

This optimal use guide is provided for information purposes only and should not replace the practitioner's judgement. For efficacy data on other related diseases, go to iness.qc.ca.

GENERAL

- ▶ Particular caution should be exercised when using drugs (acetylcholinesterase inhibitors (AChEIs) and/or NMDA glutamatergic receptor antagonists (memantine)) to treat Alzheimer's disease (AD) or mixed dementia, given their modest efficacy, their safety profile and the cost of treatment.
- ▶ The decision to use or not use pharmacotherapy is based on an **assessment of the risks and benefits** for the patient and on **their values and preferences**, as well as those of their caregivers. This shared decision is made after an **informed discussion** between the physician, the patient and the caregivers.

BENEFITS AND RISKS ASSOCIATED WITH THE USE OF AChEIs IN THE TREATMENT OF ALZHEIMER'S DISEASE

AVAILABLE SCIENTIFIC DATA

Results	<ul style="list-style-type: none"> ▶ Modest efficacy on cognitive function, the activities of daily living and the global clinical impression of change. ▶ Maximum improvement at 3 months at the therapeutic dose. ▶ No formal conclusions can be drawn from the data as regards the efficacy of AChEIs or memantine on the behavioural and psychological symptoms of dementia.
Limitations	<ul style="list-style-type: none"> ▶ Very few long-term (≥ 6 months) data. ▶ High treatment discontinuation rates in clinical trials. ▶ Not possible to identify a priori patients who will respond well to the treatment.
Conclusion	<ul style="list-style-type: none"> ▶ The clinical benefit that these drugs confer on patients over time is very difficult to assess.

NUMBER NEEDED TO TREAT TO OBSERVE AN IMPROVEMENT IN GLOBAL CLINICAL STATUS¹

Approximately 25 % of the patients who used an AChEI experienced an improvement in their global clinical status compared to 17 % of the subjects who received placebo.

An improvement in global clinical status will be observed in only **1 in approximately 12 subjects** with AD who are treated for 6 months with an AChEI instead of placebo.

NUMBER NEEDED TO TREAT TO OBSERVE ADVERSE EFFECTS LEADING TO TREATMENT DISCONTINUATION

Approximately 13 % of the patients who used an AChEI experienced adverse effects that led to treatment discontinuation compared to 6 % of the subjects who received placebo.

Adverse effects leading to treatment discontinuation will be observed in only **1 in approximately 15 subjects** with AD who are treated for 6 months with an AChEI instead of placebo.

The data presented in this table were calculated from the data from the clinical trials included in Bond and collaborators' systematic review [2012].

1. Global clinical status was measured with the CIBIC-plus scale (Clinician's Interview-Based Impression of Change Plus Caregiver Input). This scale provides a global measurement of the patient's status based on the evaluation of four domains (general, cognition, behaviour and activities of daily living).

TREATMENT OBJECTIVES

- ▶ **Set clear treatment objectives with the patient and their caregivers as soon as treatment is initiated**
 - Considering the coverage criteria in the Régie de l'assurance maladie du Québec (RAMQ)'s Public Prescription Drug Insurance Plan.
- ▶ **Set realistic expectations**
 - Pharmacological therapy will not prevent disease progression or cognitive decline. At best, cognitive decline may improve or stabilize, after which it will continue despite the medication.

PHARMACOLOGICAL TREATMENT OPTIONS¹

	AChEI (MONOTHERAPY)	MEMANTINE (MONOTHERAPY)	AChEI + MEMANTINE (COMBINATION THERAPY)
Mild AD	Indicated ²	Treatment option ³	The available evidence on the efficacy of this combination therapy does not permit a recommendation for or against its use. ^{4,5}
Moderate AD	Indicated ²	Indicated ²	
Severe AD	Treatment option ³	Indicated ²	
Mixed dementia	Treatment option ²	Treatment option ²	

1. INESSS's recommendation following a systematic review of the efficacy and safety of AChEIs and memantine, and consultation with an expert committee.
2. Covered by the RAMQ's Public Prescription Drug Insurance Plan.
3. Not covered by the RAMQ's Public Prescription Drug Insurance Plan.
4. If the AChEI is administered after treatment with memantine or if memantine is administered after treatment with an AChEI, the concomitant use of these two drugs is covered for a period of 1 month.
5. Given that the mechanisms of action are different, one can use a treatment combining an AChEI and memantine. The current data show that this combination is generally well tolerated by patients.

