



Appendix E: Comprehensive Pharmacotherapy Information for Acetylcholinesterase Inhibitors and Memantine

Acetylcholinesterase Inhibitors (AChEIs)

AChEIs include donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon®). AChEIs are approved for the symptomatic treatment of mild to moderate Alzheimer's disease. Donepezil is the only AChEI indicated for severe Alzheimer's disease. Studies report modest improvements or stabilization of dementia symptoms. Benefits were demonstrated in cognitive function, activities of daily living, behavioural and measures of global function but none of these treatment effects are large.^{1,2} Currently, there is insufficient evidence for AChEIs in the outcome measures of delayed institutionalisation, mortality, severe disease progression, and reduction of caregiver burden.³ In studies with global outcomes (subjective assessment by clinician and/or caregiver of change overall), the number needed to treat is 12 (three to six months) for one additional patient to experience stabilization or improvement on global response.⁴

Evidence regarding the long-term use of AChEIs is limited, with the majority of clinical trials being 12 months or less in duration. In one 24 month trial, there were no significant differences between donepezil and placebo on the primary endpoints of institutionalization and progression of disability; however, the results are limited by the trial design, in which patients in the treatment group were subjected to multiple interruptions in treatment.⁵

While some evidence suggests a role for AChEIs in the treatment of symptoms associated with severe Alzheimer's disease and in other types of dementias (vascular dementia and dementia with Lewy bodies),^{6,7} the clinical meaningfulness of randomized controlled trial outcome measures is controversial and donepezil is the only AChEI currently approved by Health Canada for severe Alzheimer's disease. There is no evidence of beneficial effect in progression from mild cognitive impairment to dementia at one, two, and three years of AChEI use in mild cognitive impairment.⁸

► Adverse effects

Common adverse events are gastrointestinal effects, particularly nausea, vomiting, diarrhea, and anorexia. Relative to placebo, adverse effects occur in approximately 8% more patients (number needed to harm = 12) on AChEI therapy.⁹ Adverse events are the main cause of attrition in the clinical trials, with approximately 29% and 18% of patients treated with AChEIs and placebo, respectively, withdrawing prematurely from the clinical trials.¹

Summary of the most common adverse events by AChEI type^{9, 12}

AChEI	Common adverse effects	NNH
donepezil	Diarrhea	8
	Nausea	20
galantamine	Nausea at 24mg/day	5
rivastigmine (oral)	Nausea	6
	Vomiting	7
rivastigmine (patch)	Administration site skin conditions	8
	Vomiting	33
	Nausea	50

► Alzheimer's Drug Therapy Initiative

The Alzheimer's Drug Therapy Initiative (ADTI) was started in British Columbia in 2007 to gather evidence on the efficacy, safety and cost-effectiveness of AChEIs for the treatment of mild to moderate Alzheimer's disease. The ADTI consisted of a meta-analysis and systematic review of AChEIs on patient outcomes in mild to moderate Alzheimer's disease, four research studies completed by the University of Victoria and one research study completed by the University of British Columbia.

The ADTI found that the average change in SMMSE score was +1.6 points (out of 30) in AChEI-naive patients at 6 months; this was consistent with observations in RCTs and was considered to be a small change compared to natural fluctuations between the first and second SMMSE in individual patients. There were no differences in outcomes for the different AChEIs.

The results of the ADTI showed no significant differences in clinical benefit and/or safety between the three AChEIs. The ADTI also reported insufficient evidence of therapeutic benefit of switching to a different AChEI if a patient experiences clinical ineffectiveness on one AChEI. As such, for patients new to AChEIs, prescribers should consider initiating therapy with the least costly AChEI (donepezil). Consider oral rivastigmine or galantamine in patients who are unable to tolerate donepezil.

In patients with mild to moderate Alzheimer's disease, no statistical differences in efficacy between rivastigmine patches and capsules were reported. Relative to rivastigmine capsule, low dose patches were reported to have fewer nausea, vomiting, weight loss, dizziness, decreased appetite, and headache events, but higher rates of diarrhea. High dose patches and capsules demonstrated higher rates of adverse events as compared to low dose patches. The rivastigmine patch is substantially more costly than oral formulations of AChEIs (refer to Appendix F for drug cost and drug coverage information).

For further information on the ADTI research, visit www.gov.bc.ca/pharmacareprescribers.

