioration Scale (GDS) stage 4, 5 or 6 | • The MMSE is a validated method of screening for Alzheimer’s disease. However, the MMSE is a proprietary test that requires the purchase of an official test form.  
• MoCA is intended as a screening instrument for mild cognitive dysfunction; although scores for severities of cognitive decline have been used [http://www.mocatest.org/faq/], these severity ranges have not been validated.  
[MoCA scores: 18-26 = mild cognitive impairment (MCI), 10-17= moderate cognitive impairment and less than 10= severe cognitive impairment].  
• Our cut-offs have been made based on clinical input, information from the official MoCA website and newly published data from Saczynski et al. (J Am Geriatr Soc 2015;63:2370-4)  
• Other tests that have been used in clinical trials for cholinesterase inhibitors to evaluate cognition include ADAS-cog and Clinical Dementia Rating (CDR) scale (both considered too long to administer for standard testing).  
• Other tests have been used for staging Alzheimer’s disease (e.g., FAST scale and Global Deterioration Scale). The Global Deterioration Scale (GDS) is well validated for staging dementia. These tests are used in conjunction with cognitive tests for determining eligibility for ChEi in other jurisdictions across Canada. |
| Patients will be reimbursed for a period of up to 3 months after which continued treatment must be reassessed | None | • Historically, the 3 months was used as a cut-off as the manufacturers provided a free trial of medication for the first 3 months. |
| **LU Authorization Period: 1 year.** | LU Authorization Period: 1 year | • Continued assessment of benefit/harms |
| **Continuation** |                   |           |
| Further reimbursement will be made available to those patients whose disease has not progressed/deteriorated while on this drug | Patient has clinically meaningful response as determined by stabilization or improvement while on therapy  
AND  
• Patient has not progressed to Global Deterioration Scale (GDS) stage 7 | • A systematic review and meta-analysis on discontinuation of cholinesterase inhibitors (O’Regan et al. J Clin Psychiatry 2015;76:e1424-1431) suggests that discontinuation may lead to significant decline in cognition and behavior in patients with mild, moderate and moderate-severe AD.  
• In a randomized controlled trial, discontinuation of cholinesterase inhibitors in long-term residents with moderate to severe dementia (mean MMSE score 8.1 ±5.2) was safe and well-tolerated although the presence of hallucinations and delusions may result in clinical deterioration.(Herrmann N et al. J Am Med Dir Assoc 2016;17:142-7.)  
• Patients with severe AD best assessed with non-cognitive scales (e.g., Global Deterioration Scale). |
| Patients must continue to have a MMSE score of 10-26. | None | • Continued assessment of benefit/harms |
| LU Authorization Period: 1 year. | LU Authorization Period: 1 year | }