Cognitive Enhancers for Treatment of Alzheimer’s Disease

FINAL Report: Environmental Scan and Local/Historical Context

August 10th, 2015
Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally
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. All agents are available as generic formulations for at least one dosage form.

Cholinesterase inhibitors (namely oral donepezil, galantamine, rivastigmine) are available as Limited Use on the Ontario Drug Benefit formulary. Donepezil rapid disintegrating tablet, rivastigmine transdermal patch, and memantine 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. Across Canada, all public drug plans provide coverage for cholinesterase inhibitors as a restricted benefit; memantine is only available in Quebec. In Australia, cholinesterase inhibitors are available under the “authority required-streamlined” system (similar to the Limited Use system in Ontario). Memantine requires prior authorization for coverage. New Zealand only provides coverage for donepezil (generic-single source) and rivastigmine patch (when nausea and vomiting is associated with donepezil).

Part B: Guidelines for the treatment of patients with Alzheimer’s disease
Five guidelines/consensus recommendations were reviewed for treatment of patients with Alzheimer’s disease. All guidelines recommend the use of cholinesterase inhibitors for treatment of patients with mild to moderate Alzheimer’s disease; use in patients with severe disease is recommended in one guidelines. Memantine for treatment of patients with moderate/severe disease is recommended as monotherapy in four guidelines. Two guidelines commented that there is insufficient evidence to recommend combination of memantine and a cholinesterase inhibitor. Choice of cholinesterase inhibitor will depend on cost, adverse effect profile, ease of use and familiarity with specific product.

Part C: Impact of different drug reimbursement schemes for cognitive enhancers in patients with Alzheimer’s disease
There is a lack of literature investigating various reimbursement schemes for cholinesterase inhibitors and memantine for patients with Alzheimer’s disease.

Part D: Rapid review of selected topics
Cognitive Rating Scales for Alzheimer’s Disease: There are numerous rating scales that have been used in the assessment and monitoring of patients with Alzheimer’s disease. The most common cognitive scales that are used in clinical trials include the MMSE, CDR and ADAS-cog. However, the CDR and the ADAS-cog are lengthy to administer and not practical in a clinical setting. The MMSE is advocated for use
Use of cholinesterase inhibitors in patients with mild cognitive impairments: Cholinesterase inhibitors are not currently recommended for patients with mild cognitive impairment because they have not been found to prevent dementia and/or consistently improve cognition, and they are associated with adverse events, particularly gastrointestinal effects such as nausea and diarrhea.

Discontinuation of Cholinesterase inhibitors: There is limited data to guide clinicians regarding discontinuation of cholinesterase inhibitors in patients with Alzheimer’s disease. Based on review of the evidence, some groups suggest that discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer’s disease may lead to worsening of cognitive function.

Use of cholinesterase inhibitors for Parkinson’s disease dementia: Cholinesterase inhibitors are currently recommended for patients with Parkinson’s disease dementia because they have been found to produce positive effects on cognitive function, behavioural disturbances and mortality. However, it is important to note that adverse effects, including increased tremor rates, gastrointestinal side effects and agitation, have been reported with cholinesterase inhibitors in patients with Parkinson’s disease dementia.

Health Canada warnings and advisories: Health Canada issued an advisory in 2015 for donepezil warning of the risk of two potentially serious conditions: rhabdomyolysis and neuroleptic malignant syndrome. An advisory was issued in 2010 regarding symptoms associated with overdose related to medication error/incorrect use of Exelon Patch (rivastigmine transdermal patch). An advisory was issued in 2014 regarding the risk of serious skin reactions associated with the use of Reminyl ER (galantamine). In 2005, Health Canada issued an advisory regarding safety information in association with galantamine (Reminyl) in patients with mild cognitive impairment. 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.
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A special thank you to all of the provincial and territorial representatives in Canada from the respective Ministries of Health as well as the representative from the Non-Insured Health Benefits for First Nations and Inuit (NIHB) who participated in the telephone survey.
Introduction

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 with 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, with approximately 50% of new dementia cases diagnosed 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 cognitive deterioration with memory loss and the management of behavioural and psychological symptoms of dementia (BPSD). 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.

The objectives of this report are:

- **Part A:** To summarize coverage of cognitive enhancers through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- **Part B:** To summarize the guidelines for management of elderly patients with Alzheimer’s disease
- **Part C:** To review the evidence relating to the impact of different drug reimbursement schemes for cognitive enhancers on patient access and/or utilization and costs
- **Part D:** To provide summary information on selected topics

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

**Availability and Costs of Cognitive Enhancers in Canada**

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) (Table 1). They are available as oral formulations (e.g., tablet, rapidly disintegrating tablets, capsules, oral solution, extended release capsules). Rivastigmine is also available as a transdermal patch. All oral formulations, with the exception of Exelon Oral Solution, are available generically.
### Exhibit 1: Cognitive enhancers available in Canada

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Availability</th>
<th>Dosage form</th>
<th>Indication</th>
<th>Generic available</th>
<th>Monthly cost*</th>
<th>Date available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinesterase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>Pfizer</td>
<td>5, 10mg</td>
<td>Oral tablet</td>
<td>Mild, moderate, severe AD</td>
<td>Yes</td>
<td>151.04</td>
<td>Aug 1997</td>
</tr>
<tr>
<td>Generic</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37.02</td>
<td>Dec 2013</td>
</tr>
<tr>
<td>Aricept RDT</td>
<td>Aricept</td>
<td>Pfizer</td>
<td>5, 10mg</td>
<td>Rapidly disintegrating tablet</td>
<td></td>
<td>Yes</td>
<td>108.53†</td>
<td>Jan 2006</td>
</tr>
<tr>
<td>Generic</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>156.86†</td>
<td>Dec 2013</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Reminyl ER</td>
<td>Janssen</td>
<td>8, 16, 24 mg</td>
<td>Extended release capsule</td>
<td>Mild, moderate AD</td>
<td>Yes</td>
<td>154.30</td>
<td>Apr 2005</td>
</tr>
<tr>
<td>Generic</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37.40</td>
<td>Nov 2010</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon</td>
<td>Novartis</td>
<td>1.5, 3, 4.5, 6mg</td>
<td>Oral capsule</td>
<td>Mild, moderate dementia of AD, PD</td>
<td>Yes</td>
<td>156.35</td>
<td>May 2000</td>
</tr>
<tr>
<td>Generic</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39.09</td>
<td>Sep 2009</td>
</tr>
<tr>
<td>Exelon</td>
<td>Novartis</td>
<td></td>
<td>2 mg/mL</td>
<td>Oral solution</td>
<td></td>
<td>No</td>
<td>195.13†</td>
<td>Dec 2002</td>
</tr>
<tr>
<td>Exelon Patch</td>
<td>Novartis</td>
<td></td>
<td>4.6mg/24hr, 9.5 mg/24hr</td>
<td>Transdermal patch</td>
<td>Mild, moderate AD</td>
<td>No</td>
<td>142.52†</td>
<td>Dec 2007</td>
</tr>
<tr>
<td><strong>N-methyl-D-aspartate (NMDA) receptor antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>Ebixa</td>
<td>Lundbeck</td>
<td>10mg</td>
<td>Tablet</td>
<td>Moderate, severe AD (monotherapy or in conjunction with cholinesterase inhibitor)</td>
<td>Yes</td>
<td>152.36†</td>
<td>Dec 2004</td>
</tr>
<tr>
<td>Generic</td>
<td>Various</td>
<td></td>
<td>5, 10mg</td>
<td></td>
<td></td>
<td></td>
<td>94.14†</td>
<td>Nov 2009</td>
</tr>
</tbody>
</table>

*Based on costs obtained from the Ontario Drug Benefit Formulary (Accessed: Apr 23, 2015)
† Based on costs obtained from McKesson (Accessed: Apr 23, 2015)

**Summary**
- Cognitive enhancers are available in various formulations including oral (tablet, capsule, extended release capsule, rapidly disintegrating tablet, solution) and transdermal patch.
- The oral formulations of the cholinesterase inhibitors as well as memantine are available as generic formulations.
- Donepezil is indicated for mild, moderate and severe dementia of the Alzheimer’s type, whereas galantamine and rivastigmine are indicated for mild and moderate AD. Rivastigmine (oral) is indicated for dementia of Alzheimer’s type and dementia associated with Parkinson’s disease.
Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. No review was completed for oral donepezil, galantamine and rivastigmine, as these products were available prior to 2003. For the newer agents that were reviewed by the CDR, a summary of recommendations is found in Exhibit 2 and Appendix A.

Exhibit 2: Summary of Common Drug Review recommendations for cognitive enhancers

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine (Ebixa)(2005)⁶</td>
<td>Monotherapy or adjunctive therapy with cholinesterase inhibitors for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer’s type</td>
<td>Do not list</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)(2008)⁷</td>
<td>Symptomatic treatment of patients with mild to moderate dementia of the Alzheimer’s type</td>
<td>Do not list</td>
</tr>
</tbody>
</table>

Product listing in Ontario

Limited Use (LU)

Limited use (LU) drugs are drugs that have been deemed to have value in certain circumstances, although they may not be appropriate for general listing in the Formulary. Cholinesterase inhibitors (namely oral donepezil, galantamine, rivastigmine) are available as Limited Use on the Ontario Drug Benefit formulary. Donepezil rapid disintegrating tablet, rivastigmine oral solution, rivastigmine transdermal patch, and memantine are not listed on the ODB formulary; rivastigmine oral solution is available through the Exceptional Access Program.

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.

Committee to Evaluate Drugs:
The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care’s independent expert advisory committee on drug-related issues. In 2008, the CED recommended that donepezil
rapidly dissolving tablet not be listed on the ODB formulary as this new dosage form provides little added therapeutic benefit. As well, given that patients with severe disease are the ones who have the most difficulty swallowing, the Committee was concerned that the rapidly dissolving tablet could be used inappropriately in patients with severe disease.

