Guideline for Cognitive Impairment: Dementia Diagnosis to Management

Introduction

This guideline was developed by an Alberta Clinical Practice Guidelines Program working group to assist physicians in the management of cognitive impairment/decline. A companion guideline for the diagnosis of the cognitively impaired patient accompanies this document.

Issues

- Aging population and increased prevalence of dementia in the aged
- Constraints in health-care resources
- Management of dementia requires unique clinical skills
- Increased need for primary care practitioners to participate in the management of dementia

Guideline Goals

- To improve confidence in managing dementia
- To support primary care physicians in developing management plans utilizing available resources
- Management involves non-pharmacologic strategies and assessment to determine the need for pharmacologic interventions

Recommendations

- Refer patient/caregiver to the Alzheimer Society of Alberta: 1-866-950-5465 for education, support, and respite care
- Discuss wills, enduring power of attorney and personal directives with patient/caregiver.
- Explore the possibility of safety issues (see below) including gathering information about capacity to drive a motor vehicle.
- Ensure patients and families understand the value of home care services
- Support from caregivers, family, friends and community resources to maximize optimal independent functioning
- Promote a safe environment by identifying and modifying potential risks (i.e., unplug the electric stove, mark the one-touch start button on the microwave, ensure smoke detector is working)
- Healthy diet, regular exercise and smoking cessation have other health benefits and may help dementia patients as well.
- Provide opportunities for caregiver respite to prevent caregiver burn-out

Non-pharmacologic

- PHARMACOLOGIC MANAGEMENT

Both pharmacologic and non-pharmacologic approaches are the subject of intense research activity. As time goes on, new approaches will be developed and the practitioner should remain alert to them.

The above recommendations are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. They should be used as an adjunct to sound clinical decision making.
Alzheimer Disease (AD)

- Donepezil (Aricept®)
  - Initiate with 5 mg once daily
  - May be increased to 10 mg daily after at least 4 weeks
  - should not exceed 10 mg daily
  - Available as a tablet and rapidly disintegrating tablet in 2 sizes for each formulation

- Rivastigmine (Exelon®)
  - 1.5 mg bid for 4 weeks, then
  - 3 mg bid for 4 weeks, then
  - 4.5 mg bid for 4 weeks, then
  - 6 mg bid
  - Titrate to maximum tolerated dose
  - Taken with food
  - The drug is available as a tablet (various sizes), oral solution and transdermal patch in 2 strengths.

- Galantamine (Reminyl®)
  - Initiate with 8 mg ER daily
  - Increase dose to 16 mg ER after at least 4 weeks
  - Dose can be increased to 24 mg ER after an additional 4 weeks
  - Recommended dose 16 mg to 24 mg daily
  - Taken with food
  - Available as a tablet and an extended release tablet in various dosage strengths.

Note:
- With all three compounds, patients and caregivers should be alerted about the possible development of GI side effects shortly after exposure (i.e., anorexia, nausea, vomiting, diarrhea or weight loss) as well as headache or muscle cramps. Rarely delirium can develop shortly after initial exposure.
- Side effects can be serious and include: delirium, confusion, hypotension, syncope, seizures, arrhythmias, bradycardia and prolonged QT interval.

CAUTION WHEN PRESCRIBING CHOLINESTERASE INHIBITORS IF:

- Epilepsy or history of seizures
- Asthma
- Cardiac arrhythmia (except atrial fib.)
- Peptic ulcer disease
- Urinary tract blockage or difficult urination

Vascular Dementia (VaD)

- Manage vascular risk factors (i.e., hypertension, diabetes, smoking, sedentary lifestyle, lipid abnormalities, arrhythmias and valvular heart disease).
- There is ongoing research looking at the utility of cholinesterase inhibitors in the treatment of VaD. This is not currently an accepted indication for the use of cholinesterase inhibitors
- In mixed dementia (AD + vascular), cholinesterase inhibitors likely have a role because of the presence of Alzheimer pathology. A reasonable approach would be to manage vascular risk factors and give a trial of a cholinesterase inhibitor.

Dementia with Lewy Bodies (DLB)

- Case studies, case series and one randomized controlled trial have shown that cholinesterase inhibitors, in particular Rivastigmine (Exelon®), can have a beneficial effect on the symptoms of this type of dementia. To date though, cholinesterase inhibitors have not
been approved for this indication.
- Many, if not most, patients with DLB also have Alzheimer pathology. If Alzheimer pathology is suspected, a trial of a cholinesterase inhibitor should be considered.
- Patients with DLB have an exaggerated response to neuroleptics (e.g., haloperidol, loxapine, risperidone); therefore the use of these agents is hazardous and requires specialized skill.

