Institut national d'excellence en santé et en services sociaux
Québec

QUEBEC'S MEDICAL PROTOCOL **Nº 628014**

Adjusting acetylcholinesterase inhibitors (AChEIs) and/or memantine in patients with a major neurocognitive disorder (NCD)

Developed in collaboration with an advisory committee consisting of Québec clinicians and experts.

Validated by the Comité d'excellence clinique en usage optimal du médicament, des protocoles médicaux nationaux et ordonnances of the Institut national d'excellence en santé et en services sociaux (INESSS).

CLINICAL SITUATION OR TARGET POPULATION

Any patient who has been diagnosed with one of the following major neurocognitive disorders (NCDs):

- Alzheimer's disease (AD)
- Mixed dementia[1]
- Lewy body dementia

CONTRAINDICATIONS TO THE APPLICATION OF THIS PROTOCOL

- A patient with a major NCD other than those listed above in the section "Clinical situation or target population".

INSTRUCTIONS

GENERAL INFORMATION ABOUT TREATMENT

Given the modest efficacy of AChEIs and memantine, their safety profile and the cost associated with their use, the decision to treat pharmacologically should be based on a shared decision-making process between the physician, the patient and the caregiver following an informed discussion of the benefits and potential risks of such treatment (Appendix I).

There are no reliable clinical data indicating a difference in efficacy between the three AChEIs. The factors to be considered when choosing initial drug therapy are listed in Appendix II.

Patients who are likely to be hypersensitive to adverse effects should start treatment with a lower dose (see tables in Section 3.2).

! *Pharmacotherapy is only part of the management of patients with a major NCD. For additional information on overall management, refer to the INESSS tools summarized in Appendix III and to the MSSS publication on* Front line interdisciplinary clinical process.

1. ASSESSMENT OF HEALTH STATUS WHEN MAKING THE ADJUSTMENT

- Document the following
  - The occurrence of adverse events after the treatment is initiated or adjusted
  - The emergence of a contraindication to medication after its initiation or adjustment (see tables in Section 3.2)
  - A lack of cooperation in taking the medication (oral form), a problem with adherence to the treatment, or forgetting transdermal patches on the body (if applicable)
  - A lack of response to the treatment
  - A deterioration in kidney or liver function

[1] The term "mixed dementia" refers here to Alzheimer's disease combined with vascular dementia or Lewy body dementia.

- A change (onset or decrease) in the symptoms associated with the major NCD since the treatment was initiated or adjusted (Appendix IV)
- Progression to an advanced stage where the treatment's clinical relevance is questionable
- The patient or caregiver wishes to stop the treatment

► Look for or inquire about other situations that could require a special follow-up or further investigation
- A rapid deterioration in the patient's physical and cognitive status despite the treatment
- An atypical course of the major NCD for which the current treatment was initially prescribed
- The presence of confounding factors that could be responsible for a worsening of the patient's health (adverse effects, a mental health issue, a physical health problem, the abuse of certain substances - Appendix V).
- The presence of behavioural and psychological symptoms of dementia (BPSD) - (affective and emotional, behavioural, psychotic and neurovegetative disorders - Appendix VI).

► Inquire about other situations that could require special attention or a re-evaluation
- Weight loss or the refusal to eat or drink
- A recent health problem and/or taking new medications or natural products since the treatment was initiated or adjusted
- Changes in the patient's psychosocial environment, which could affect the course since the treatment was initiated or last adjusted

2. LABORATORY TESTS PERTAINING TO ADJUSTMENT

► Read the results of the laboratory tests performed before the start of treatment.
- **If applicable,** ensure that paraclinical tests/examinations required for the follow-up and the adjustment of the treatment are recorded in the patient's chart (e.g., ECG, liver function, renal function, etc.).

► Consider revising the laboratory tests or paraclinical examinations in the event of adverse effects, an atypical course or unexplained symptoms.