Rivastigmine patch (Exelon Patch) was reviewed in 2008, and it was recommended that this product not be listed on the ODB formulary nor be reimbursed through the Exceptional Access Program. A review of memantine (Ebixa) was done in 2005, and this product was NOT recommended for listing on the ODB formulary nor on the Exceptional Access Program (formally known as the Individual Clinical Review).

Summary
- In Ontario, 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.

Public Plan Listings in Canada
Part 1: Listing Status

In order to determine the listing of cognitive enhancers across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix 2). In Canada, cognitive enhancers are available as a restricted benefit in all jurisdictions. The restricted benefit is enforced (e.g., prescriber is required to provide information, often in writing, regarding justification for use of cognitive enhancers). A summary of the various listings is found in Exhibit 3.

Exhibit 3: 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>
</tr>
</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>No</td>
</tr>
<tr>
<td>Exelon oral solution</td>
<td>Res</td>
<td>Res</td>
<td>No</td>
<td>Res</td>
<td>Res</td>
<td>Res</td>
<td>No</td>
<td>Res</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Exelon patch</td>
<td>Res</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>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
FB=full benefit
Current as of April 24, 2015
**Restriction Criteria**

In order for patients to be eligible for publically funded cognitive enhancers, various jurisdictions use restriction criteria as part of the special authorization process (see Appendix 3).

**Part 2: Telephone Interview with Public Drug Program Representatives**

A representative from each public drug program invited to participate in a 30 minute telephone interview (see Appendix 4) to gather further information about formulary listing of cognitive enhancers. Exhibit 4 summarizes the information obtained in the interviews.

**Exhibit 4: Summary of interviews with representative from public drug program**

<table>
<thead>
<tr>
<th>Province</th>
<th>Listing</th>
<th>What was the basis for listing/change in listing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>Restricted</td>
<td>All cholinesterase inhibitors, including Exelon patch, are available through the Alzheimer’s Drug Therapy Initiative program (special authority request). Currently reviewing utilization data from 2007 to 2012 to help determine formulary listing of these agents. Require MMSE (10-26) and Global Deterioration Scale (4-6) for coverage. Coverage for patients with Alzheimer’s disease (with or without other components)</td>
</tr>
<tr>
<td>Ontario</td>
<td>Limited use (Restricted, passive)</td>
<td>Cholinesterase inhibitors are listed on the ODB formulary as Limited Use. Require MMSE (10-26) for coverage. Coverage for patients with Alzheimer’s disease.</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>Restricted</td>
<td>Cholinesterase inhibitors available as Exceptional Status Drugs. Require MMSE (10-30) and Functional Assessment Staging Test (FAST) for coverage. Coverage for patients with Alzheimer’s disease (with or without other components)</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>Restricted</td>
<td>Cholinesterase inhibitors available Special Authorization program. Require MMSE (10-24; 25 and 26 on advice of a neurologist, psychiatrist or geriatrician) Coverage for patients with Alzheimer’s disease</td>
</tr>
<tr>
<td>NIHB</td>
<td>Restricted</td>
<td>Cholinesterase inhibitors covered under Limited Use program (require prior approval) Require MMSE (10-26) and Global Deterioration Scale (4-6) for coverage. Coverage for patients with Alzheimer’s disease (with or without other components) Exelon patch is covered in exceptional cases</td>
</tr>
<tr>
<td>Province</td>
<td>Listing</td>
<td>What was the basis for listing/change in listing?</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>Restricted</td>
<td>Cholinesterase inhibitors available as under Special Authorization program. Require MMSE (10-30) and Functional Assessment Staging Test (FAST) for coverage. Coverage for patients with Alzheimer’s disease (with or without other components)</td>
</tr>
<tr>
<td>Yukon</td>
<td>Restricted</td>
<td>Cholinesterase inhibitors available as Exceptional Use medication. Require MMSE (10-26) for coverage. Coverage for patients with Alzheimer’s disease. Exelon patch covered in cases where patients unable to swallow. No coverage for patients in a dementia care facility.</td>
</tr>
</tbody>
</table>

**Summary**
- All public drug plans in Canada provide coverage for cholinesterase inhibitors as a restricted benefit, whereas memantine is only available in Quebec.
- All jurisdictions provide coverage for patients with mild to moderate Alzheimer’s disease. No jurisdiction provides coverage for patients with severe disease.
- The MMSE is used for assessment of cognition in all jurisdictions. Alberta also permits the use of the InterRAI-Cognitive Performance Scale.
- Seven jurisdictions require assessment of functional status for coverage.
- Initial approval of cholinesterase inhibitors varies from 3 months (3 jurisdictions) to 24 months (in Alberta). Six jurisdictions have an initial approval period of 6 months.
- Subsequent approval varies from 6-24 month, with 12 months being the most common approval period in 6 jurisdictions.

**Selected International Jurisdictions**

**United States**
As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list (“formulary”) has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider. For example, in Illinois (Medicaid), the preferred cholinesterase inhibitor is donepezil (generic). Other cholinesterase inhibitors including rivastigmine and galantamine are considered “non-preferred”.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list. Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays
provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval. In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix 5 for examples of copayments with tiered formulary systems). (Exhibit 5)
### Exhibit 5: Listing of cognitive enhancers for select plans in the United States

<table>
<thead>
<tr>
<th>Drug Plan</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AETNA Preferred List (<a href="http://www.aetna.com">www.aetna.com</a>)</td>
<td>G: preferred</td>
<td>G: preferred</td>
<td>G: preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>Amerigroup Medication Formulary (Medicaid markets in</td>
<td>G: preferred</td>
<td>Non-preferred</td>
<td>G: preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) (<a href="http://www.providers.amerigroup.com">www.providers.amerigroup.com</a>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue Cross Blue Shield of Texas Standard Preferred Drug List (October 2014) (<a href="http://www.bcbstx.com">www.bcbstx.com</a>)</td>
<td>G: preferred</td>
<td>G: preferred</td>
<td>Non-preferred</td>
<td>Non-preferred</td>
</tr>
<tr>
<td>Illinois Medicaid Preferred Drug List* (<a href="http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf">www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf</a>)</td>
<td>G: preferred</td>
<td>Non-preferred</td>
<td>Non-preferred</td>
<td>Non-preferred</td>
</tr>
</tbody>
</table>

*Approved for patients with mild to severe dementia; other cholinesterase inhibitors will be approved for patients with mild to moderate dementia; **Approved for patients with moderate to severe dementia; G: generic; B: brand name
Other Countries

*Australia:* In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts cognitive enhancers (see Exhibit 6). The cholinesterase inhibitors are available as Authority Required (streamlined), which is similar to Limited Use in Ontario. Memantine is available as Authority Required, which requires prior authorization.

Exhibit 6: Cognitive Enhancers in Australia

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage form</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Tablet</td>
<td>Mild to moderately severe Alzheimer disease</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Capsule, patch, oral solution</td>
<td><em>Treatment Phase: Initial</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Clinical criteria:</strong></td>
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<tr>
<td></td>
<td></td>
<td>Patient must have a baseline Mini-Mental State Examination (MMSE) or</td>
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<tr>
<td></td>
<td></td>
<td>Standardised Mini-Mental State Examination (SMMSE) score of 10 or more,</td>
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<td></td>
<td></td>
<td><strong>AND</strong></td>
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<td></td>
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<td>The condition must be confirmed by, or in consultation with, a specialist/</td>
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<td></td>
<td></td>
<td>consultant physician (including a psychiatrist),</td>
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<td></td>
<td><strong>AND</strong></td>
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<td></td>
<td></td>
<td>The treatment must be the sole PBS-subsidised therapy for this condition.</td>
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<tr>
<td></td>
<td></td>
<td>The authority application must include the result of the baseline</td>
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<td>MMSE or SMMSE. If this score is 25 - 30 points, the result of a baseline</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Capsule</td>
<td>Alzheimer Disease Assessment Scale, cognitive sub-scale (ADAS-Cog) may</td>
</tr>
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<td></td>
<td></td>
<td>also be specified.</td>
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<td>The application must be made in writing, but initial supply may be</td>
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<td></td>
<td></td>
<td>sought by telephone.</td>
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<td></td>
<td></td>
<td>For telephone applications, up to a maximum of 2 months' initial</td>
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<td></td>
<td></td>
<td>therapy will be authorised. This telephone application must be followed</td>
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<td></td>
<td></td>
<td>by a written authority application for no more than 1 month's therapy</td>
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<td></td>
<td></td>
<td>and sufficient repeats to complete a maximum of up to 6 months' initial</td>
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<tr>
<td></td>
<td></td>
<td>treatment. For written applications where no prior telephone approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>has been issued, up to a maximum of 1 month's therapy plus 5 repeats</td>
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<tr>
<td></td>
<td></td>
<td>will be authorised.</td>
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<tr>
<td>Product</td>
<td>Dosage form</td>
<td>Criteria</td>
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</tr>
</tbody>
</table>
| Donepezil   | Tablet, Capsule, patch, patch, oral solution Capsule | - **Mild to moderately severe Alzheimer disease**  
*Treatment Phase: Initial*  
**Clinical criteria:**  
Patient must have a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 9 or less,  
AND  
The condition must be confirmed by, or in consultation with, a specialist/consultant physician (including a psychiatrist),  
AND  
The treatment must be the sole PBS-subsidised therapy for this condition.  
A patient who is unable to register a score of 10 or more for reasons other than their Alzheimer disease, as specified below.  
Such patients will need to be assessed using the Clinicians Interview Based Impression of Severity (CIBIS) scale. The authority application must include the result of the baseline (S)MMSE and specify to which group(s) (see below) the patient belongs.  
Patients who qualify under this criterion are from 1 or more of the following groups:  
(1) Unable to communicate adequately because of lack of competence in English, in people of non-English speaking background;  
(2) Limited education, as defined by less than 6 years of education, or who are illiterate or innumerate;  
(3) Aboriginal or Torres Strait Islanders who, by virtue of cultural factors, are unable to complete an (S)MMSE test;  
(4) Intellectual (developmental or acquired) disability, e.g. Down's syndrome;  
(5) Significant sensory impairment despite best correction, which precludes completion of an (S)MMSE test;  
(6) Prominent dysphasia, out of proportion to other cognitive and functional impairment.  
The application must be made in writing, but initial supply may be sought by telephone.  
For telephone applications, up to a maximum of 2 months' initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month's therapy and sufficient repeats to complete a maximum of up to 6 months' initial treatment.  
For written applications where no prior telephone approval has been issued, up to a maximum of 1 month's therapy plus 5 repeats will be authorised.  