Referral for Management
- There are a number of instances where referral may be useful. These include:
  - Atypical course or lack of response to standard treatment
  - Symptoms that are causing acute distress or jeopardising safety
  - Difficult behavioural problems

Treating Alzheimer Disease (AD)
All patients diagnosed with dementia should be assessed for their suitability for pharmacologic treatment.

Pharmacologic Treatment
The pathological changes in AD involve the cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. A decrease in the function of these cholinergic pathways has been proposed to account for some of the clinical manifestations of dementia such as core cognitive, behavioural and functional symptoms.
Comparison of Donepezil, Rivastigmine and Galantamine

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 5 mg qd 4-6 weeks, then</td>
<td>• 1.5 mg bid x 4 weeks then</td>
<td>• 8 mg ER daily x 4 weeks then</td>
<td>• 5 mg daily x 1 week then</td>
</tr>
<tr>
<td></td>
<td>• Increase to 10 mg qd if tolerated</td>
<td>• 3 mg bid x 4 weeks then</td>
<td>• 16 mg ER daily if tolerated</td>
<td>• 5 mg bid x 1 week then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 4.5 mg bid x 4 weeks then</td>
<td>• After 4 weeks or more at 16 mg option to increase to 24 mg ER daily</td>
<td>• 5 mg daily + 10 mg daily x 1 week then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 6 mg bid if tolerated</td>
<td>• Take with food</td>
<td>• 10 mg bid</td>
</tr>
</tbody>
</table>

| Drug Interaction Risk | Potentially because of protein binding (96%) and metabolism by cytochrome P450 (2D6 and 3A4) | Low | • 18% protein binding | • 45% protein binding  |
|                      |                                               |     | • CYD2D6 and CYP3A4 are the major enzymes involved in galantamine metabolism | • carbonic anhydrase inhibitors, Na bicarb decreased clearance by 80% (produce alkaline conditions pH 8) |
|                      |                                               |     | • Galantamine did not inhibit metabolic pathways of CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1 (low inhibitory potential on cytochrome P450 enzymes) | • drugs using the same renal cation transport system as Memantine could potentially alter levels of either agent (cimetidine, ranitidine, quinidine, hydrochlorothiazide, trimaterene, nicotine) |
|                      |                                               |     |                         | • excreted mostly unchanged in urine            |

| Bioavailability | • 100% | • 35.5% due to 1st pass effect from liver esterases | • 88% | • 100% |
| Selectivity     | • Selective for AChE | • Selective for AChE and BuChE | • Selective for AChE | • NMDA-receptor controlled cation channels |
| Mechanism of Action | • Reversible mixed inhibitor of AChE binding mainly outside the active site | • “Pseudo-irreversible” competitive inhibitor of AChE and BuChE binding at active site | • Acetylcholinesterase inhibitor | • Low-moderate, uncompetitive NMDA-receptor antagonist |
| Common Side Effects | 10 mg/day* | 6 to 12 mg/day | 16 mg/day | NA** |
|                   | 6% | 15% | 4% | 2.8% |
|                   | 9% | 9% | 5% | 9% |
|                   | 3% | 3% | NA** | NA** |
|                   | 5% | 14% | NA** | NA** |
|                   | 3% | 4% | NA** | NA** |
|                   | 6% | NA** | NA** | NA** |
|                   | 3% | NA** | NA** | NA** |
|                   | NA** | NA** | NA** | NA** |
|                   | NA** | NA** | NA** | NA** |
|                   | NA** | NA** | NA** | NA** |
|                   | Very low - not above placebo levels | Very low in comparison to placebo | Very low in comparison to placebo |

*Incidence seen after 6 - week initial treatment with 5 mg/day *

*Not available in product monographs
New therapies have emerged for AD over the past five years. The most successful to date have been the cholinesterase inhibitors (ChEIs). They partially correct the cholinergic deficit seen in AD by inhibiting the breakdown of acetylcholine. The ChEIs include donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®). All of these compounds exert a favourable symptomatic effect on the course of AD. This impact is seen in cognitive, functional, behavioural, and global assessments.

Initially, these medications were believed to be useful only for the early stages of AD but evidence is now available to show a response of patients with moderately advanced to severe stages of the disease. Donepezil, rivastigmine and galantamine have a positive effect on the behavioural changes in the later stage AD, particularly apathy, anxiety and depression.