3. TREATMENT APPROACH FOR THE ADJUSTMENT

3.1 General principles

► Gradually increase the medication until the recommended adjustment is achieved or the maximum tolerated dose is reached.
► If adverse effects occur, reduce the dose or consider switching to another drug.
- Unless a serious adverse effect occurs, avoid discontinuing the medication abruptly if the patient has been taking it for several months and opt for gradual withdrawal instead. If necessary, special monitoring over a period of a few weeks should be carried out to check for any rapid deterioration in the patient's health.

► Consider switching to another AChEI or modifying the dosage form if
- There is a lack of cooperation in taking the drug, in order to facilitate its administration (Appendix VII)
- There are adverse events that do not respond to a slower adjustment or a dose decrease (Appendix VII)
- There has been no clinical benefit during the 6 months following the start of treatment (Appendix VII)

► Consider reassessing the patient's health status if he or she
- Has been treated for more than 6 months with no observable benefit
- Has been treated for over a year and a loss of benefit has been observed

► A loss of benefit, especially if the patient has been taking the drug for over a year, does not warrant
- Switching from one AChEI to another or to memantine because this loss is generally related to the natural course of the disease and because the clinical benefits of this practice have not been demonstrated
- Combined treatment with an AChEI and memantine because the clinical benefits of a combination have not been demonstrated

3.2 General information on the drugs and adjustment details

The general information on AChEIs and memantine presented below is not exhaustive.

For further information on coverage requests for AChEIs and memantine, see Appendix VIII.

For additional information on drug interactions involving AChEIs and memantine, see Appendix IX.

For further information on AChEIs and memantine, see Appendix X.

3.2.1 Class of AChEIs

CLASS OF AChEIs				
Name of drug	**DONEPEZIL**	**GALANTAMINE**	**TRANSDERMAL RIVASTIGMINE**	**ORAL RIVASTIGMINE**
Treatment options[1]	• Mild, moderate and severe AD[1] • Mixed dementia • Mild, moderate and severe Lewy body dementia[1,2]			
Absolute contraindications	• A history of allergic reactions to any of the product's components or to other piperidine derivatives	• A history of allergic reactions to any of the product's components • Severe renal or hepatic impairment	• A history of allergic reactions to any of the product's components or to other carbamates • Severe hepatic impairment	
Relative contraindications	• First-degree or higher atrioventricular block • Bradycardia (resting heart rate less than 55 beats per minute) • Sick sinus syndrome • The use of beta-blockers and/or calcium channel blockers • The use of drugs that increase the QT interval (especially donepezil) *An **isolated** right or left branch block is not a contraindication.*			
Precautions	• Patients at risk for a peptic ulcer. • Patients with a history of asthma, chronic obstructive pulmonary disease, peptic ulcer or seizures. • Patients who are hypersensitive to adverse effects[3] • Patients at risk for rhabdomyolysis or malignant neuroleptic syndrome (donepezil)			
Most common adverse effects	• Gastrointestinal effects[4]: dyspepsia, nausea, vomiting, diarrhea, anorexia, weight loss • Central nervous system effects: agitation, headache, confusion, dizziness, insomnia, dreams/nightmares with motor agitation • Cardiovascular effects: bradycardia, heart block, syncope • Fatigue • Muscle cramps • Pollakiuria • Allergies or signs of intolerance to transdermal rivastigmine: erythema, pruritus • Rhinorrhea (donepezil)			

Abbreviations: AChEI: acetylcholinesterase inhibitor; AD: Alzheimer's disease.
1- Based on scientific data, best clinical practice recommendation, and experiential knowledge from Quebec clinicians and experts. Certain indications are not covered by the RAMQ (Appendix VIII).
2- Galantamine: only in cases of intolerance to donepezil and rivastigmine.
3- Patients who weigh less than 50 kg, who are over 85 years of age or who are frail.
4- The gastrointestinal adverse effects are dose-dependent and generally occur at the start of treatment. They are generally mild and transient.