- **Mild to moderately severe Alzheimer disease**  
*Treatment Phase: Continuing*  
**Clinical criteria:**  
Patient must have received six months of sole PBS-subsidised initial therapy with this drug,  
AND  
Patient must demonstrate a clinically meaningful response to the initial treatment,  
AND  
The treatment must be the sole PBS-subsidised therapy for this condition.  
Prior to continuing treatment, a comprehensive assessment must be undertaken and documented, involving the patient, the patient’s family or carer and the treating physician to establish agreement that treatment is continuing to produce worthwhile benefit.  
Treatment should cease if there is no agreement of benefit as there is always the possibility of harm from unnecessary use.  
Re-assessments for a clinically meaningful response are to be undertaken and documented every six months.  
Clinically meaningful response to treatment is demonstrated in the following areas:  
Patient’s quality of life including but not limited to level of independence and happiness;
<table>
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<tr>
<th>Product</th>
<th>Dosage form</th>
<th>Criteria</th>
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<tr>
<td></td>
<td></td>
<td>Patient’s cognitive function including but not limited to memory, recognition and interest in environment; Patient’s behavioural symptoms, including but not limited to hallucination, delusions, anxiety, marked agitation or associated aggressive behaviour.</td>
</tr>
</tbody>
</table>
| Memantine | Tablet      | • **Moderately severe Alzheimer disease**  
**Treatment Phase: Initial**  
**Clinical criteria:**  
Patient must have a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 10 to 14,  
**AND**  
The condition must be confirmed by, or in consultation with, a specialist/consultant physician (including a psychiatrist),  
**AND**  
The treatment must be the sole PBS-subsidised therapy for this condition.  
The authority application must include the result of the baseline MMSE or SMMSE of 10 to 14.  
The application must be made in writing, but initial supply may be sought by telephone.  
For telephone applications, up to a maximum of 2 months’ initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month’s therapy and sufficient repeats to complete a maximum of up to 6 months’ initial treatment.  
For written applications where no prior telephone approval has been issued, up to a maximum of 1 month’s therapy plus 5 repeats will be authorised. |
<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage form</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Memantine | Tablet | • **Moderately severe Alzheimer disease**  
 *Treatment Phase: Initial*  
 **Clinical criteria:**  
 Patient must have a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 9 or less,  
 AND  
 The condition must be confirmed by, or in consultation with, a specialist/consultant physician (including a psychiatrist),  
 AND  
 The treatment must be the sole PBS-subsidised therapy for this condition.  
 A patient who is unable to register a score of 10 to 14 for reasons other than their Alzheimer disease, as specified below.  
 Such patients will need to be assessed using the Clinicians Interview Based Impression of Severity (CIBIS) scale. The authority application must include the result of the baseline (S)MMSE and specify to which group(s) (see below) the patient belongs.  
 Patients who qualify under this criterion are from 1 or more of the following groups:  
 (1) Unable to communicate adequately because of lack of competence in English, in people of non-English speaking background;  
 (2) Limited education, as defined by less than 6 years of education, or who are illiterate or innumerate;  
 (3) Aboriginal or Torres Strait Islanders who, by virtue of cultural factors, are unable to complete an (S)MMSE test;  
 (4) Intellectual (developmental or acquired) disability, eg Down's syndrome;  
 (5) Significant sensory impairment despite best correction, which precludes completion of an (S)MMSE test;  
 (6) Prominent dysphasia, out of proportion to other cognitive and functional impairment.  
 The application must be made in writing, but initial supply may be sought by telephone.  
 For telephone applications, up to a maximum of 2 months’ initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month’s therapy and sufficient repeats to complete a maximum of up to 6 months’ initial treatment.  
 For written applications where no prior telephone approval has been issued, up to a maximum of 1 month’s therapy plus 5 repeats will be authorised.  
 • **Moderately severe Alzheimer disease**  
 *Treatment Phase: Continuing*  
 **Clinical criteria:**  
 Patient must have received six months of sole PBS-subsidised initial therapy with this drug,  
 AND  
 Patient must demonstrate a clinically meaningful response to the initial treatment,  
 AND  
 The treatment must be the sole PBS-subsidised therapy for this condition.  
 Prior to continuing treatment, a comprehensive assessment must be undertaken and documented, involving the patient, the patient’s family or carer and the treating physician to establish agreement that treatment is continuing to produce worthwhile benefit.  
 Treatment should cease if there is no agreement of benefit as there is always the possibility of harm from unnecessary use.  
 Re-assessments for a clinically meaningful response are to be undertaken and documented every six months.  
 Clinically meaningful response to treatment is demonstrated in the following areas:  
 Patient’s quality of life including but not limited to level of independence and happiness;  
 Patient’s cognitive function including but not limited to memory, recognition and interest in |
<table>
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<tr>
<th>Product</th>
<th>Dosage form</th>
<th>Criteria</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Patient’s behavioural symptoms, including but not limited to hallucination, delusions, anxiety, marked agitation or associated aggressive behaviour.</td>
</tr>
</tbody>
</table>

**New Zealand**¹²: In New Zealand, the Pharmaceutical management Agency (PHARMAC) is the agency that decides which medicines, medical devices and related products are subsidized. Exhibit 7 outlines the funding of drugs for the treatment of dementia. Note that in May 2015, only one generic brand is funded for donepezil.

**Exhibit 7: Drugs for the treatment of dementia (New Zealand)**

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage form</th>
<th>Special authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Tablet</td>
<td>None</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Patch</td>
<td><strong>Initial application</strong> from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria: Both: 1. The patient has been diagnosed with dementia; and 2. The patient has experienced intolerable nausea and/or vomiting from donepezil tablets. <strong>Renewal</strong> from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria: Both: 1. The treatment remains appropriate; and 2. The patient has demonstrated a significant and sustained benefit from treatment.</td>
</tr>
</tbody>
</table>

**Scotland**:
In Scotland, cognitive enhancers have been evaluated for use within NHS Scotland.¹³ See Exhibit 8 for advice for cognitive enhancers in Scotland.

**Exhibit 8: Cognitive Enhancers (Scotland)**

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage form</th>
<th>Special authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (2007)</td>
<td>Orodispersible tablet</td>
<td>Recommended for symptomatic treatment of mild to moderately severe Alzheimer’s dementia in patients for whom donepezil is appropriate and who have difficulty in swallowing solid oral dose formulations.</td>
</tr>
<tr>
<td>Rivastigmine (2007)</td>
<td>Transdermal patch</td>
<td>Recommended for symptomatic treatment of moderately severe Alzheimer’s dementia only. It is suitable for patients in whom rivastigmine is an appropriate choice of acetylcholinesterase inhibitor and in whom a transdermal patch is an appropriate choice of formulation.</td>
</tr>
<tr>
<td>Product</td>
<td>Dosage form</td>
<td>Special authority</td>
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</tr>
<tr>
<td>Galantamine (2005)</td>
<td>Capsules (prolonged release)</td>
<td>Recommended for Reminyl XLP®P prolonged-release capsules is accepted for use in NHS Scotland for the treatment of mild-to-moderately severe dementia in Alzheimer’s disease in patients for whom therapy with galantamine is appropriate. It allows the reduction of dosing frequency to once daily and, at a given dose, involves no additional cost compared with immediate-release formulations of galantamine.</td>
</tr>
<tr>
<td>Memantine (2004)</td>
<td>Tablet</td>
<td>Not recommended for use within NHS Scotland</td>
</tr>
</tbody>
</table>

**Summary**

- In the United States, most drug plans (in particular Medicaid-based plans) provide coverage for all of the available cholinesterase inhibitors (generic versions) as well as memantine. Most plans do not require prior authorization for coverage.
- In Australia, cholinesterase inhibitors are available under the “authority required-streamlined” system (similar to the Limited Use system in Ontario). Memantine requires prior authorization for coverage.
- New Zealand only provides coverage for donepezil (generic-single source) and rivastigmine patch (when nausea and vomiting is associated with donepezil).
Part B: Guidelines for the pharmacological interventions for the cognitive symptoms of Alzheimer’s disease

Various consensus recommendations and guidelines are available for the management of patients with Alzheimer’s disease and other dementias.

Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: Pharmacological recommendations for the symptomatic treatment of dementia (2013)

The fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia reviewed previous recommendations and revised where necessary, in light of new data from randomized controlled trials.

Recommendations:

- ChEIs are recommended as a treatment option for AD disease with cerebrovascular disease.
- We recommend ChEIs as a treatment option for dementia associated with Parkinson’s disease.
- There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available ChEIs for the treatment of vascular dementia.
- All three ChEIs have demonstrated efficacy for mild to severe AD. We recommend a trial of a ChEIs for most patients with AD.
- Direct comparisons do not suggest differences between ChEIs. Selection of which agent to be used will be based on the adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.
- There is insufficient evidence to recommend for or against the combination of a ChEI and memantine.
- Discontinuing ChEIs in patients with moderate to severe AD may lead to worsening of cognitive function and greater functional impairment as compared with continued therapy. This risk must be balanced with the risk for known side-effects and drug costs if therapy continues. It is suggested that ChEIs be discontinued when:
  (i) the patient and/or their proxy decision-maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation;
  (ii) the patient is sufficiently nonadherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
  (iii) the patient’s rate of cognitive, functional, and/or behavioral decline is greater on treatment compared with that prior to being treated;
  (iv) the patient experiences intolerable side effects that are definitely or probably related to the ChEI;
  (v) the comorbidities of the patient make continued use of the agent either unacceptably risky or futile (for example, terminally ill); or
  (vi) the patient’s dementia progresses to a stage (for example, Global Deterioration Scale stage 7) where there would be no clinically meaningful benefit from continued therapy.
When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, the suggestion is that the dose be tapered before stopping the agent and that the patient be monitored over the next 1 to 3 months for evidence of an observable decline. If this decline occurs, it is suggested that consideration be given to reinstating therapy.