CHOOSING THE INITIAL THERAPY

There are no reliable clinical data indicating a difference in efficacy between the three AChEIs. The factors to be considered when choosing the initial pharmacotherapy are the adverse effects profile, the ease of administration, the pharmacokinetic differences and certain patient-related factors.

PATIENT-RELATED FACTOR	OPT FOR THE FOLLOWING DRUGS :
Severe AD	Donepezil and memantine (monotherapy): official Health Canada indication for treating severe AD.
Dysphagia or lack of cooperation from the patient	Donepezil: available as a rapidly dissolving tablet (Aricept® RDT). Rivastigmine: available as a transdermal patch (Exelon® Patch). Make sure that a reliable caregiver assists the patient in managing the administration of the patch and marks the date on it. AChEIs can be administered as follows ¹ : <ul style="list-style-type: none"> ▶ Donepezil: the tablet can be crushed and mixed with food (e.g., stewed fruit). ▶ Galantamine: the capsule can be opened and its contents mixed with food (e.g., stewed fruit), but the granules should not be chewed or crushed. ▶ Oral rivastigmine: the capsules can be opened and their contents mixed with food (e.g., stewed fruit). ▶ Rivastigmine oral solution: can be mixed with a cold beverage (water, juice or soft drink).
Gastrointestinal intolerance	Of the orally administered AChEIs, donepezil appears to cause the fewest gastrointestinal adverse effects, while rivastigmine appears to cause the most. Of all the AChEIs, the transdermal formulation of rivastigmine is associated with the lowest incidence of gastrointestinal adverse effects.
Treatment adherence	Once-daily administration: donepezil, galantamine and the transdermal formulation of rivastigmine. Once- or twice-daily administration: memantine.
Polypharmacy	Rivastigmine and memantine are not metabolized by cytochrome P450 isoenzymes, which considerably reduces the risk of drug interactions.
Hepatic or renal impairment	Donepezil, rivastigmine: no dosage adjustment if the patient has hepatic or renal impairment. ²
Monthly cost³ of the drug	<ul style="list-style-type: none"> ▶ Donepezil: \$35.42/month ▶ Galantamine: \$37.40/month ▶ Rivastigmine capsules: \$39.08/month ▶ Rivastigmine oral solution: \$114.77/month ▶ Transdermal formulation of rivastigmine (Exelon® Patch 10): \$131.63/month ▶ Memantine: \$37.85/month

1. Based on the clinical experience of the members of INESSS's expert committee, these procedures should be done only at time the drug is administered to the patient.
2. Rivastigmine: contraindicated in the presence of severe hepatic impairment.
3. Provided as information only. Monthly cost of treatment based on the recommended maximum dosage and determined using the price, in the March 2015 edition of the List of Medications, of the generic formulations and the lowest price method, when the latter is applicable. It does not include the average cost of the pharmacist's professional services or the wholesaler's markup.