DOSAGE ADJUSTMENT DETAILS					
Name of drug		**DONEPEZIL**	**GALANTAMINE**	**TRANSDERMAL RIVASTIGMINE**	**ORAL RIVASTIGMINE**
Recommended minimum and maximum doses		5 to 10 mg QD	8 to 24 mg QD	5- to 10-cm^2 patch QD[2] (release of 4.6 to 9.5 mg/24 hrs)	1.5 to 6 mg BID
Initial dose		5 mg QD	8 mg QD	5-cm^2 patch QD[2] (release of 4.6 mg/24 hrs)	1.5 mg BID
Minimum effective dose		5 mg QD	16 mg QD	10-cm^2 patch QD[2] (release of 9.5 mg/24 hrs)	3 mg BID
Population	**Patients with no particular condition**	↑ by 5 mg QD every 4 wks, if tolerated	↑ by 8 mg QD every 4 wks, if tolerated	↑ by 5 cm^2 QD every 4 wks, if tolerated	↑ by 1.5 mg BID every 2-4 wks, if tolerated
	Patients hypersensitive to adverse effects[1]	Initial dose 2.5 mg QD ↑ to 5 mg after 2 wks, if tolerated Maximum dose 5 mg QD	N/A	N/A	Initial dose 1.5 mg QD ↑ to 1.5 mg BID after 2 wks, if tolerated[3]
	Patients intolerant to the initially prescribed AChEI	Adjust the dose downward, as shown in the next row, and switch to another AChEI if the adverse effects persist.			
		Discontinue the treatment and wait for the complete resolution of the adverse effects (5-7 days), then ↓ to 2.5 mg QD. If intolerance is observed again, switch to another AChEI after the complete resolution of the adverse effects.	Discontinue the treatment and switch to another AChEI after the complete resolution of the adverse effects (5-7 days).	If skin reactions, discontinue the treatment and wait for the complete resolution of the adverse effects (5-7 days), then switch to the oral form of rivastigmine**!** For any other type of intolerance, switch to another AChEI after the complete resolution of the adverse effects (5-7 days).	Discontinue the treatment and wait for the complete resolution of the adverse effects (5-7 days), then ↓ to 1.5 mg QD. If intolerance is observed again, switch to another AChEI after the complete resolution of the adverse effects.
	Patients with renal impairment (RI)	N/A	ClCr 9-60 ml/min: maximum 16 mg/day ClCr < 9 ml/min: contraindicated	N/A	ClCr < 50 ml/min: Initial dose 1.5 mg QD ↑ to 3 mg after 2 wks, if tolerated Maximum dose: 3 mg BID
	Patients with hepatic impairment (HI)	N/A	Moderate HI: maximum 16 mg/day Severe HI: contraindicated	Mild to moderate HI: 5-cm^2 patch QD (release of 4.6 mg/24 hrs) Severe HI: contraindicated	Mild to moderate HI: Initial dose 1.5 mg QD ↑ to 3 mg after 2 wks, if tolerated Maximum dose: 3 mg BID Severe HI: contraindicated

Abbreviations: AChEI: acetylcholinesterase inhibitor; CrCl: creatinine clearance; HI: hepatic impairment; hrs: hours; N/A: not applicable; RI: renal impairment; wk: week.

1- For example, patients who weigh less than 50 kg, who are over 85 years of age or who are frail.

2- 15-cm2 patch (release of 13.3 mg/24 hrs): in case of clinical worsening with treatment with 10 cm2 QD that has been stable for several months.

3- Adjust gradually (1.5 mg every 2 weeks), taking into account individual tolerability and under close monitoring for adverse effects, which may be more common in these patients.

! Patients with application site reactions suggestive of allergic contact dermatitis to transdermal rivastigmine and whose condition requires treatment with rivastigmine can switch to the oral form of the drug only after a negative allergy test result and under close medical supervision.