NICE (National Institute for Health and Care Excellence): Dementia-supporting people with dementia and their carers in health and social care (CG42)\(^{15}\)

This guideline, which was initially developed in 2007 and updated in 2011, is based on the best available evidence for the treatment and care of people with dementia. In April 2015, a decision was made to update the current guideline (http://www.nice.org.uk/guidance/ta217/documents/ta217-alzheimers-disease-donepezil-galantamine-rivastigmine-and-memantine-review-decision-april-2015) The recommendations related to the pharmacologic interventions for the cognitive symptoms of Alzheimer’s disease are as follows:

- **Recommendation 1.6.2:** The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine are recommended as options for managing mild to moderate Alzheimer’s disease under all of the conditions specified in 1.6.2.3 and 1.6.2.4.
- **Recommendation 1.6.2.2:** Memantine is recommended as an option for managing Alzheimer’s disease for people with:
  - moderate Alzheimer’s disease who are intolerant of or have a contraindication to AChE inhibitors or
  - severe Alzheimer’s disease.
    - Treatment should be under the conditions specified in 1.6.2.3.
- **Recommendation 1.6.2.3:** Treatment should be under the following conditions:
  - Only specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people) should initiate treatment. Carers’ views on the patient’s condition at baseline should be sought.
  - Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.
  - Patients who continue on treatment should be reviewed regularly using cognitive, global, functional and behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care. Carers’ views on the patient’s condition at follow-up should be sought.
- **Recommendation 1.6.2.4:** If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence,
medical comorbidity, possibility of drug interactions and dosing profiles.

- **Recommendation 1.6.2.5**: When using assessment scales to determine the severity of Alzheimer’s disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural backgrounds.

- **Recommendation 1.6.2.6**: When assessing the severity of Alzheimer’s disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include:
  - if the cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient’s dementia because of the patient’s learning difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education or
  - if it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia or
  - if there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia. In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment.

- **Recommendation 1.6.2.7**: For people with learning disabilities, tools used to assess the severity of dementia should be sensitive to their level of competence. Options include:
  - Cambridge Cognitive Examination (CAMCOG)
  - Modified Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)
  - DMR
  - Dementia Scale for Down Syndrome (DSDS), which can be useful in diagnosis of dementia in people with learning disabilities who do not have Down’s syndrome.

**EFNS guidelines for the diagnosis and management of Alzheimer’s disease**

The European Federation of Neurological Societies guideline for the diagnosis and management of Alzheimer’s disease was revised in 2010. Recommendations for the treatment using cognitive enhancers in patients with Alzheimer’s disease were made.

- In patients with AD, treatment with ChEIs (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues.
  - Benefits on cognitive and non-cognitive symptoms have been demonstrated in those with mild, moderate and severe disease. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (good practice point).
In patients with moderate to severe AD, treatment with memantine should be considered taking into account expected therapeutic benefits and potential safety issues (Level A).

- Benefits on cognitive and noncognitive symptoms are apparent, some non-cognitive symptoms (agitation, delusions) may respond better than others (Level B). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (good practice point).

**EFNS-ENS/EAN: Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer’s disease**

The EFNS recently developed guidelines for the concomitant use of cholinesterase inhibitors and memantine in Alzheimer’s disease.

- Use of a combination of cholinesterase inhibitors plus memantine rather than cholinesterase inhibitors alone may provide useful benefits in patients with moderate to severe Alzheimer’s disease. Despite statistically significant differences, the observed treatment effects remain modest in terms of clinical management of individual patients. The overall strength of recommendation was weak.

**British Association for Psychopharmacology: Clinical practice with anti-dementia drugs-a revised (second) consensus statement**

An expert consensus group from the British Association for Psychopharmacology convened to review and grade the strength of current evidence, and to consider revised guidelines for the use of anti-dementia drugs. The following recommendations were made for patients with Alzheimer’s disease:

- There is evidence to the efficacy of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer’s disease and evidence for memantine in moderate to severe Alzheimer’s disease.
- There is evidence to support the switching of one cholinesterase inhibitor to another if the first is not tolerated or effective.
- There is some evidence for adding memantine to a cholinesterase inhibitor, but also a negative study. Until further studies are available the benefits of combination therapy is unclear.

**American Psychiatric Association: Practice guideline for the treatment of patients with Alzheimer’s disease and other dementias**

The American Psychiatric Association Work Group on Alzheimer’s Disease and other Dementias developed guidelines for the treatment of patients with dementia, including Alzheimer’s disease. Recommendations for the use of cholinesterase inhibitors are as follows:

- Cholinesterase inhibitors should be offered to patients with mild to moderate Alzheimer’s disease after a thorough discussion of their potential risks and benefits, and they may be helpful for patients with severe Alzheimer’s disease.
- Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson’s disease.
• Cholinesterase inhibitors can be considered for patients with dementia with Lewy bodies.
• Memantine may be considered for use in patients with moderate and severe Alzheimer’s disease.

Summary

• Five guidelines/consensus recommendations were reviewed for treatment of patients with Alzheimer’s disease.
• All guidelines recommend the use of cholinesterase inhibitors for treatment of patients with mild to moderate Alzheimer’s disease; use in patients with severe disease is recommended in one guideline. Memantine for treatment of patients with moderate/severe disease is recommended as monotherapy in four guidelines. However, two guidelines commented that there is insufficient evidence to recommend combination of memantine and a cholinesterase inhibitor.
• Choice of cholinesterase inhibitor will depend on cost, adverse effect profile, ease of use and familiarity with specific product.

Part C: Impact of different drug reimbursement schemes for cognitive enhancers

Methods

A literature search was conducted in Pubmed using the terms: (cholinesterase inhibitors OR rivastigmine OR donepezil OR galantamine or memantine) AND (healthcare accessibility OR health policy OR reimbursement incentive OR national health programs OR cost sharing) and dementia. Bibliographies of identified articles were scanned for additional relevant articles.

Results

Different drug reimbursement schemes for cholinesterase inhibitors and memantine, including prior authorization and step therapy, have been used in public drug plans. However, the impact of these drug reimbursement schemes on outcomes (e.g., time to institutionalization) has not been investigated. One study was identified that examined the appeal process in Taiwan for cholinesterase inhibitors for patients denied coverage through prior authorization. Another study was identified that examined the usage of cholinesterase inhibitors in dually eligible Medicare and Medicaid beneficiaries compared to private Medicare supplements.

In Taiwan, the National Health Insurance plan requires prior authorization for use of cholinesterase inhibitors for outpatient care. Criteria for approval included approval by specialists (neurologist or psychiatrists) as having probable mild to moderate Alzheimer’s disease (MMSE 10-26 or Clinical Dementia Rating of 1 or 2). A total of 12,237 cases of donepezil and 6,975 cases of rivastigmine were submitted for prior authorization between 2000 and 2002. The authorization rate was 72.6% for
donepezil and 66.5% for rivastigmine. Of those patients initially denied authorization, only 124 cases were submitted as appeal; only 14 (10.5%) patients were granted authorization. Reasons for denial of prior authorization included insufficient evidence for an accurate diagnosis of Alzheimer’s disease, insufficient documentation or evaluation of severity, and failure to rule out the suspected causes of non-Alzheimer’s disease-related dementia.

A cross-sectional prevalence study was done to establish estimates of use of agents to treat Alzheimer’s disease, including cholinesterase inhibitors. A lower level of use of cholinesterase inhibitors was noted in dually eligible Medicare and Medicaid beneficiaries than in patients with other sources of Medicare supplementation. In LTC settings, residents covered by Medicaid were approximately half as likely to be treated with a cholinesterase inhibitor as those with a private Medicare supplemental policy (19.2% vs 37.8%). This was similar in the community, although rates of drug use were lower (15.5% vs 29.4%, respectively). It is unknown whether these differences are due to payment policy or other factors not addressed in this study.

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<th>Summary</th>
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<tr>
<td>• There is a lack of literature investigating various reimbursement schemes for cholinesterase inhibitors and memantine for patients with Alzheimer’s disease.</td>
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**Part D: Summary of Selected Topics**

**Rating scales for Alzheimer’s disease**

Rating scales have been used for the diagnosis of Alzheimer’s disease, as well as staging, assessment and monitoring of symptoms associated with Alzheimer’s disease as well as for the evaluation of treatment effects. Many scales have been developed that measure various domains of Alzheimer’s disease, including cognition, function (able to carry out activities of daily living) and behavior. Other scales including overall dementia severity and caregiver burden are also used in the assessment of patients with Alzheimer’s disease.

Although many Alzheimer’s disease assessment scales focused on cognition, it has been recognized that functional and behavioural symptoms may be more relevant to the patient’s quality of life, institutionalization as well as caregiver burden. Clinical trials evaluating treatment modalities for patients with Alzheimer’s disease routinely measure cognition, behavior, function as well as an assessment of patient’s global impression.