Of those patients who can tolerate the medication, about half will demonstrate some benefit in cognition, activities of daily living, caregiver observations, or some combination of the three. Some, possibly a quarter to a third will show short term improvement; the other responders appear to stabilize and decline less rapidly after the initiation of therapy. Attention tends to improve most (less apathy) while function can also heighten. There is growing evidence that these drugs might help with the behavioural problems seen late in the course of AD.

When considering a cholinesterase inhibitor it is important to review past history for features that would add risk when using this class of medication.

- Caution use is recommended for patients with: seizures, asthma, arrhythmias (except atrial fibrillation), active peptic ulceration and bladder outlet obstruction.
- Potential adverse effects of treatment need to be considered including: arrhythmia, prolonged QT, bradycardia, syncope, hypotension, delirium, confusion, loss of appetite and weight loss.

These potential adverse effects need to be weighed against the potential benefits prior to use.

**Donepezil**

Donepezil (Aricept®) is a reversible inhibitor of acetylcholinesterase (AChE) approved in Canada for the symptomatic treatment of mild to moderate dementia of the Alzheimer’s type. It exerts its therapeutic effect through inhibition of the hydrolysis of acetylcholine (ACh) by AChE.

Clinical trials have demonstrated that Donepezil treatment does result in modest improvement in cognition scores and in the slowing of the rate of decline of cognition as well as measures of behaviour and general functioning. When Donepezil is discontinued there is a rapid decline over the following six weeks to the level of function that would have resulted if treatment had never occurred. This effect may appear to caregivers as an acceleration of the disease and should be carefully explained. A decline after discontinuation indicates benefit. Consideration should be given to reintiation of treatment within 2 to 3 weeks. Treatment should be initiated with 5 mg daily in the morning and continued for 4 to 6 weeks. An increase to 10 mg after this time may give some additional benefit. Doses over 10 mg should not be used.
Common side effects are predictable from the drug’s effect on the cholinergic nervous system, i.e., nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. Side effects are usually mild and resolve without the need to discontinue the drug or change the dose. Slower dosage titration usually results in a lower incidence of adverse drug reactions. Caution should be exercised in patients with a history of arrhythmias, gastrointestinal ulcers, urinary retention, seizures, asthma or obstructive pulmonary disease. There have been reports of mania associated with donepezil use in patients with dementia and another concurrent psychiatric disorder.\(^5\)

**Rivastigmine**

Rivastigmine is a reversible inhibitor of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The activity of BuChE is known to increase with increasing severity of dementia; however, the significance of therapeutic change to this activity is not known. Two double-blind placebo controlled studies, of 6 months duration, in patients with mild to moderately severe AD, have shown positive effects on cognition, behaviour and activities of daily living.

Rivastigmine (Exelon®) is indicated for the treatment of mild to moderate AD. The dose range is 3.0 mg to 12.0 mg daily. The usual maintenance dose is 6 to 12 mg per day. Titration needs to be slow (2- to 4-week intervals) to reduce the gastrointestinal side effects. Titrate to maximum tolerated doses.

**Galantamine**

Galantamine (Reminyl®) is stated to be a modulator of nicotinic receptors as well as cholinesterase inhibitor. The potential benefits of the dual action remain unproven. The drug affects the same receptor as ACh but attaches to a different binding site, not de-sensitizing the receptors as do nicotinic agonists. Galantamine is now available daily at an ER preparation. The standing dose is 8 mg x 1 month, working up to 16 - 24mg daily.

**Memantine**

Memantine (Ebixa®) is a N-methyl-D-aspartate (NMDA) receptor antagonist that acts as a partial receptor blocker for the excitatory amino acid glutamate. Glutamate regulates the movement of calcium in the cells, which is necessary for memory and learning. In AD, there are excessive amounts of glutamate because there are fewer brain cells available to take in the calcium. Memantine does not stop progression of AD but, compared with placebo, it improves function, cognition, and global scores in advanced dementia patients. There is emerging evidence of benefits to disruptive behaviors that may exceed the behavioural benefits of Cholinesterase inhibitors.