3.2.2 Class of NMDA receptor antagonists

CLASS OF NMDA RECEPTOR ANTAGONISTS	
Name of drug	**MEMANTINE**
Treatment options[1]	• Moderate to severe AD • Mixed dementia
Absolute contraindications	• A history of allergic reaction to any of the product's components • Severe renal or hepatic impairment
Relative contraindications	None
Precautions	• A history of seizures, e.g., a patient with epilepsy • Conditions that alter urine pH • Patients who are hypersensitive to adverse effects[2] • Cardiovascular disorders (low incidence): bradycardia, hypertension, heart failure
Most common drug adverse effects	• Central nervous system effects: agitation, headache, confusion, dizziness, insomnia • Constipation • Hypertension

Abbreviations: AD: Alzheimer's disease; NMDA: N-methyl-D-aspartate.
1- Based on best clinical practice recommendations and experiential knowledge from Quebec clinicians and experts.
2- Patients who weigh less than 50 kg, who are over 85 years of age or who are frail.

DOSAGE ADJUSTMENT DETAILS		
Name of drug		**MEMANTINE**
Recommended minimum and maximum doses		5 mg QD to 10 mg BID
Initial dose		5 mg QD
Minimum effective dose		5 mg BID
Population	**Patients with no particular condition**	↑ by 5 mg QD per wk, if tolerated
	Patients who are hypersensitive to adverse effects[1]	↑ by 5 mg QD every 2 wks. if tolerated
	Patients with intolerance	Discontinue the treatment and wait for complete resolution of the adverse effects (5-7 days), then↓ to 2.5 mg QD, if tolerated Discontinue the treatment if intolerance at 2.5 mg QD
	Patients with renal impairment (RI)	ClCr 30-49 ml/min: maximum 5 mg BID[2] ClCr 15-29 ml/min: maximum 5 mg BID ClCr < 15 ml/min: contraindicated
	Patients with hepatic impairment (HI)	Severe HI: contraindicated

Abbreviations: CrCl: creatinine clearance; HI: hepatic impairment; N/A: not applicable; RI: renal impairment; wk: week.
1- For example, patients who weigh less than 50 kg, who are over 85 years of age or who are frail.
2- If warranted by the clinical response, provided the dose is well tolerated after at least 7 days of treatment, the dose can be increased to 10 mg BID in accordance with the usual dosage adjustment details.

4. INFORMATION TO BE PROVIDED

Give the patient and the caregiver the information below on the treatment, the precautions and the reasons for consulting a health professional again.

Give the patient or the caregiver an information sheet, such as the one produced by INESSS:

General information concerning the treatment
▶ Dosage and dosing schedule ▶ The importance of adhering to the treatment ▶ What to do in the event of a missed dose ▶ The frequency of follow-up visits
Precautions
▶ Medication: adverse effects, interactions with prescription or over-the-counter drugs and natural products ▶ Healthy life habits: diet, alcohol or tobacco use, physical activity, social activities ▶ Comorbidity management (if applicable)
Reasons for consulting a health professional again
▶ The occurrence of bothersome or intolerable adverse effects after the treatment is adjusted ▶ The occurrence of an allergic reaction to the drug after the treatment is adjusted ▶ The patient or caregiver wishes to discontinue the treatment

If necessary, consult Steps to be taken after the diagnosis and during the follow-up.

5. FOLLOW-UP

- Arrange for the next follow-up encounter (e.g., phone call, appointment with the prescriber).
- Determine if laboratory tests are required and how soon.
- Inquire about the most recent patient-specific changes that could affect the adjustment or the relevance of continuing the treatment (Section 1).
- Check the patient's tolerance and adherence to the treatment during the 3 months following its initiation or adjustment and proceed to the adjustment or switch to another drug, if appropriate.
- Using validated tools, assess the extent to which the objective have been met 6 months after the treatment is initiated or adjusted and reassess the clinical relevance of adjusting or continuing the pharmacological treatment.
- If necessary, consult the other points to be taken into consideration during the follow-up.