An ideal scale to use in routine clinical practice should be: 1) practical, easy and quick to administer; 2) validated for Alzheimer’s disease; 3) multi-domain including cognition, activities of daily living, behaviour, communication/social interaction and quality of life; 4) applicable to all Alzheimer’s disease severity stages; 5) able to monitor disease progression; and 6) sensitive to measure therapy effects.
Cognitive decline is the most characteristic feature of Alzheimer’s disease. An appropriate test to measure cognitive decline must show adequate reliability and validity in detecting the presence and severity of cognitive dysfunction. There should be easy and more difficult items in each of the cognitive domains (e.g., language, spatial skills, memory). The sensitivity of the test is limited if there is a lack of difficult items to assess patients with milder cognitive dysfunction; this is known as a “ceiling” effect. In contrast, sensitivity is hampered if there is a lack of easier items for patients with more severe cognitive dysfunction, leading to “floor” effects.  

A recent systematic review and meta-analysis evaluated the diagnostic performance of cognitive tests for the detection of dementia. Eleven screening tests were identified among 140 studies with over 49,000 participants. The most frequently used test was the MMSE, with a sensitivity and specificity for the detection of dementia at 0.81 (95% CI, 0.78-0.84) and 0.89 (95% CI, 0.87-0.91), respectively. The Mini-Cog test and Addenbrooke’s Cognitive Examination-Revised (ACE-R) had the best diagnostic performances, comparable to the MMSE (Mini-Cog, 0.91 sensitivity and 0.86 specificity; ACE-R, 0.92 sensitivity and 0.89 specificity). The Montreal Cognitive Assessment had comparable performance to the MMSE on detection of mild cognitive impairment with 0.89 sensitivity and 0.75 specificity.

The Montreal Cognitive Assessment (MoCA) is a commonly used cognitive test in the community. MoCA assesses attention/concentration, executive functions, conceptual thinking, memory, language, calculation and orientation. The MoCA was designed as a screening tool for mild cognitive impairment (MCI); however, it is too difficult for patients with moderate and severe Alzheimer’s disease, and therefore is not considered appropriate for use in this population. Although not validated, the following ranges may be used to grade severity: 18-26 = mild cognitive impairment, 10-17 = moderate cognitive impairment and less than 10 = severe cognitive impairment.

A review of all rating scales for Alzheimer’s disease is beyond the scope of this rapid review. Rather an overview of cognitive scales that have been used in clinical trials. These scales were chosen based on the frequency of use in a systematic review of clinical trials evaluating treatment in patients with Alzheimer’s disease. A total of 135 (97 primary studies and 38 companion reports) studies were included, and assessment scales used in the evaluation of patients with Alzheimer’s disease were reviewed. A total of 80 cognitive scales were identified, of which the most frequently used scales were:

- Mini Mental State Exam (82 studies)
- Alzheimer’s Disease Assessment Scale-Cognitive subscale (63 studies)
- Clinical Dementia Rating Scale (15 studies)

Mini-Mental State Examination (MMSE): This assessment tool is easy to administer in the clinical setting, takes approximately 5-10 minutes to administer and measures cognitive function in the areas of orientation, memory, attention and calculation, language and visual construction, on a 30-point scale, with higher values indicating higher cognitive function. The MMSE has decreased utility for detecting dementia in patients with minimal cognitive deficits or those with low education levels; however MMSE is useful in diagnosing and monitoring patients with mild to moderate dementia. The MMSE score, for
example, denotes the severity of cognitive impairment as follows: mild Alzheimer’s disease: MMSE 21–26, moderate Alzheimer’s disease: MMSE 10–20, moderately severe Alzheimer’s disease: MMSE 10–14, severe Alzheimer’s disease: MMSE less than 10.\textsuperscript{30} Note that the MMSE is a licensed and copyright test, available for purchase.\textsuperscript{31}

Alzheimer’s Disease Assessment Scale-Cognitive section (ADAS-cog)\textsuperscript{32}: is a detailed cognitive assessment for dementia used primarily in clinical trials. It takes approximately 40 minutes to administer, making it an impractical tool for assessment in a clinical setting. A four-point difference between treatment groups is considered a clinically important difference.\textsuperscript{22}

Clinical Dementia Rating (CDR) scale\textsuperscript{33}: This scale is based on semi-structured interview of the patient and a reliable informant (e.g., caregiver) and characterizes six domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. It classifies people with dementia into four categories: questionable, mild, moderate and severe. Limitations of the CDR scale include length of time to administer the test (approximately 60-90 minutes) and reliance on clinical judgment and collateral source information.\textsuperscript{34}
The Washington University Alzheimer’s Disease Research Center (ADRC) holds the United States Copyright for the Clinical Dementia Rating (CDR) and associated training materials.

A study evaluated the Mini-Mental State Examination (MMSE) scores onto the Clinical Dementia Rating scale categories in 524 individuals with probably Alzheimer’s disease. The MMSE discriminated well between CDR stages questionable (0.5), mild (1), moderate (2) and severe (3) but performed poorly in the separation between CDR stages zero and 0.5.\textsuperscript{35} The MMSE range for mild AD (CDR 1) was 21-25, for moderate (CDR score 2) 11-20, and for severe (CDR score 3) less than 10.

Summary: There are numerous rating scales that have been used in the assessment and monitoring of patients with Alzheimer’s disease. The most common cognitive scales that are used in clinical trials include the MMSE, CDR and ADAS-cog. However, the CDR and the ADAS-cog are lengthy to administer and not practical in a clinical setting. The MMSE is advocated for use in patients with Alzheimer’s disease. However, the scale is copyrighted and a license should be obtained prior to the use of this scale. The MoCA, an assessment tool that is used by many clinicians, has not been validated in patients with moderate or severe Alzheimer’s disease.

Discontinuation of Cholinesterase Inhibitors
The optimal duration of therapy with cholinesterase inhibitors has not been established, in particular when to discontinue a cholinesterase inhibitor because of a perceived lack of clinical benefit. Duration of treatment during randomized controlled trials has been relatively short, generally ranging from 3-6 months.\textsuperscript{29} Although there have been several open-label extension and observational studies that have used enrolled patients for more than one year, since these studies are uncontrolled, their results should be interpreted with caution.\textsuperscript{36,37}

In the DOMINO (Donepezil and Memantine in Moderate to Severe Alzheimer’s Disease) study, patients
with moderate-to-severe Alzheimer’s disease were treated with donepezil for a minimum of 3 months and then randomized to continue donepezil, stopping donepezil, stopping donepezil and starting memantine, or adding memantine. Patients who continued on the donepezil scored on average 1.9 points higher on a standardized MMSE (minimum clinically important difference 1.4) than patients who had donepezil discontinued (95% CI, 1.3 to 2.5). In a double-blind trial, institutionalized patients (n=40) with moderate to severe Alzheimer’s disease and treated with a cholinesterase inhibitor for at least two years were randomized to cholinesterase inhibitor continuation or discontinuation for 8 weeks. There was no significant difference in proportion of patients with global worsening (based on Clinicians’ Global Impression of Change scale) in the two groups.

In a retrospective cohort study of nursing home residents (n=178) treated with cholinesterase inhibitor monotherapy, patients who discontinued a cholinesterase inhibitor were significantly more likely than those who continued on the cholinesterase inhibitor to show behavioural worsening, and to exhibit symptoms of repetitive behavior. The decision to discontinue a cholinesterase inhibitor based on perceived lack of efficacy is challenging. In a questionnaire that obtained Canadian clinician’s perceptions on discontinuation of a cholinesterase inhibitor, most respondents agreed that progression to a severe stage (i.e., Global Deterioration Scale 7 indicating development of swallowing difficulties) was a trigger to discontinue the medication. However, the MMSE was seen as unhelpful for making decisions about discontinuation.

The Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (2012) indicates that discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer’s disease may lead to worsening of cognitive function and greater functional impairment as compared with continued therapy. They suggest that cholinesterase inhibitors be discontinued when:

a. The patient and/or their proxy decision-maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation
b. The patient is sufficiently nonadherent with the medication
c. The patients’ rate of cognitive, function and/or behavioural decline is greater on treatment compared with that prior to being treated
d. The patient experiences intolerable side effects
e. The comorbidities of the patient make continued use of the agent unacceptably risk or futile (e.g., terminally ill)
f. The patient’s dementia progresses to a stage (for example, Global Deterioration Scale stage 7) where there would be no clinically meaningful benefit from continued therapy.

Although there are no trials investigating whether tapering is needed before discontinuation of a cholinesterase inhibitor, some clinicians recommend tapering. If the patient shows significant deterioration in their symptoms after discontinuation, then consideration should be made to restart therapy.

**Summary:** There is limited data to guide clinicians regarding discontinuation of cholinesterase inhibitors
in patients with Alzheimer’s disease. Based on review of the evidence, some groups suggest that discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer’s disease may lead to worsening of cognitive function. However, these findings may not be applicable to patients with moderate to severe Alzheimer’s disease who are institutionalized.

Use of Cholinesterase Inhibitors on Patients with Mild Cognitive Impairments

Dementia is a process which occurs over time in Alzheimer’s Disease. Mild cognitive impairment (MCI) is a precursor stage to dementia. The newest published criteria define MCI as “a change in cognition, impairment in one or more cognitive domains, preservation of independence in functional abilities...[and absence of dementia]”, although there is not a clear consensus on the definition of MCI in the literature. Another common definition is a Mini Multiple State Examination (MMSE) of 24-30, having a memory complaint, showing abnormal memory for one’s age group and absence of dementia. The prevalence of MCI was found to be 3-42% in patients over 65 years of age in the literature. This large variation in prevalence is primarily due to different definitions of MCI in different settings. In a Canadian study based on the Canadian Study of Health and Aging in 2003, the prevalence of MCI was found to be 3.02%.

Being able to identify and treat a precursor stage to dementia, which is irreversible, could have extremely beneficial public health implications. As such, several studies have evaluated the use of cholinesterase inhibitors (ChEI), which are currently used to treat Alzheimer’s Disease, in patients with MCI, in order to improve cognition and/or delay/prevent progression to Alzheimer’s-induced dementia.