► Initiation of therapy

Decision to initiate AChEI therapy requires an individualized patient assessment, involving the patient and caregivers in the following discussion points:

- Clinician, patient, and caregiver expectations of benefit with AChEI therapy.
- Presence of comorbidities and life expectancy.
- Potential drug interactions with concurrent medications.
- Ability of the patient or caregiver to adhere to pharmacotherapy.
- Potential benefits as compared to potential harms of AChEI therapy.
- Patient and caregiver preferences, including cost of therapy.

If a trial of AChEI therapy is to be initiated, develop and implement a monitoring plan:

- Document baseline symptoms and define goals for therapy.
- Encourage caregivers to maintain a written record of symptoms, adverse drug reactions, sleep disturbances, and personal impressions to support ongoing patient assessment.
- Carefully monitor for adverse effects, particularly during the first three months of therapy. A three month titration period is required to develop tolerance and minimize adverse effects.¹
- Assess tolerability and adverse effects two weeks after medication initiation and two weeks after each dosage change.¹⁰
- Until a stable maintenance dose is achieved, schedule regular follow up appointments based on the titration schedule of the medication.
- Once a maintenance dose is reached, monitor for efficacy by assessing changes in cognition, function, behaviour, and global assessment of change every three months. Continue to monitor for adverse effects every three months.¹⁰

► Management strategies for adverse effects of AChEIs^{1, 2, 10–19}

- Use a longer titration period. Gastrointestinal adverse effects, such as nausea, vomiting, and diarrhea, are dose related.
- Titration period of up to 12 weeks may be required to develop tolerance and minimize adverse effects.
- Administer oral doses with food.
- A short course of an antiemetic, such as domperidone, may be administered during the titration period. Avoid antiemetics with anticholinergic properties, such as dimenhydrinate, as these agents may worsen cognition or cause delirium.

Rivastigmine transdermal patch ^{11, 12, 15, 16, 17, 19, 20}

- Rotate application site of rivastigmine patch daily. Do not use the same application site within 14 days.
- Application to upper arm, upper back or chest may reduce the risk of skin irritation relative to application to the abdomen or upper thigh.
- Minimize the use of harsh soaps and do not apply patch immediately after cleansing.
- Trimming hair at application site, as opposed to shaving, may reduce skin irritation.
- Remove patch slowly and delicately.
- Management of dermatitis at the application site by pre-treating the skin site with two puffs of aerolized fluticasone propionate (250µg/puff) prior to patch application has been documented. Following patch removal, the skin site was treated with once daily application of 0.05% betamethasone dipropionate glycol ointment for three days.²⁰

See *Appendix F: Medication Table (for the treatment of cognitive impairment in the elderly)*

► Relative contraindications

- Patients with serious cardiovascular disease were excluded from clinical trials. Avoid use in patients with cardiac conduction abnormalities (except right bundle branch block), such as sick sinus syndrome, bradycardia, atrioventricular block, or unexplained syncope. Use cautiously in active coronary artery disease and congestive heart failure.
- Increased gastric acid secretion may result from increased cholinergic activity. Use cautiously in patients at risk of ulceration, such as those with peptic ulcer disease or concurrent non-steroidal anti-inflammatory drug use.
- Use cautiously in obstructive urinary disease, as AChEIs may worsen symptoms.
- Use cautiously in patients with history of seizure or seizure disorder, as AChEI may increase seizure risk.
- Increased cholinergic activity due to AChEIs may worsen symptoms in significant bronchospastic disease.
- Dose adjustments or avoidance of use may be necessary in severe renal or hepatic disease (see *Appendix F: Medication Table* for dosing details).

► Potential drug interactions

All AChEIs

- Avoid concurrent cholinomimetic agents, such as succinylcholine, neuromuscular blocking agents, or cholinergic agonists, due to synergistic effects (i.e., may potentiate muscle relaxants used during anaesthesia).
- Avoid concurrent use of agents with anticholinergic properties, such as oxybutinin, tricyclic antidepressants, including cyclobenzaprine (Flexeril), paroxetine, or certain nonprescription medications such as dimenhydrinate and diphenhydramine, due to antagonistic effects.
- Monitor closely if medications with similar adverse effects as AChEIs are administered concurrently.
- Review product monographs at hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php and regularly review current Health Canada advisories, warnings and recalls at www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index_e.html.

Donepezil and galantamine

- Substrates of cytochrome P450.
- CYP2D6 and CYP3A4 inhibitors, such as paroxetine, erythromycin, ketoconazole, or quinidine, may increase the risk of toxicity of donepezil and galantamine.
- Cimetidine does not significantly affect metabolism of donepezil, but does increase the bioavailability of galantamine by approximately 16%.¹²
- CYP2D6 and CYP3A4 inducers, such as carbamazepine, phenytoin, phenobarbital, dexamethasone, or rifampin, may decrease the therapeutic effect of donepezil and galantamine.