It is indicated as monotherapy or as adjunctive therapy with cholinesterase inhibitors for the symptomatic treatment of patients with moderate to severe AD (patients with an MMSE of 14 or below). Side effects include headache, nausea, agitation, dizziness, hallucinations, and lowered seizure threshold. Concurrent use of amentadine, dextromethorphan, and ketamine should be avoided. If renal function is low (creatinine clearance 40-60 ml/min/1.73m2) daily dose should be reduced to 10 mg/day.
Treating Vascular Dementia
Prevention of VaD is potentially possible by the management of vascular risk factors. Interventions could include the use of antihypertensives, agents for lipid abnormalities, anticoagulants for certain arrhythmias and other types of heart disease, and platelet inhibitors (e.g., ASA) for secondary prevention in high risk individuals. VaD appears to present with similar acetylcholine deficits as AD and indeed may coexist with AD. Preliminary evidence suggests that these patients may derive as much or more benefit from AChE inhibition.

Treating Dementia with Lewy Bodies
DLB is another cause of established cognitive impairment that primary care physicians should understand. This entity contains pathological findings of both AD (cholinergic depletion) and Parkinson’s Disease (dopaminergic depletion). There is a 2:1 male predominance. Such patients present with fluctuating cognitive decline (resembles delirium) associated with falls, extrapyramidal rigidity, and frequently, visual hallucinations and sensitivity to neuroleptics. The usual span of this illness from onset of symptoms to death tends to be 3 to 6 years, shorter than that of AD (8 to 12 years). The response to cholinesterase inhibitors (Exelon® best studied) tends to be positive.

Treatment of behavioural disturbances with traditional neuroleptics in DLB should be undertaken with care because these drugs may result in a severe adverse drug reaction including deterioration in cognitive function, parkinsonism, drowsiness and some features of neuroleptic malignant syndrome.

While the use of any neuroleptic is risky with DLB, the atypical neuroleptics (e.g., olanzapine, quetiapine, and clozapine) might be safer to use than the traditional neuroleptics. If used, monitor carefully and only prescribe in small doses.

Other Treatments

Vitamin E
Regarding Vitamin E in the prevention and/or treatment of AD, the Canadian Consensus Conference on Dementia concluded:

“There is currently insufficient evidence to recommend the use of Vitamin E for the treatment or prevention of AD. At the doses evaluated in clinical trials, there were side effects in some patients. The benefits of the treatment or prevention on AD of low dose Vitamin E has not been evaluated.”

There was a dissenting opinion which supported its use. There are as yet no proven benefits and the increased risk of hemorrhagic stroke with even 400

Ginkgo Biloba
Regarding Ginkgo Biloba and the treatment for AD, the Canadian Consensus Conference on Dementia concluded that:
Other herbal strategies for dementia have unproven benefit.

**Estrogen**

In a study by Mulnard and colleagues, 10 120 women with mild to moderate AD were randomized to estrogen 0.625 mg/day or 1.25 mg/day or placebo. Cognitive, global and other outcome measures were evaluated at screening, baseline, and 2, 6, 12 and 15 months. The authors concluded that the women taking high or low dose estrogen showed no improvement in their cognition and no slowing of the disease progression. Overall the results of studies on hormone replacement therapy for dementia are inconclusive. Some studies with early use of estrogen found benefit while others found no benefit. At present there is insufficient evidence to support use of estrogens for Alzheimer disease prevention or treatment. The potential side-effects of estrogen use are significant and therefore extra caution is recommended since the benefits of this treatment for dementia remain unproven.

Research is being done on other hormonal factors such as LH agonists.

**NSAIDs**

Aspirin and other NSAIDs have been proposed in the treatment because of epidemiological data to protect against the development of AD. 11 One theory is cytokines promote synthesis of amyloid precursor protein, which is precursor of betaamyloid. There has been observed a low rate of AD in patients with rheumatoid arthritis and several reports with NSAID use suggest a lower rate of AD in patients on these medications. However, the utility of NSAIDs in the prevention of AD is still under investigation. 12 Recent therapeutic studies have been negative.
2. Exelon product monograph, CPS 2001
3. Aricept product monograph, CPS 2001
7. Alberta Health and Wellness Drug Benefit List, Refreshed August 1, 2001
15. McKeith I; Del Ser T; Spano P; Emre M; Wesnes K; Anand R; Cicin-Sain A; Ferrara R; Spiegel R. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000 Dec 16;356(9247):2031-6.
Toward Optimized Practice (TOP) Program
Arising out of the 2003 Master Agreement, TOP succeeds the former Alberta Clinical Practice Guidelines program, and maintains and distributes Alberta CPGs. TOP is a health quality improvement initiative that fits within the broader health system focus on quality and complements other strategies such as Primary Care Initiative and the Physician Office System Program.