A 2012 Cochrane meta-analysis of randomized controlled trials (RCT) of cholinesterase inhibitors in patients with MCI reviewed nine studies of 5149 individuals. The review found no overall effect of ChEIs on conversion to dementia at one or three years (0.69; 95% confidence interval (CI) 0.47 to 1.00); (0.84; 95% CI 0.70 to 1.02). The review did find a decreased risk of conversion (0.67; 95% CI 0.55 to 0.83) at two years; however, this estimate originated from two studies in the same paper, and should be interpreted with caution. In addition, the review found an increased risk of adverse events, such as muscle spasms/leg cramps, headaches, syncope, insomnia, dizziness and abnormal dreams, in the ChEI group compared to placebo (RR 1.09; 95% CI 1.02 to 1.16, p<0.05).

A 2013 meta-analysis reviewed eight RCTs on the effects of donepezil, rivastigmine, galantamine or memantine on cognition. This meta-analysis demonstrated that ChEIs did not improve cognition (Mini–Mental State Examination: 3 randomized clinical trials [RCTs], mean difference [MD] 0.14, 95% confidence interval [CI] –0.22 to 0.50; Alzheimer’s Disease Assessment Scale — cognition subscale: 3 RCTs, standardized MD –0.07, 95% CI–0.16 to 0.01)) or function (Alzheimer’s Disease Cooperative Study activities of daily living inventory: 2 RCTs, MD 0.30, 95% CI –0.26 to 0.86) in patients with MCI. The study also confirmed an association between the ChEIs reviewed, and risk of nausea and diarrhea (nausea: 4 RCTs, RR 3.04, 95% CI 2.52 to 3.66, \( I^2 = 21\% \); diarrhea: 4 RCTs, RR 2.33, 95% CI 1.74 to 3.13, \( I^2 = 55\%)\).

**Summary:** ChEIs are not currently recommended for patients with MCI because they have not been
found to prevent dementia and/or consistently improve cognition, and they are associated with adverse events, particularly gastrointestinal effects such as nausea and diarrhea.

**Use of cholinesterase inhibitors for Parkinson’s disease dementia**

Parkinson’s disease dementia (PDD) occurs when an individual has been diagnosed with Parkinson’s disease, and has a diagnosis of dementia at least twelve months later, with no apparent cause identified. Dementia is defined as severe cognitive impairment that interferes with day-to-day occupational and social functioning. The prevalence of PDD is 25-30% in Parkinson’s Disease patients, 30 per 100,000 inhabitants in the general population and 150-500 per 100,000 in the elderly population, aged 65 years or over.

Two recent meta-analyses were identified that reviewed the use of cholinesterase inhibitors in the treatment of patients with Parkinson’s disease dementia. A 2012 study, which included six randomized controlled trials (RCTs), pooled data from four studies that examined cholinesterase inhibitors administered in patients with PDD only, and two others that included other types of dementia, including dementia with Lewy bodies. The study found positive results, and therefore, recommended cholinesterase inhibitor use in PDD patients. Improvement was observed on the Clinicians Global Impression of Change scale (−0.38, 95% confidence interval (CI) -0.56 to -0.24, p <0.0001), cognitive function as measured by the Mini Mental State Examination (MMSE) (weighted mean difference (WMD) 1.09, 95% CI 0.45 to 1.73, p=0.0008), Alzheimer’s Disease Assessment Scale – Cognition (ADAS-COG) (WMD -2.72, 95% CI -3.61 to -1.83, p < 0.00001) and the Delis-Kaplan Executive Function System (WMD 2.80, 95% CI 1.47 to 4.13, P < 0.0001). The study also found an improvement in behavioural disturbances in patients with PDD treated with cholinesterase inhibitors (SMD -0.20, 95% CI -0.36 to -0.04, P < 0.05). Although the pooled estimate for behavioural disturbances also included a study on Lewy Bodies dementia, this study was negative and likely decreased the estimate of the effect.

A more recent, 2014 meta-analysis, which focused on PDD only, pooled four RCTs, and showed similar results. The study found that cholinesterase inhibitors slowed cognitive decline, as measured by the MMSE (MD=−1.123, 95% CI=−1.638 to −0.608; p=0.001; I²=44.6%) and ADAS-cog (SMD=−0.266, 95% CI −0.399 to −0.133; p<0.0001; I²=0%). Moreover, the treated patients experienced an improvement in global assessment (SMD=−0.287, 95% CI −0.423 to −0.151; p<0.0001; I²=0%) and decreased behavioural disturbances (SMD=−0.152, 95% CI −0.285 to −0.019; p<0.01; I²=0%). The rate of death was also decreased in patients who were treated with cholinesterase inhibitors (OR=0.295, 95% CI 0.108 to 0.806; p<0.05; I²=0%). Additionally, the meta-analysis found that cholinesterase inhibitors did not affect the risk of falls (OR=1.134, 95% CI 0.622 to 2.067; p>0.05; I²=0%) or extent of disability (SMD=−0.134, 95% CI −0.270 to −0.002; p=0.05; I²=38.5%) in treated patients. However, adverse events such as tremor rates (OR=2.805, 95% CI 1.513 to 5.578; p<0.01; I²=0%) and adverse drug reactions such as nausea, vomiting, diarrhea and worsening psychosis and agitation (OR=1.860, 95% CI 1.330 to 2.601; p<0.0001; I²=0%) were significantly increased by cholinesterase inhibitors. The studies reviewed used donepezil and rivastigmine, suggesting a drug class effect, although there was no evidence for galantamine.
**Summary:** Cholinesterase inhibitors are currently recommended for patients with PDD because they have been found to produce positive effects on cognitive function, behavioural disturbances and mortality. However, it is important to note that adverse effects, including increased tremor rates, gastrointestinal side effects and agitation, have been reported with cholinesterase inhibitors in patients with PDD.

**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.  
- 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).
- An advisory was issued in 2014 by Health Canada regarding the risk of serious skin reactions associated with the use of Reminyl ER (galantamine). 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. 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.

**Discussion**

**Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally**

**Availability in Canada**

- Cognitive enhancers are available in various formulations including oral (tablet, capsule, extended release capsule, rapidly disintegrating tablet, solution) and transdermal patch.
- The oral formulations of the cholinesterase inhibitors as well as memantine are available as generic formulations.
- Donepezil is indicated for mild, moderate and severe dementia of the Alzheimer’s type, whereas galantamine and rivastigmine are indicated for mild and moderate AD. Rivastigmine (oral) is indicated for dementia of Alzheimer’s type and dementia associated with Parkinson’s disease.

**Public Plan Listing in Ontario**

- In Ontario, cholinesterase inhibitors are available on the ODB formulary as Limited Use for patients with mild to moderate Alzheimer’s disease.
- Memantine, rivastigmine patch, rivastigmine oral solution and donepezil rapid disintegrating tablet are not listed on the ODB formulary nor are they available through the Exceptional Access Program.
Public Plan Listing in Canada

- All public drug plans in Canada provide coverage for cholinesterase inhibitors, whereas memantine is only available in Quebec.
- All jurisdictions provide coverage for patients with mild to moderate Alzheimer’s disease. No jurisdiction provides coverage for patients with severe disease.
- The MMSE is used for assessment of cognition in all jurisdictions. Alberta also permits the use of the InterRAI-Cognitive Performance Scale.
- Seven jurisdictions require assessment of functional status for coverage.
- Initial approval of cholinesterase inhibitors varies from 3 months (3 jurisdictions) to 24 months (in Alberta). Six jurisdictions have an initial approval period of 6 months.
- Subsequent approval varies from 6-24 month, with 12 months being the most common approval period in 6 jurisdictions.

Selected International Jurisdictions

- In the United States, most drug plans (in particular Medicaid-based plans) provide coverage for all of the available cholinesterase inhibitors (generic versions) as well as memantine. Most plans do not require prior authorization for coverage.
- In Australia, cholinesterase inhibitors are available under the “authority required-streamlined” system (similar to the Limited Use system in Ontario). Memantine requires prior authorization for coverage.
- New Zealand only provides coverage for donezepil (generic-single source) and rivastigmine patch (when nausea and vomiting is associated with donepezil).

Part B: Guidelines for the pharmacological interventions for the cognitive symptoms of Alzheimer’s disease

- Five guidelines/consensus recommendations were reviewed for treatment of patients with Alzheimer’s disease.
- All guidelines recommend the use of cholinesterase inhibitors for treatment of patients with mild to moderate Alzheimer’s disease; use in patients with severe disease is recommended in one guidelines. Memantine for treatment of patients with moderate/severe disease is recommended as monotherapy in four guidelines. However, two guidelines commented that there is insufficient evidence to recommend combination of memantine and a cholinesterase inhibitor.
- Choice of cholinesterase inhibitor will depend on cost, adverse effect profile, ease of use and familiarity with specific product.

Part C: Impact of different drug reimbursement schemes for cognitive enhancers

- There is a lack of literature investigating various reimbursement schemes for cholinesterase inhibitors and memantine for patients with Alzheimer’s disease.
Part D: Rapid Reviews of Selected Topics

- **Cognitive Rating Scales for Alzheimer’s Disease:** There are numerous rating scales that have been used in the assessment and monitoring of patients with Alzheimer’s disease. The most common cognitive scales that are used in clinical trials include the MMSE, CDR and ADAS-cog. However, the CDR and the ADAS-cog are lengthy to administer and not practical in a clinical setting. The MMSE is advocated for use in patients with Alzheimer’s disease. However, the scale is copyrighted and a license should be obtained prior to the use of this scale. The MoCA, an assessment tool that is used by many clinicians, has not been validated in patients with moderate or severe Alzheimer’s disease.

- **Use of Cholinesterase Inhibitors on Patients with Mild Cognitive Impairments:** Cholinesterase inhibitors are not currently recommended for patients with mild cognitive impairment because they have not been found to prevent dementia and/or consistently improve cognition, and they are associated with adverse events, particularly gastrointestinal effects such as nausea and diarrhea.