Rivastigmine

- Primarily metabolized via hydrolysis; therefore, the risk of cytochrome P450 interactions is expected to be minimal.

► Switching therapy

There is insufficient evidence demonstrating differences in clinical efficacy between donepezil, galantamine, and rivastigmine.^{1, 18, 21} However, tolerability can vary among patients.¹⁰ Considerations in the selection of an alternate AChEI include adverse effect profile, dosing profile, adherence, drug interactions, and comorbidities. When switching to an alternate AChEI, taper the first agent over one to two weeks, while starting the second agent at the lowest possible dose using the same titration schedule as initiation of new therapy.

► Discontinuing therapy

In patients with advanced Alzheimer's disease, practitioners and caregivers should routinely re-evaluate the value of continuing therapy. There is insufficient evidence to guide the difficult decision of continuation or discontinuation of AChEI therapy in advanced Alzheimer's disease. Discontinue treatment when the risks of therapy are assessed to outweigh the perceived benefits. Although further research is warranted, discontinuation of donepezil appears to be generally well tolerated.^{9,22} It is important to ensure prompt assessment by a practitioner should symptoms acutely worsen upon discontinuation of an AChEI. To attenuate potential withdrawal symptoms, consider gradual tapering of AChEIs, as opposed to abrupt discontinuation.

N-methyl-D-aspartate Receptor Antagonist - Memantine

Memantine (Ebixa[®]) is approved by Health Canada as monotherapy or as adjunctive therapy with AChEIs for the symptomatic treatment of patients with moderate to severe Alzheimer's disease. Memantine is not indicated for the treatment of MCI.¹²

Studies suggest that 20 mg per day of memantine offers symptomatic benefit on cognition, behaviour, mood, and functional measures of daily living in moderate to severe Alzheimer's disease at six months.²³ In mild to moderate Alzheimer's disease, studies suggest a marginal benefit in cognitive outcomes and lack of effect on measures of behaviour and activities of daily living.²³ The magnitude of clinical significance and clinically important benefits of memantine remains uncertain.¹⁸ The DOMINO study reported no statistically significant benefits on cognition, function, and behaviour with the addition of memantine to donepezil as compared to donepezil monotherapy in moderate to severe Alzheimer's disease.²⁴ Memantine may be an option for the symptomatic treatment of moderate to severe Alzheimer's disease in patients with intolerance to or contraindications to AChEI treatment.¹⁸

► Adverse effects

Memantine is generally well tolerated and attrition rates from clinical trials are similar between the treatment and placebo groups.²³ The most common adverse effects of memantine include dizziness, headache, somnolence, constipation, and hypertension.

► Relative contraindications

- Renal disease or conditions causing alkalinization of urine, such as renal tubular acidosis, severe urinary tract infection, or drastic dietary changes, may reduce systemic elimination of memantine.
- Use cautiously in patients with history of seizure disorder, as these patients were excluded from clinical trials and memantine may increase seizure risk.
- Use cautiously in patients with cardiovascular conditions, as cardiovascular adverse effects have been observed in clinical trials.
- Hepatic disease (see *Appendix F: Medication Table* for dosing details).
- Ophthalmic disease.

► Potential drug interactions

- Not significantly metabolized by cytochrome P450.
- Primarily renally excreted. Elimination of memantine may be reduced with concurrent use of drugs which alkalinize urine, such as sodium bicarbonate or carbonic anhydrase inhibitors.
- Exercise caution with concomitant use of agents which are renally excreted, such as cimetidine, ranitidine, hydrochlorothiazide, triamterene, quinidine, metformin, or nicotine. Plasma levels of both agents may be altered.
- Avoid concurrent use of agents with properties similar to N-methyl-D-aspartate antagonists, such as amantadine, ketamine, or dextromethorphan, due to increased risk of adverse effects (especially central nervous system effects).
- Therapeutic effects of levodopa, dopaminergic agonists, and anticholinergics may be enhanced and may necessitate dosage adjustment of these agents.
- Review product monographs at hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php and regularly review current Health Canada advisories, warnings and recalls at www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index_e.html.

Other agents

Use of ginkgo biloba, vitamin E, anti-inflammatory drugs (e.g., NSAIDs), estrogen, and statins as pharmacotherapy for dementia is not recommended. There is insufficient evidence of treatment efficacy and/or concerns have been raised regarding the potential risk of negative health impacts.

See *Appendix F: Medication Table*

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