6. SITUATIONS REQUIRING SPECIAL ATTENTION, REASSESSMENT OR FURTHER INVESTIGATION

- No response to the treatment, the cause not being a therapeutic adherence problem
- Delirium
- New symptoms associated with the major NCD for which the treatment was initially prescribed
- The emergence of a contraindication to the use of AChEIs or memantine during the treatment
- A deterioration in the patient's renal or hepatic function
- A deterioration of the patient's psychosocial situation since the start of treatment or the last adjustment
- A rapid deterioration in the patient's physical and cognitive status despite the treatment
- An atypical course of the major NCD for which the treatment was prescribed
- A lack of cooperation in taking the drug
- The persistence of adverse effects following a dose reduction
- Weight loss or refusing to eat or drink
- Confounding factors that could be responsible for a worsening of the patient's health (adverse effects, a mental health issue, a physical health problem, the abuse of certain substances - Appendix V)

- BPSD that are jeopardizing home safety or significantly impairing the patient's functional status or relationship with family members (affective and emotional, behavioural, psychotic and neurovegetative disorders – Appendix VI)
- Bothersome or intolerable adverse effects
- A situation listed as a relative contraindication or a precaution in the tables in Section 3.2
- Progression to an advanced stage of the disorder where the treatment's clinical relevance is questionable
- The patient or caregiver wishes to discontinue the treatment, or the patient has a clinical condition that requires discontinuing a treatment that he or she has been taking for several months
- The recent occurrence of a health problem and/or the use of new drugs

REFERENCES

This protocol is based on the latest scientific data and best practice recommendations, which were enhanced with contextual information and experiential knowledge provided by Quebec clinicians, experts and patients. For further details on the process used to develop this medical protocol and to consult the references, see the report in support of this protocol (ajouter l'hyperlien).

APPENDIX I – BENEFITS AND RISKS ASSOCIATED WITH THE USE OF AChEIs AND MEMANTINE IN THE TREATMENT OF MAJOR NCDs

AVAILABLE SCIENTIFIC DATA	
Results	• 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	• 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	• The clinical benefit that these drugs confer to patients over time is very difficult to assess.
NUMBER NEEDED TO TREAT TO OBSERVE AN IMPROVEMENT IN GLOBAL CLINICAL STATUS[1]	
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 as opposed to 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 as opposed to placebo.	

The data presented in this table were calculated from the data from the clinical trials included in the following systematic review [2012]: 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.

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).

Taken from the Optimal use guide on pharmacological treatment of Alzheimer's disease and mixed dementia.

APPENDIX II – 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. Rivastigmine: available as a transdermal 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]: • 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 a soft drink).
Gastrointestinal Intolerance	Donepezil appears to be the orally administered AChEI that causes the fewest gastrointestinal adverse effects, while rivastigmine appears to cause the most. Of 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 and rivastigmine: no dosage adjustment if the patient has hepatic or renal impairment.[2]

1. Based on the clinical experience of the members of INESSS's expert committee, these procedures should be done only at the time the drug is administered to the patient.
2. Contraindicated in the presence of severe renal impairment. Contraindicated in the presence of severe hepatic impairment.

Taken from the Optimal use guide on pharmacological treatment of Alzheimer's disease and mixed dementia.

APPENDIX III: MANAGEMENT SUPPORT TOOLS FOR PATIENTS WITH A NEUROCOGNITIVE DISORDER

To access the different decision support tools, click directly on the buttons or links below, consult INESSS's website (www.inesss.qc.ca) or download the apps from App Store or Google Play.

SECTION 1 OF 6 SCREENING

SECTION 2 OF 6 THE PROCESS LEADING TO THE DIAGNOSIS

SECTION 3 OF 6 OBJECTIVE ASSESSMENT USING SCREENING TOOLS

SECTION 4 OF 6 DISCLOSING THE DIAGNOSIS

SECTION 5 OF 6 FOLLOW-UP

SECTION 6 OF 6 STEPS TO BE TAKEN AFTER THE DIAGNOSIS AND DURING THE FOLLOW-UP

> For assistance in identification and the process leading to a diagnosis, consult the screening checklist.