- **Discontinuation of Cholinesterase inhibitors:** There is limited data to guide clinicians regarding discontinuation of cholinesterase inhibitors in patients with Alzheimer’s disease. Based on review of the evidence, some groups suggest that discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer’s disease may lead to worsening of cognitive function. However, these findings may not be applicable to patients with moderate to severe Alzheimer’s disease who are institutionalized.

- **Use of cholinesterase inhibitors for Parkinson’s disease dementia:** Cholinesterase inhibitors are currently recommended for patients with PDD because they have been found to produce positive effects on cognitive function, behavioural disturbances and mortality. However, it is important to note that adverse effects, including increased tremor rates, gastrointestinal side effects and agitation, have been reported with cholinesterase inhibitors in patients with PDD.

Health Equity

In Ontario, cholinesterase inhibitors are available on the Public Drug formulary as Limited Use for patients with mild to moderate Alzheimer’s disease. The clinical criteria for cholinesterase inhibitors includes coverage for patients with mild to moderate Alzheimer’s disease, and excludes patients with severe disease. Memantine is not available on the ODB formulary, nor through the Exceptional Access Program.

Conclusion

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 agents are available as generic formulations for at least one oral dosage form.

In Ontario, all cholinesterase inhibitors (most oral formulations) are available as Limited Use on the Ontario Drug Benefit formulary. Across Canada, all public drug plans provide coverage for cholinesterase inhibitors but require special authorization; memantine is only available in Quebec.
Guidelines recommend the use of cholinesterase inhibitors for treatment of patients with mild to moderate Alzheimer’s disease; use in patients with severe disease is recommended in only one guideline.

Cholinesterase inhibitors have been studied in the treatment of patients with mild cognitive impairment as well as in patients with Parkinson’s disease dementia. Cholinesterase inhibitors are not currently recommended for patients with mild cognitive impairment because they have not been found to prevent dementia and/or consistently improve cognition, and they are associated with adverse events, particularly gastrointestinal effects such as nausea and diarrhea. However, cholinesterase inhibitors are recommended for patients with Parkinson’s disease dementia because they have been found to produce positive effects on cognitive function, behavioural disturbances and mortality.
Reference List


(13) Scottish Medicines Consortium. SMC Advice Directory. http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory?ds=Y&searchtext=symbicort&category=&submissionType=&fromDate=From%3A&toDate=To%3A&acceptedForUseCheck=Y&acceptedForRestrictedUseCheck=Y&notRecommendedForUseCheck=Y [2013]


(24) Nyenhuis D, Garron D. Psychometric considerations when measuring cognitive decline in


Appendix 1: Common Drug Review Recommendations

Memantine (Ebixa) (2005)

Recommendation: Do not list
Reasons for recommendation:
- The committee considered the efficacy findings from three randomized controlled trials (RCTs), two comparing memantine to placebo (24-28 weeks) and one comparing memantine plus donepezil to donepezil alone (24 weeks) in patients with moderate to severe Alzheimer’s disease (MMSE 3-14) who were residing in the community. No randomized trials compared memantine to donepezil, galantamine or rivastigmine. Two of the three RCTs reported statistically significant, but numerically small, group mean improvement in instruments measuring activities of daily living and cognition. There is insufficient scientific evidence to establish the clinical importance of these small differences. One trial reported no statistically significant improvement in functional, cognitive, behavioural and global assessments.
- Time to institutionalization was only reported in one study in which very low institutionalization rates were observed (1 of 90 patients on memantine vs 5 of 76 patients on placebo) during the six month study.
- The pharmacoeconomic model submitted by the manufacturer, comparing memantine to standard care, was based on two important assumptions: reduced hospitalization and institutionalization for patients treated with memantine. However, the RCTs did not find any differences in these clinical endpoints in favour of memantine.

Rivastigmine Patch (Exelon Patch) (2008)

Recommendation: Do not list
Reasons for recommendation:
- Compared with placebo, Exelon Patch results in statistically, but clinical very small differences in some of the outcomes measures considered important in Alzheimer’s disease.
- Exelon Patch is associated with a higher incidence of treatment-related adverse events when compared with placebo.
- The Committee had concerns regarding the cost-effectiveness of Exelon Patch relative to best supportive care.
Appendix 2: Webpages for Provincial Drug Formularies

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<thead>
<tr>
<th>Province</th>
<th>Webpage for Drug Formulary</th>
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<tbody>
<tr>
<td>Alberta</td>
<td><a href="https://idbl.ab.bluecross.ca/">https://idbl.ab.bluecross.ca/</a></td>
</tr>
<tr>
<td>Ontario</td>
<td><a href="https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp">https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp</a></td>
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</tr>
<tr>
<td>Prince Edward Island</td>
<td><a href="http://healthpei.ca/formulary">http://healthpei.ca/formulary</a></td>
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</table>
### Appendix 3: Restriction Criteria for Cognitive Enhancers in Canada

<table>
<thead>
<tr>
<th>Province</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Alberta</td>
<td><strong>Cholinesterase inhibitors</strong></td>
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</table>
|                | "For the treatment of Alzheimer’s disease in patients with an MMSE (Mini Mental State Exam) score between 10-26 and/or an InterRAI-Cognitive Performance Scale score between 1-4. Coverage cannot be provided for two or more medications used in the treatment of Alzheimer’s disease (donepezil, galantamine, rivastigmine) when these medications are intended for use in combination. Special authorization coverage may be granted for a maximum of 24 months per request. For each request, an updated MMSE score or InterRAI-Cognitive Performance Scale score and the date on which the exam was administered must be provided. Renewal requests may be considered for patients where the updated MMSE score is 10 or higher or the InterRAI-Cognitive Performance Scale is 4 or lower while on this drug."  
All requests (including renewal requests) for donepezil HCI must be completed using the Donepezil/Galantamine/Rivastigmine Special Authorization Request Form (ABC 30776).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| British Columbia | **Cholinesterase inhibitors**                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                | For coverage, diagnosis must be Alzheimer’s disease, Alzheimer’s disease with a vascular component, Alzheimer’s disease with Lewy bodies or mixed dementia with predominant Alzheimer’s disease.  
**Initiation of coverage in a cholinesterase inhibitor-naïve patient:**  
Coverage will be provided for an initial 6-month period, when the following criteria are met:  
► a Standardized Mini Mental State Examination (SMMSE) score of ≥ 10 to ≤ 26, AND  
► a Global Deterioration Scale (GDS) stage of 4, 5 or 6.  
*Note: Check for tolerability in naïve patients within the first 1 - 3 months.*  
**Continuation of coverage for 6-month periods:**  
Coverage is continued for patients in 6-month increments when:  
► the information provided indicates that the patient remains in the mild to moderate stage of Alzheimer’s disease (if repeat SMMSE testing at 6-month intervals results in scores of ≥ 10  
► a GDS stage of 4, 5 or 6  
AND  
► there is demonstrated stabilization or improvement during the previous six months of therapy.  
**Coverage of another cholinesterase inhibitor is provided for an initial 6 months if:**  
► the clinician documents the reason for discontinuing the previous cholinesterase inhibitor on the Special Authority Renewal/ Switching Form. *Note: Coverage of another cholinesterase inhibitor is provided in the same manner as the previous one (check for tolerability within the first 1 - 3 months, coverage to be renewed in 6-month increments if criteria continue to be met).* |
### Saskatchewan

| Cholinesterase inhibitors | (a) A diagnosis of probable Alzheimer’s disease as per DSM-IV criteria.  
(b) A mild to moderate stage of the disease with a MMSE score of 10-26 established within 60-days prior to application for coverage by a clinician or nurse practitioner.  
(c) A Functional Activities Questionnaire (FAQ) must be completed within 60- days prior to initial application for coverage by a clinician or nurse practitioner.  
(d) Patients must discontinue all drugs with anticholinergic activity at least 14 days before the MMSE and FAQ are administered. Drugs with anticholinergic activity are not to be used concurrently with donepezil (rivastigmine, galantamine) therapy. List all current medications patient was taking at the time of assessment.  
(e) Patients intolerant to one drug may be switched to another drug in this class. Intolerance should be observed within the first month of treatment.  

- **Eligible patients currently taking donepezil** (rivastigmine, galantamine) would require assessment at 6 month intervals. To continue receiving donepezil (rivastigmine, galantamine), patients must not have both a greater than 2 point reduction in MMSE and a 1 point increase in FAQ 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 (rivastigmine, galantamine). During the 3 month trial, patients must exhibit an improvement from the initial MMSE or FAQ to continue treatment with donepezil (rivastigmine, galantamine). The improvement must be at least 2 MMSE points or -1 FAQ. Patients who meet these requirements will be re-evaluated at 6 month intervals. To continue receiving donepezil (rivastigmine, galantamine), patients must not have both a greater than 2 point reduction in MMSE and a 1 point increase in FAQ in a 6 month evaluation period. Scores are compared to the most recent test results.  
- The MMSE score must remain at 10 or greater at all times to be eligible for coverage.  
- Patients who do not meet criteria to continue donepezil (rivastigmine, galantamine) can be re-evaluated within 3 months to confirm deterioration before coverage is discontinued.  
- Donepezil (rivastigmine, galantamine) does not need to be discontinued prior to MMSE or FAQ testing.  
- A patient intolerant of one 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

| Cholinesterase inhibitors | Confirmed diagnosis of Alzheimer’s Disease with DSMIV criteria with: (a) Memory impairment (impaired ability to learn new information or to recall previously learned information); plus b) at least one 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 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: CBC, TSH, Electrolytes,Vitamin B12, and Glucose; and The initial MMSE score must be between 10 and 26 and measured within 30 days of the application. |
### Quebec