CHARACTERISTICS AND DOSAGE

ALZHEIMER'S DISEASE AND MIXED DEMENTIA

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	DONEPEZIL	GALANTAMINE	ORAL RIVASTIGMINE	TRANSDERMAL RIVASTIGMINE	MEMANTINE
Trade name	Aricept® Aricept® RDT	Reminyl® ER	Exelon®	Exelon® Patch 5 Exelon® Patch 10 Exelon® Patch 15 ¹	Ebixa®
Mechanism of action	Reversible AChE inhibitor.	Reversible AChE inhibitor and allosteric nicotinic receptor modulator.	Pseudo-irreversible AChE and BuChE inhibitor.		Low- to moderate-affinity, uncompetitive NMDA receptor antagonist.
Elimination half-life	70 hours	7 to 8 hours	1 to 2 hours		60 to 80 hours
Dosage titration regimen	5 mg QD for 4 weeks, then 10 mg QD, if tolerated.	8 mg QD for 4 weeks, 16 mg QD for 4 weeks, then 24 mg QD, if tolerated.	1.5 mg BID for 2 to 4 weeks, 3 mg BID for 2 to 4 weeks, 4.5 mg BID for 2 to 4 weeks, then 6 mg BID, if tolerated. TID dosing may reduce the adverse effects.	5 cm ² QD for 4 weeks, then 10 cm ² QD, if tolerated. 15 cm ² if clinical worsening while on 10 cm ² QD stable for the past several months.	5 mg QD AM for 1 week, 5 mg BID for 1 week, 10 mg QD AM and 5 mg QD in the evening for 1 week, then 10 mg BID, if tolerated.
Dosage titration regimen : patients hypersensitive to adverse effects²	The initial dose can be 2.5 mg QD (and be increased 2 weeks later, if well tolerated). Maximum dosage: 5 mg QD	N/A	The initial dose can be 1.5 mg QD (and be increased 2 weeks later, if well tolerated). Maximum dosage: 3 mg BID	N/A	N/A
Minimum dosage	5 mg QD	16 mg QD	3 mg BID	10 cm ² QD (release rate of 9.5 mg/24 hours)	5 mg BID
Information regarding administration	Take in the morning. Take with food. If dysphagia or lack of cooperation from the patient, Aricept® RDT may be useful.	Take in the morning. Take with food.	Take in the morning and evening. Take with food. An oral solution is available.	Apply the patch on the back, chest or upper arm. Change the application site every day. If intolerance to the glue, consider applying a spray of fluticasone under the patch.	Take with food. Can be administered QD or BID. If BID, take in the morning and at dinnertime (or in the morning and at bedtime, if drowsiness).
Dosage adjustment if renal impairment	No	ClCr 9-60 ml/min : maximum 16 mg/day ClCr < 9 ml/min : contraindicated	No (See "Dosage titration regimen : patients hypersensitive to adverse effects")		ClCr 30-49 ml/min : 5 mg BID ³ ClCr 15-29 ml/min : 5 mg BID ClCr < 15 ml/min : contraindicated
Dosage adjustment if hepatic impairment	No	Moderate HI : maximum 16 mg/day Severe HI : contraindicated	Mild to moderate HI : see "Dosage titration regimen : patients hypersensitive to adverse effects". Severe HI : contraindicated.		Severe HI : contraindicated

AChE : acetylcholinesterase; BuChE : butyrylcholinesterase; NMDA : N-methyl-D-aspartate; RI : renal impairment; ClCr : creatinine clearance; HI : hepatic impairment; N/A : not applicable.

1. Not covered by the RAMQ's Basic Prescription Drug Insurance Plan.

2. For example, patients with a low body weight, aged > 85 years, etc.

3. If well tolerated after at least 7 days of treatment, and based on the clinical response, the dose may be increased up to 10 mg BID according to the standard dosage titration regimen.

MOST COMMON ADVERSE EFFECTS

ACETYLCHOLINESTERASE INHIBITORS	MEMANTINE
<ul style="list-style-type: none"> ▶ Gastrointestinal effects¹: dyspepsia, nausea, vomiting, diarrhea, anorexia, weight loss ▶ Headache ▶ Dizziness ▶ Insomnia ▶ Cardiovascular effects: bradycardia, heart block, syncope ▶ Fatigue 	<ul style="list-style-type: none"> ▶ Dreams with motor agitation, nightmares ▶ Muscle cramps ▶ Confusion ▶ Agitation ▶ Rhinorrhea (donepezil) ▶ Pollakiuria ▶ Adverse effects specific to transdermal rivastigmine: erythema, pruritus
	<ul style="list-style-type: none"> ▶ Dizziness ▶ Constipation ▶ Confusion ▶ Headache ▶ Hypertension ▶ Agitation ▶ Insomnia

1. Gastrointestinal effects are dose-dependent and generally occur at the start of treatment. They are generally mild and temporary.

CONTRAINDICATIONS AND PRECAUTIONS

	DONEPEZIL	GALANTAMINE	ORAL RIVASTIGMINE	TRANSDERMAL RIVASTIGMINE	MEMANTINE
Absolute contra-indications	Hypersensitivity to any of the product's components or to other piperidine derivatives.	Hypersensitivity to any of the product's components. Severe renal or hepatic impairment.	Hypersensitivity to any of the product's components or to other carbamates. Severe hepatic impairment.		Hypersensitivity to any of the product's components. Severe renal or hepatic impairment.
Relative contra-indications	<p>Before prescribing an AChEI, consideration should be given to doing the following in all patients:</p> <ul style="list-style-type: none"> ▶ Administering a cardiovascular questionnaire to identify any arrhythmia, bradycardia, syncope or presyncope; ▶ Measuring the patient's resting pulse to detect any bradycardia (pulse < 55 beats per minute); ▶ Performing an electrocardiogram (ECG), if easily accessible. This is a good practice but is not mandatory. If the patient has indications of any of the signs or symptoms listed above, an ECG should be done from the outset. <p>Before prescribing an AChEI, it is also necessary to specifically check the patient for the following:</p> <ul style="list-style-type: none"> ▶ Sinus bradycardia ▶ Sick sinus syndrome ▶ First-degree or higher atrioventricular block ▶ The use of beta-blockers and/or calcium-channel blockers ▶ The use of drugs that increase the QT interval <p>If any of these apply to the patient, a referral to a specialist, a modification to the concomitant medications and/or the placement of a pacemaker should be considered.</p> <p><i>An isolated right or left bundle-branch block is not a contraindication.</i></p>				N/A
Precautions	<p>Patients at risk for a peptic ulcer.</p> <p>Patients with a history of asthma, COPD, peptic ulcer or seizures.</p>				<p>Genitourinary problems that increase urinary pH (renal tubular acidosis, severe Proteus urinary tract infections).</p> <p>A history¹ of seizures, uncontrolled HT, recent infarction or uncompensated HF.</p>

HF: heart failure; HT: hypertension; COPD: chronic obstructive pulmonary disease; N/A: not applicable.

1. Patients with the health problems listed here were excluded from the clinical studies.

DRUG INTERACTIONS

	DONEPEZIL	GALANTAMINE	RIVASTIGMINE	MEMANTINE
Metabolism	Substrate of cytochrome P450 isoenzymes 2D6 and 3A4	Substrate of cytochrome P450 isoenzymes 2D6 and 3A4	Nonhepatic (hydrolysis)	Nonhepatic (renal)
Pharmacokinetic interactions	Exercise vigilance when administering strong CYP 2D6 and 3A4 inducers (phenytoin, carbamazepine, phenobarbital, rifampin, etc.) or inhibitors (ketoconazole, quinidine, paroxetine, etc.).		N/A	N/A
Pharmacodynamic interactions	<ul style="list-style-type: none"> ▶ Anticholinergics (antagonistic action), e.g., tricyclic antidepressants, SSRI antidepressants, antihistamines, antimuscarinics (treatment of overactive bladder), benzodiazepines, antiarrhythmic (disopyramide), gastrointestinal antispasmodics, muscle relaxants, narcotic analgesics, antiemetics, antipsychotics, atropine and atropine-like drugs (scopolamine, etc.), certain diuretics, certain antiparkinsonians, certain antiepileptics, etc. ▶ Cholinergic agonists (synergistic cholinergic effect), e.g., bethanecol, etc. ▶ Bradycardic agents (additive effect on the heart rate), e.g., beta-blockers, diltiazem, verapamil, digoxin, amiodarone, carbamazepine, etc. ▶ NSAIDs (increased risk of ulcers). ▶ Antipsychotics (increased risk of extrapyramidal effects). ▶ Over-the-counter medications, e.g., antihistamines, ranitidine, dimenhydrinate, loperamide, codeine-containing syrups, NSAIDs, etc. 		<ul style="list-style-type: none"> ▶ Drugs that make urine alkaline (reduced renal excretion of memantine), e.g., sodium bicarbonate, carbonic anhydrase inhibitors, etc. ▶ NMDA receptor antagonists (possible increase in adverse effects), e.g., amantadine, ketamine, dextromethorphan, etc. ▶ Over-the-counter medications, e.g., antacids, H₂-antihistamines, syrups containing dextromethorphan, etc. 	

NSAID : nonsteroidal antiinflammatory drug; NMDA : N-methyl-D-aspartate; N/A : not applicable.