APPENDIX IV – SYMPTOMS ASSOCIATED WITH THE MAJOR NCDs

WARNING SIGN	EXAMPLES OF EVERYDAY MANIFESTATIONS
Memory changes (amnesia)	• Difficulty learning and retaining new information. • Forgetting important information (recent conversations, scheduled or past events, appointments, birthdays), repetitive speech.
Loss of functional autonomy in the instrumental activities of daily living (IADL)/activities of daily living (ADL)	• Deterioration or change in the ability to function independently (daily tasks, managing medications), being a decline from the previous level of functioning.
Problems organizing, planning and reasoning (executive functions)	• Difficulty adjusting to new things or change. • Changes in the ability to organize and plan complex tasks. • Impaired judgment and difficulty making decisions.
Impaired visual recognition (agnosia)	• Difficulty recognizing objects in the home, images or people they know (family members, celebrities) that cannot be explained by defective vision.
Language and speech disorders (aphasia)	• Difficulty expressing themselves (word-finding hesitations, word substitutions or the use of deformed words, incomplete or incomprehensible sentences). • Changes in spelling or handwriting skills (shape of letters). • Decreased ability to understand instructions, follow conversations, read or understand texts.
Impaired ability to perform a motor activity, despite intact motor capabilities (apraxia)	• Difficulty planning complex tasks; unusual slowness or difficulty coordinating movements for performing daily tasks (use of everyday objects, getting dressed or drawing).
Personality, behaviour and mood changes	• See the complete list of BPSD in Appendix VI.

Taken from the decision support tool/sheet Screening of Alzheimer's disease and other neurocognitive disorders.

APPENDIX V – CONFOUNDING FACTORS THAT CAN EXACERBATE THE PATIENT'S CONDITION

CONFOUNDING FACTORS TO BE TAKEN INTO CONSIDERATION
The following situations or medical conditions can be the cause of the identified NCD or a source of exacerbation: • An adverse effect of a drug or a combination of drugs, a new drug, a drug interaction or a cascade of adverse effects of several drugs; • A mental health problem; • A physical health problem (a metabolic or deficiency disorder, a systemic disorder[1], sleep apnea, delirium); • The abuse of certain substances (drugs or alcohol).

1. A disorder that can affect several systems of the human body. Certain diseases, such as heart or respiratory failure and certain systemic infections or sexually transmitted and blood-borne infections (STBIs), can affect cognitive functions.

Taken from the decision support tool/sheet The process leading to the diagnosis of Alzheimer's disease and other neurocognitive disorder.

APPENDIX VI – LIST OF THE MOST COMMONLY OBSERVED BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA IN INDIVIDUALS WITH A MAJOR NCD

THE EARLIEST BPSD IN AD	CLASSIFICATION OF BPSD
Apathy/indifference* Loss of or decrease in motivation affecting behaviour, thoughts and emotions. **Depression*** Sadness, crying, despair, a feeling of powerlessness, low self-esteem, guilt. **Anxiety*** A feeling of an imminent, undetermined danger. An internal state characterized by**:** • Thoughts (apprehension, various worries); • Emotions (anxiety, fear); • Physical sensations (muscle tension, shortness of breath, sweating, gastrointestinal discomfort, headaches); • Behaviours (avoidance, repetitive requests, excessive dependence, agitation). **Irritability*** Irritability of mood, low tolerance threshold. **Aggression*/agitation*** Verbal (shouting, screaming, talking constantly) and physical (throwing things, spitting, pinching, scratching) agitation, with or without aggression.	**Affective and emotional disorders** • Depression • Anxiety • Apathy • Irritability • Emotional lability • Exaltation of mood (euphoria*) **Behavioural disorders** • Wandering • Repetitive vocalizations • Repetitive or stereotyped movements • Aggressive disinhibition • Sexual disinhibition • Gluttony • Utilization behaviours • Imitation behaviours **Psychotic disorders** • Hallucinations* • Delusions* • Identification disorders **Neurovegetative disorders** • Sleep (night wandering, sundowning, sleep-wake cycle reversal)* • Inappropriate eating behaviours and hyperorality

* 12 behavioural disorders that can be identified with the short version of the neuropsychiatric inventory (NPI-R).