The TOP program supports physician practices, and the teams they work with, by fostering the use of evidence-based best practices and quality initiatives in medical care in Alberta. The program offers a variety of tools and out-reach services to help physicians and their colleagues meet the challenge of keeping practices current in an environment of continually emerging evidence.

To Provide Feedback
The TOP Program encourages your feedback. If you need further information or if you have difficulty applying this guideline, please contact:

Toward Optimized Practice Program
12230 - 106 Avenue NW
EDMONTON, AB T5N 3Z1
T 780. 482.0319
TF 1-866.505.3302
F 780.482.5445
E-mail: cpg@topalbertadoctors.org

Adult Insomnia: Assessment to Diagnosis. February 2006.
Revised February 2007.
Reviewed 2008
### Special Authorization for Donepezil HCL, Rivastigmine Hydrogen Tartrate, and Reminyl

For the treatment of Alzheimer’s disease in patients with a Mini Mental State Exam (MMSE) score between 10 – 26.

This drug must be initiated by a designated prescriber for new patients (individuals who have never taken Aricept™ before or who have taken the drug for 60 days or less) with an MMSE score between 10 – 13 inclusive.

Specialists in Geriatric Medicine, Neurology, and Psychiatry are deemed designated prescribers by virtue of their specialty in medical practice. All other practitioners will be added to the list of designated prescribers if they have successfully completed MAINPRO C Credits through the College of Family Practice (physicians).

All requests (including renewal requests) for Aricept must be completed using the Aricept™/Exelon™ Special Authorization Request Form (ABC 30776). For each request, an updated MMSE score and the date on which the exam was administered must be provided. The MMSE score must be within 3 months of the time of the application (including renewal requests). Renewal requests, for patients where the updated MMSE score is greater than 26 while on Aricept™, may also be considered.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Formulation</th>
<th>Batch Number</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>Oral Tablet</td>
<td>00002232043</td>
<td>ARICEPT™</td>
</tr>
<tr>
<td>10 mg</td>
<td>Oral Tablet</td>
<td>00002232044</td>
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</tbody>
</table>

### Rivastigmine Hydrogen Tartrate


This drug must be initiated by a designated prescriber for new patients (individuals who have never taken Exelon™ before or who have taken the drug for 60 days or less) with an MMSE score between 10 – 13 inclusive.

Specialists in Geriatric Medicine, Neurology, and Psychiatry are deemed designated prescribers by virtue of their specialty in medical practice. All other practitioners will be added to the list of designated prescribers if they have successfully completed MAINPRO C Credits through the College of Family Practice (physicians).

All requests (including renewal requests) for Exelon must be completed using the Aricept™/Exelon™ Special Authorization Request Form (ABC 30776). For each request, an updated MMSE score and the date on which the exam was administered must be provided. The MMSE score must be within 3 months of the time of the application (including renewal requests). Renewal requests, for patients where the updated MMSE score is greater than 26 while on Exelon™, may also be considered.

<table>
<thead>
<tr>
<th>Strength (Base)</th>
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<th>Batch Number</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>1.5 mg</td>
<td>Oral Capsule</td>
<td>00002242115</td>
<td>EXELON™</td>
</tr>
<tr>
<td>3 mg</td>
<td>Oral Capsule</td>
<td>00002242116</td>
<td>EXELON™</td>
</tr>
<tr>
<td>4.5 mg</td>
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<td>EXELON™</td>
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<td>6 mg</td>
<td>Oral Capsule</td>
<td>00002242118</td>
<td>EXELON™</td>
</tr>
</tbody>
</table>
Reminyl
For the treatment of Alzheimer’s disease in patients with an Mini Mental State Exam (MMSE) score between 10-26.

This drug must be initiated by a designated prescriber for new patients (individuals who have never taken Reminyl before or who have taken the drug for 60 days or less) with an MMSE score between 10-13 inclusive.

Specialists in Geriatric Medicine, Neurology, and Psychiatry are deemed designated prescribers by virtue of their specialty in medical practice. All other practitioners will be added to the list of designated prescribers if they have successfully completed MAINPRO-C credits through the College of Family Practice (Physicians) or the Care of the Elderly Six-month/One-year Fellowship Program through the Department of Family Medicine.

All requests (including renewal requests) for Reminyl must be completed using the Aricept/Exelon/Reminyl Special Authorization Request Form (ABC 30776). For each request, an updated MMSE score and the date on which the exam was administered must be provided. The MMSE score must be within 3 months of the time of the application (including renewal requests).

Renewal requests for patients where the updated MMSE score is greater than 26 while on Reminyl, may also be considered.