FOLLOW-UP

- ▶ After initiating treatment with an AChEI and/or memantine, there should be:
 - A **telephone or in-person follow-up within 3 months** to assess tolerance and treatment adherence.
 - A **medical visit and a clinical follow-up at 6 months** to evaluate the drug's effectiveness on intellectual functioning, mood, behaviour, and autonomy in the activities of daily living, the instrumental activities of daily living and social interactions, and to renew the prescription, if necessary.
- ▶ The patient and the caregiver should be **seen again at least once or twice a year** thereafter (or more often at the clinician's discretion).
- ▶ At each of these visits, the following should be checked or assessed:
 - The treatment's effectiveness in terms of the therapeutic objectives that had been set.
 - The presence of adverse effects.
 - Therapeutic adherence.
 - The management of drug interactions (including over-the-counter medications and natural health products).
 - The caregiver's burden and needs.
 - Weight.
 - Vital signs.
 - Baseline liver and kidney function profile, with an annual follow-up thereafter.
 - The condition of the patient's eyes if they are taking memantine.

SWITCHING AChEIs

Switching AChEIs is not recommended because of a loss of benefits, especially if the patient has been taking a particular AChEI for more than a year, as this loss is usually associated with the natural course of the disease.

POINTS TO CONSIDER BEFORE SWITCHING FROM ONE AChEI TO ANOTHER

- ▶ Therapeutic adherence problems.
- ▶ New medical comorbidities (e.g., depression or delirium).
- ▶ Drug interactions with co-prescribed drugs, over-the-counter medications or natural health products.
- ▶ Appropriate dosage adjustment attempts must have been made.

PROCEDURE FOR SWITCHING FROM ONE AChEI TO ANOTHER IN MILD TO SEVERE ALZHEIMER' DISEASE

Intolerance to the first AChEI	No clinical benefit with the first AChEI in the first 6 months after the start of treatment
<ul style="list-style-type: none"> ▶ Stop the first AChEI. ▶ Wait for the complete resolution of the adverse effects, that is, 5 to 7 days. ▶ Start administering the second AChEI at the usual initial dose and titrate the dosage according to the recommended titration regimen. 	<ul style="list-style-type: none"> ▶ The switch can be made overnight. ▶ Administer the last dose of the first AChEI. ▶ The next day, start the second AChEI at the recommended initial dose and titrate the dosage at least to the minimum effective dose (the titration can be done more quickly than according to the recommended titration regimen).

This table is based on the following article : Massoud F, Desmarais JE, Gauthier S. Switching cholinesterase inhibitors in older adults with dementia. *Int Psychogeriatr* 2011;23(3):372-8.

WITHDRAWAL OF TREATMENT

FACTORS THAT CAN WARRANT WITHDRAWAL OF TREATMENT

- ▶ The patient experiences bothersome or intolerable adverse effects.
- ▶ The patient's clinical status worsens after the treatment is initiated.
- ▶ The patient's other illnesses make the risk associated with the treatment unacceptable or are so serious that treatment is pointless.
- ▶ The patient and/or their mandatary decides to stop the treatment after having been informed of the risks and benefits of continuing or stopping it.
- ▶ The patient's dementia has progressed to an advanced stage (e.g., stage 7 on the Global Deterioration Scale).
- ▶ The patient is nonadherent to the dosage, and a system cannot be put in place to remedy the problem: continuing the treatment would therefore be pointless.

Adapted from the 4th Canadian Consensus Conference on the diagnosis and treatment of dementia [Gauthier *et al.*, 2012].

- ▶ Withdrawing AChEIs in patients with moderate to severe AD can worsen their cognitive and functional impairments.
- ▶ It is recommended that the doses be gradually reduced over a 2- to 4-week period before withdrawing the drug completely.
- ▶ Close monitoring of the patient during the first month after the treatment is withdrawn is recommended to detect any significant deterioration. If appropriate, consideration may be given to resuming the treatment.

MAIN REFERENCES

- Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, *et al.* The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): A systematic review and economic model. *Health Technol Assess* 2012;16(21):1-470.
- Gauthier S, Patterson C, Chertkow H, Gordon M, Herrmann N, Rockwood K, *et al.* 4th Canadian Consensus Conference on the diagnosis and treatment of dementia. *Can J Neurol Sci* 2012;39(6 Suppl 5):S1-8.
- Massoud F, Desmarais JE, Gauthier S. Switching cholinesterase inhibitors in older adults with dementia. *Int Psychogeriatr* 2011;23(3):372-8.