Taken from the decision support tool/sheet Screening of Alzheimer's disease and other neurocognitive disorders.

If necessary, consult the MSSS publication on the pharmacological approach to treating BPSD.

APPENDIX VII – SWITCHING AChEIs

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, or over-the-counter drugs or natural products. • Appropriate dosage adjustment attempts must have been made.	
PROCEDURE FOR SWITCHING FROM ONE AChEI TO ANOTHER IN MILD TO SEVERE ALZHEIMER'S DISEASE	
Intolerance to the first AChEI	**No clinical benefit with the first AChEI in the 6 months after the start of treatment**
• 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 dose according to the recommended regimen.	• 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 up to the minimum effective dose (the titration can be done faster 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.

Taken from the Optimal use guide on pharmacological treatment of Alzheimer's disease and mixed dementia.

APPENDIX VIII – GENERAL INFORMATION ON COVERAGE REQUESTS

COVERAGE OF THE CLASS OF AChEIs				
Name of drug	**DONEPEZIL**	**GALANTAMINE**	**TRANSDERMAL RIVASTIGMINE**	**ORAL RIVASTIGMINE**
Criteria for an initial request to the RAMQ	• Monotherapy in patients with mild to moderate Alzheimer disease • The patient must meet the following criteria: - An MMSE score between 10 and 26, or 27 or 28 with relevant justification; - Medical confirmation of the degree of impairment (domain intact or mild, moderate or severe impairment) in the following five domains: 1) intellectual functioning (including memory); 2) mood; 3) behaviour; 4) independence in the activities of daily living and the instrumental activities of daily living; and 5) social interaction (including the ability to have a conversation). • Maximum duration of the authorization: 6 months. • If the AChEI follows treatment with memantine, the concomitant use of these two medications is authorized for a period of one month.			
Criteria for subsequent requests to the RAMQ	• The physician must provide evidence of a beneficial effect confirmed by each of the following: - An MMSE score of 10 or higher, unless there is relevant justification; - A maximum decrease in the MMSE score of 3 points per 6-month period relative to the previous assessment, or a greater decrease accompanied by relevant justification; - Stabilization or improvement in symptoms in one or more of the following areas: 1) intellectual functioning (including memory); 2) mood; 3) behaviour; 4) independence in performing the activities of daily living and the instrumental activities of daily living; and 5) social interaction (including the ability to have a conversation). • Maximum duration of the authorization: 12 months.			

COVERAGE OF THE CLASS OF NMDA ANTAGONISTS	
Name of drug	**MEMANTINE**
Criteria for an initial request to the RAMQ	• As monotherapy in patients with moderate to severe Alzheimer's disease living at home, i.e., not living in a public long-term care residential facility or a private one under agreement. • The patient must meet the following criteria: - An MMSE score of 3 to 14; - Medical confirmation of the degree of impairment (domain intact or mild, moderate or severe impairment) in the following five domains: 1) intellectual functioning (including memory); 2) mood; 3) behaviour; 4) independence in the activities of daily living and the instrumental activities of daily living; and 5) social interaction (including the ability to have a conversation). • Maximum duration of the authorization: 6 months. • If memantine follows treatment with an AChEI, the concomitant use of these two medications is authorized for a period of one month.
Criteria for subsequent requests to the RAMQ	• The physician must provide evidence of a beneficial effect confirmed by a stabilization or improvement in symptoms in at least three of the following areas: 1) intellectual functioning (including memory); 2) mood; 3) behaviour; 4) independence in the activities of daily living and the instrumental activities of daily living; and 5) social interaction (including the ability to have a conversation). • Maximum duration of the authorization: 6 months.

APPENDIX IX – DRUG INTERACTIONS

The potential for drug interactions should be assessed when making any addition or change to a patient's medication profile.

CLASS OF AChEIs				
Name of drug	**DONEPEZIL**	**GALANTAMINE**	**TRANSDERMAL RIVASTIGMINE**	**ORAL RIVASTIGMINE**
Metabolism	Substrate of cytochrome P450 isoenzymes 2D6 and 3A4	Substrate of cytochrome P450 isoenzymes 2D6 and 3A4	Nonhepatic (hydrolysis)	
Drug interactions (list not exhaustive)	• Exercise vigilance when administering strong CYP 2D6 and 3A4 inducers (phenytoin, carbamazepine, phenobarbital, rifampin) or inhibitors (ketoconazole, quinidine, paroxetine, bupropion, clarithromycine). • **Anticholinergics (antagonistic action)**, for example, tricyclic antidepressants, SSRI antidepressants (paroxetine), first-generation antihistamines, antimuscarinics (treatment of overactive bladder), antiarrhythmics (disopyramide), gastrointestinal antispasmodics, muscle relaxants, narcotic analgesics (meperidine), antiemetics (dimenhydrinate, prochlorperazine), antipsychotics (olanzapine, clozapine, quetiapine, chlorpromazine, methotrimeprazine, loxapine), atropine and atropine-like drugs (scopolamine, etc.), certain antiparkinsonians (procyclidine, benztropine, trihexyphenidyl, amantadine), certain antiepileptics (carbamazepine and oxcarbazepine), cannabis and cannabinoids. • **Benzodiazepines (exacerbate cognitive disorders) and non-benzodiazepine sedatives** (zopiclone, zolpidem). • **Cholinergic agonists (synergistic cholinergic effect)**, e.g., bethanechol and pyridostigmine. • **Bradycardic agents (additive effect on the heart rate)**, e.g., beta-blockers, diltiazem, verapamil, digoxin, amiodarone, carbamazepine, ivabradine and clonidine. • **NSAIDs (increased risk of ulcer).** • **Antipsychotics (increased risk of extrapyramidal effects).** • **Over-the-counter medications**, e.g., antihistamines, dimenhydrinate, loperamide, codeine-containing syrups, and NSAIDs.			

CLASS OF NMDA RECEPTOR ANTAGONISTS	
Name of drug	**MEMANTINE**
Metabolism	Non-hepatic (renal)
Drug interactions (list not exhaustive)	• **Drugs that alkalinize urine (decreased renal elimination of memantine),** e.g., sodium bicarbonate, potassium citrate, carbonic anhydrase inhibitors (acetazolamide, methazolamide). • **NMDA receptor antagonists (possible increase in adverse effects),** e.g. amantadine, ketamine and dextromethorphan. • **Over-the-counter medications**, e.g., syrups containing dextromethorphan. • Trimethoprim.[1]

1. The mechanism of action is not clear.

Taken from the Optimal use guide on pharmacological treatment of Alzheimer's disease and mixed dementia.

APPENDIX X – ADDITIONAL INFORMATION ON AChEIs AND MEMANTINE

	DONEPEZIL	GALANTAMINE	TRANSDERMAL RIVASTIGMINE	ORAL RIVASTIGMINE	MEMANTINE
Mechanism of action	Reversible AChEI inhibitor	Reversible AChEI 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 or 8 hours	1 or 2 hours		60 to 80 hours
Information regarding administration	Take in the morning. Take with food. If dysphagia or lack of patient cooperation, fast-dissolving donepezil may be helpful.	Take in the morning. Take with food.	Apply the patch on the back, chest or upper arms. Change the application site daily and do not use the same application site again for 14 days. If intolerance to the glue, consider applying a fluticasone spray under the patch.	Take in the morning and evening. Take with food. An oral solution is available. .	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).

Abbreviations: AChE: acetylcholinesterase; BuChE: butyrylcholinesterase; NMDA: N-methyl D-aspartate.

Taken from the Optimal use guide on pharmacological treatment of Alzheimer's disease and mixed dementia.