| Cholinesterase inhibitors | As monotherapy for persons suffering from Alzheimer’s disease at the mild or moderate stage. Upon the initial request, the following elements must be present: an MMSE score of 10 to 26, or as high as 27 or 28 if there is proper justification; medical confirmation of the degree to which the person is affected (intact domain, mildly, moderately or severely affected) in the following five domains:  
- intellectual function, including memory;  
- mood;  
- behaviour;  
- autonomy in activities of daily living (ADL) and in instrumental activities of daily living (IADL);  
- social interaction, including the ability to carry on a conversation.  
The duration of an initial authorization for treatment with donepezil is six months from the beginning of treatment. However, where the cholinesterase inhibitor is used following treatment with memantine, the concomitant use of both medications is authorized for one month. Upon subsequent requests, the physician must provide evidence of a beneficial effect confirmed by each of the following elements: an MMSE score of 10 or more, unless there is proper justification; a maximum decrease of 3 points in the MMSE score per six-month period compared with the previous evaluation, or a greater decrease accompanied by proper justification; stabilization or improvement of symptoms in one or more of the following domains:  
- intellectual function, including memory;  
- mood;  
- behaviour;  
- autonomy in activities of daily living (ADL) and in instrumental activities of daily living (IADL);  
- social interaction, including the ability to carry on a conversation.  
The maximum duration of authorization is 12 months. |
<table>
<thead>
<tr>
<th>New Brunswick</th>
<th><strong>Cholinesterase inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memantine</strong></td>
<td>As monotherapy for person suffering from Alzheimer’s disease at the moderate or severe stage who are living at home, specifically, who do not live in a residential and long-term care centre that is either a public institution or a private institution under agreement. Upon the initial request, the following elements must be present: an MMSE score of 3 to 14; medical confirmation of the degree to which the person is affected (intact domain, mildly, moderately or severely affected) in the following five domains:  - intellectual function, including memory;  - mood;  - behaviour;  - autonomy in activities of daily living (ADL) and in instrumental activities of daily living (IADL);  - social interaction, including the ability to carry on a conversation. The duration of an initial authorization for treatment with memantine is six months from the beginning of treatment. However, where memantine is used following treatment with a cholinesterase inhibitor, the concomitant use of both medications is authorized for one month. Upon subsequent requests, the physician must provide evidence of a beneficial effect confirmed by stabilization or improvement of symptoms in at least three of the following domains:  - intellectual function, including memory;  - mood;  - behaviour;  - autonomy in activities of daily living (ADL) and in instrumental activities of daily living (IADL);  - social interaction, including the ability to carry on a conversation. The maximum duration of the authorization is six months.</td>
</tr>
<tr>
<td><strong>New Brunswick</strong></td>
<td>For a patient being started on a first cholinesterase inhibitor (ChEi): Patients who meet all of the following reimbursement criteria will be approved for an initial 6 months of therapy: a. a diagnosis of probable Alzheimer’s disease or possible Alzheimer’s disease with vascular component or Lewy bodies; b. a Mini Mental Score Exam (MMSE) score of 10 to 30; and c. a Functional Assessment &amp; Staging Test (FAST) score of 4 to 5 For a patient who has previously taken no more than one other ChEi and is switching: Patients will be approved for an initial 6 months of therapy with a second ChEi when the following information is provided: • the reason for discontinuing the first ChEi Requests to switch from one agent in the class to another will not be considered beyond the initial 6 month approval. To continue therapy for 1 year period (once initial 6 month approval has been completed): Patients who meet the following monitoring criteria will be approved for 1 year periods of therapy: a. MMSE score of 10 to 30 (Note: MMSE score must be provided 6 months after starting a ChEi and then only annually thereafter.); AND b. FAST score of 4 to 5 (Note: FAST score must be provided 6 months after starting a ChEi and then only annually thereafter.) Note: Monitoring of target symptoms will no longer be required; however, physicians will be asked at the initial and subsequent reassessments if, in their opinion, the patient is benefiting from the drug.</td>
</tr>
<tr>
<td>Province</td>
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</tr>
<tr>
<td><strong>Cholinesterase inhibitors</strong></td>
<td></td>
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<tr>
<td><strong>Ontario Drug Policy Research Network</strong></td>
<td></td>
</tr>
</tbody>
</table>
| For the treatment of mild to moderate probable Alzheimer’s disease or possible Alzheimer’s disease with vascular component, with Lewy bodies who meet the following criteria:  
· a Mini-Mental State Examination (MMSE) score of 10 to 30 AND  
· a Functional Assessment Staging Test (FAST) score of 4 to 5  
- initial requests for reimbursement will be considered for a maximum 4 month approval; subsequent requests may be considered for a maximum 12 month approval. Requests to switch from one agent in the class to another will not be considered beyond the initial 4 month approval |
| **PEI** |
| For the treatment of patients with a diagnosis of mild to moderate probable Alzheimer’s Disease (AD) or possible Alzheimer’s Disease with a vascular component, with Lewy bodies, or other factors (as specified) and who meet the following criteria:  
1. Initial 90-day Trial  
An initial 90-day trial using an available ChEI is available to patients who:  
   a. Have a diagnosis of probable or possible AD, AND  
   b. 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 a neurologist, psychiatrist or geriatrician supporting the diagnosis and treatment), AND  
   c. Have not previously used a ChEI, AND  
   d. Have a Mini Mental State Examination (MMSE) score of between 10 and 24. An MMSE 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. All MMSEs must be completed within 90-days of the request for coverage. Patients unable to tolerate the first ChEI or where their MMSE score remained between 10 and 24, but declined significantly during the trial, may also qualify for a second 90-day trial using a different ChEI. Patients must stop the first ChEI before coverage for the second 90-day trial of a ChEI will be approved.  
2. Continued Coverage Continued coverage of ChEIs may be available to patients who  
   a. Participated in a 90-day trial of a ChEI during which their MMSE score remained between 10 and 24 and either stabilized or improved, OR  
   b. Have been previously approved for 12-months of coverage, during which their MMSE score remained above 10 and either stabilized or improved. All MMSEs must be completed within 90-days of the request for coverage. Continued coverage will not be approved for patients where their latest MMSE score is less than 10 or has dramatically decreased during the previous trial or monitoring period. Continued coverage will be approved for a maximum of twelve (12) months at a time. |
| **Yukon** |
| For mild or moderate Alzheimer’s (with MMSE score 10-26 within previous 3 months). Reviewed on a case-by-case basis. Review after first 6 months, then yearly. Reapply with updated MMSE score each time. Only one drug approved at any time; no combination therapy. Not for patients already living in a dementia care facility. |
| **Newfoundland** |
| For the treatment of patients with a diagnosis of mild to moderate Alzheimer’s Disease or possible Alzheimer’s Disease with vascular component, with Lewy bodies or other (as specified) who meet the following criteria:  
Initiation of coverage of a cholinesterase inhibitor (ChEI) - New Request:  
Patients who meet all of the following reimbursement criteria will be approved for an initial 180 days of therapy. Coverage is provided for an initial 180 days when all the following criteria are met:  
   A Mini-Mental State Examination (MMSE) score of 10 to 30 AND;  
   A Functional Assessment Staging Test (FAST) score of 4 to 5;  
Request for Continuation of Cholinesterase Inhibitor - Renewal Request: Patients who meet the following monitoring criteria will be approved for 12 months of therapy at a time:  
   A MMSE score of 10 to 30 (Note: A MMSE test must be performed no sooner than 2 months prior to the expiry date of the previous approval of the ChEI.);  
   A FAST score of 4 to 5 (Note: A FAST test must be performed no sooner than 2 months prior to the expiry date of the previous approval of the ChEI.); and  
   Evidence of benefit: Is the patient benefiting from this drug? Please describe. (only for initial reassessment) |
| NIHB Cholinesterase inhibitors | Limited use benefit (prior approval required).  
Initial six month coverage for cholinesterase inhibitors:  
• Diagnosis of mild to moderate Alzheimer's disease; AND  
• Mini Mental State Exam (MMSE) score of 10-26, established within the last 60 days; AND  
• Global Deterioration Scale (GDS) score between 4 to 6, established within the last 60 days  
• Continued coverage beyond 6 months will be based on improvement or stabilization of cognition, function or behaviour.  
Criteria for coverage at every six month interval:  
• Diagnosis is still mild to moderate Alzheimer's disease; AND  
• MMSE score > 10; OR GDS score between 4 to 6; AND  
• Improvement or stabilization in at least one of the following domains (please indicate improved, worsened, or no change) 1. Memory, reasoning and perception (e.g., names, tasks, MMSE) 2. Instrumental activities of daily living (IADLs: e.g., telephone, shopping, meal preparation) 3. Basic activities of daily living (e.g., bathing, dressing, hygiene, toileting) 4. Neuropsychiatric symptoms (e.g., agitation, delusions, hallucination, apathy)|
**Appendix 4: Interview Questions**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long have you listed cognitive enhancers on your provincial formulary? How are they listed (e.g., restricted, general benefit)?</td>
<td></td>
</tr>
<tr>
<td>Why did you decide to list cognitive enhancers this way?</td>
<td></td>
</tr>
<tr>
<td>What was the basis for this listing (e.g., quantity limits, general listing)?</td>
<td></td>
</tr>
<tr>
<td>Do you have any studies comparing usage/costs before and after implementation of this listing?</td>
<td></td>
</tr>
<tr>
<td>Why are certain cognitive enhancers NOT funded?</td>
<td></td>
</tr>
<tr>
<td>Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?</td>
<td></td>
</tr>
<tr>
<td>Do you have any special restrictions regarding the use of cognitive enhancers in the elderly?</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5: Tiered cost-sharing options

<table>
<thead>
<tr>
<th>Prescription Drug Plan</th>
<th>Tier 1 (generic)</th>
<th>Tier 2 (preferred brand)</th>
<th>Tier 3 (non-preferred brand)</th>
<th>Tier 4 (specialty)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan A</td>
<td>$5</td>
<td>$28</td>
<td>$55</td>
<td>25%</td>
</tr>
<tr>
<td>Plan B</td>
<td>$2</td>
<td>$20</td>
<td>$40</td>
<td>N/A</td>
</tr>
<tr>
<td>Plan C</td>
<td>$10</td>
<td>$25</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Plan D</td>
<td>$4</td>
<td>$17</td>
<td>75%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Adapted from: