

Starting, Switching, and Stopping: Cholinesterase Inhibitors *for* Alzheimer's

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Dementia is a common clinical problem encountered by Canadian family physicians. It is estimated that the average family practice serves 20 to 40 patients with dementia, and diagnoses four to eight new patients annually.

Three cholinesterase inhibitors are available in Canada for the symptomatic treatment of dementia, but studies suggest that only 20% of eligible patients are receiving trial treatment.¹

Despite efforts to educate the public and physicians about the use of cholinesterase inhibitors, there appears to be uncertainty about their use, particularly in terms of management strategies once treatment has begun.

Only 20% of eligible patients are receiving trial treatments of cholinesterase inhibitors.

What are the current indications?

Cholinesterase inhibitors are currently only approved by Health Canada for treating Alzheimer's disease (AD).^{2,3} While provincial formularies pay for cholinesterase inhibitors for patients diagnosed with AD, but not other dementias, there is a growing body of clinical experience with cholinesterase inhibitors and other dementias.

Phyllis' Case

Phyllis, 81, was recently diagnosed with Alzheimer's disease. Her Mini Mental Status Exam (MMSE) is 24/30. She is having memory complaints, some difficulty with instrumental activities of daily living and has decreased participation in many of her previous hobbies (knitting and jigsaw puzzles).



At the last visit you shared the diagnosis with her and her husband and discussed non-pharmacological management issues, such as community supports, legal issues, and referral to the Alzheimer's Society. You plan to discuss the pharmacological management of Alzheimer's with them during this visit.

Randomized, controlled trials (RCT's) studying efficacy with vascular and mixed dementia show benefits with donepezil and galantamine.^{4,5}

What are the benefits?

It is important to discuss potential benefits with patients and families, to allow them to participate in decision-making about therapy, and to guide them in monitoring the response.

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Studies and distilled clinical experience suggest:

- approximately 25% of patients taking cholinesterase inhibitors can be classified as 'non-responders,' experiencing clinical decline at the pre-treatment rate;
- approximately 25% of patients may be termed 'super-responders' with a significant and sustained improvement in function and cognition;
- the remaining patients may be expected to have modest improvement, or to be maintained at the same level without decline, over the first year of treatment.^{2,4}

It is helpful to remind patients and families that a lack of decline is a positive treatment response.

Cholinesterase inhibitors do not often have a significant impact on cognitive tests, such as the Mini Mental Status Exam (MMSE). However, benefits may be seen in global ratings by patients or caregivers, improvements in activities of daily living (ADLs), or instrumental activities of daily living (IADLs), and reduction in behavioural disturbances due to the dementia.

Specific outcomes seen in studies include:

- decreased time spent by caregivers,
- delay in institutionalization, and
- decreased psychotropic use in long-term care facilities.⁶⁻⁸



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What are the side-effects?

The most common short term side-effects are:

- nausea,
- vomiting, and
- diarrhea.

These side-effects are most common when initiating therapy or increasing the dose. Patients may develop tolerance to these effects. Gastrointestinal (GI) effects can be minimized by using titration schedules (Table 1), by temporarily decreasing the dose, and by dosing with, or shortly after, meals.⁹

Other side-effects that may be problematic during initiation or maintenance treatment include:

- sleep disturbance,
- agitation,
- muscle cramps, and
- urinary incontinence.

Remind patients and families that a lack of decline is a positive treatment response.

These side-effects may diminish with time, but can sometimes be improved by switching to another agent.

Extrapyramidal symptoms are possible, at least in part due to alteration of the balance between acetylcholine and dopamine in the brain. Patients with parkinsonism should be monitored for worsening symptoms. Drug interactions have not been identified as a significant clinical concern.

Cardiac contraindications to the use of cholinesterase inhibitors include:

- sick sinus syndrome,
- significant conduction abnormalities (left bundle branch block, > 1° heart block).

Table 1

Dose titration and pharmacology of available cholinesterase inhibitors

Dose titration	Half Life	Metabolism	Comments
Donepezil Starting dose <ul style="list-style-type: none"> • 5 mg od with a meal or at hs for 4 weeks Therapeutic dose <ul style="list-style-type: none"> • 10 mg od daily 	70 hours	CYP3A4, 2D6	<ul style="list-style-type: none"> • once daily dosing • may have higher incidence of sleep disturbance, leg cramps
Rivastigmine Starting dose <ul style="list-style-type: none"> • 1.5 mg bid with meals for minimum 4 weeks Therapeutic dose <ul style="list-style-type: none"> • 3 mg bid with meals Optional higher doses <ul style="list-style-type: none"> • 4.5 or 6 mg bid 	1-2 hours	Metabolism via esterases	<ul style="list-style-type: none"> • slow titration of dose may minimize nausea, vomiting • with frail, older patients, may start with 1.5 mg od for 2 to 4 weeks
Galantamine Starting dose <ul style="list-style-type: none"> • 4 mg bid with meals Therapeutic dose <ul style="list-style-type: none"> • 8 mg bid with meals Optional higher dose <ul style="list-style-type: none"> • 12 mg bid 	6 hours	CYP3A4, 2DS	<ul style="list-style-type: none"> • no RCT for Lewy body dementia but one RCT for vascular dementia

od: Once a day
 bid: Twice a day
 hs: At bedtime

A baseline ECG should be considered. Cholinesterase inhibitors should not be used in patients with severe asthma, COPD, or active peptic ulcer disease. Development of symptoms in any of these systems should prompt assessment.

How should patients be monitored?

Clarifying expectations with patients, families, and caregivers at the time of initiation is the first step in monitoring the response.

Global impressions of both patients and caregivers are important and relevant. These may be augmented by identifying key target issues early, or by providing a monitoring sheet with a comprehensive list of baseline and ongoing symptoms.

MMSEs are needed by most provincial formularies in order to provide coverage (the MMSE score must usually fall between 10 and 26), but the scores may be less telling than functional and global assessment in evaluating response.

Patients should be titrated from the starting dose, as recommended for the specific agent, and

a review of response should be completed at, or before, three months. Patients should not generally be termed 'non-responders' until they have received the full dose of the cholinesterase inhibitors, preferably for a duration of six months. Table 2 outlines the approach to assessing response at three months.

Patients should be reviewed at the six- or nine-month point for cognitive, behavioural, and functional response, and generally every six months afterwards. Review of the MMSE may be periodically necessary to fulfill requirements for provincial drug coverage.

When should they be switched or stopped?

Early in the course of treatment, there is little concern about switching. There is some evidence to suggest that "non-responder" patients may benefit from switching to another cholinesterase inhibitor, noting side-effects experienced with one agent may be less of a problem with another.¹⁰

If a change is being made out of a lack of response, do so at the next dosage for galantamine or rivastigmine, or the next day for donepezil.

If the switch is being made because of side-effects, then a washout period of up to seven days can be used. If the patient

Table 2

Assessing responses at three months

Caregiver/patient report improvement at 3 months

- | | |
|---|---|
| <ul style="list-style-type: none"> • MMSE same or better | <ul style="list-style-type: none"> - Continue same dose or increase to maximum dose - Reassess in 3 to 6 months |
| <ul style="list-style-type: none"> • MMSE down 2 points | <ul style="list-style-type: none"> - Increase to maximum dose - Reassess in 3 to 6 months |
| <ul style="list-style-type: none"> • MMSE down > 2 points | <ul style="list-style-type: none"> - Rule out conditions worsening cognition (<i>i.e.</i>, depression, delirium, drugs), reassess diagnosis. If no cause of decline is found, increase to maximum dose and reassess in 3 months. |

Caregiver/patient uncertain about improvement at 3 months

- | | |
|---|--|
| <ul style="list-style-type: none"> • MMSE same or better | <ul style="list-style-type: none"> - Increase to maximum dose, reassess in 3 to 6 months |
| <ul style="list-style-type: none"> • MMSE down 2 points | <ul style="list-style-type: none"> - Increase to maximum dose - Reassess in 3 to 6 months |
| <ul style="list-style-type: none"> • MMSE down > 2 points | <ul style="list-style-type: none"> - Rule out conditions worsening cognition, depression, delirium, drugs, and reassess diagnosis - If no cause of decline is found, switch to second cholinesterase inhibitor without washout |

Caregiver/patient report no improvement at 3 months (declining at pre-treatment rate)

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|---|---|
| <ul style="list-style-type: none"> • MMSE same or better | <ul style="list-style-type: none"> - Review why impression is NEGATIVE (new onset of specific behaviour due to dementia or medication side effect may affect caregiver's opinion) - If none is identified, increase to maximum dose or switch |
| <ul style="list-style-type: none"> • MMSE decreased | <ul style="list-style-type: none"> - Switch to second cholinesterase inhibitor (without washout) if no exacerbating factors identified |

MMSE: Mini Mental Status Exam

has been receiving treatment for over a year, there is a possibility of precipitous decline to baseline upon withdrawal of the medication. This decline may be irreversible if treatment is not reinitiated within several weeks.

Abrupt withdrawal at time of nursing home admission could worsen behavioural issues.

For this reason, some clinicians advocate the use of a bridging strategy when switching agents. One example is to decrease the original agent to 50% of the dose and start the lowest dose of the new drug. The new drug can be increased when appropriate and the first drug discontinued. The recommendation to use a bridging strategy is not universal.

Many geriatricians and geriatric psychiatrists advocate that patients who have responded should continue their cholinesterase inhibitors indefinitely. There is evidence that cholinesterase inhibitors can be helpful in patients with severe dementia, and for this reason, it is recommended that patients remain on them if they are admitted to a nursing home.¹¹ The abrupt withdrawal at time of nursing home admission could worsen behavioural issues and increase the need for psychotropic medications.

If a cholinesterase inhibitor is stopped, it is important to monitor for functional and cognitive decline so that treatment can be restarted promptly if needed. CME

Take-home message



- Cholinesterase inhibitors should be considered for all patients with Alzheimer's dementia.
- Physicians should be familiar with the dose titration of the three agents available in Canada, and have a strategy for dealing with side-effects and monitoring response.
- Patients who have responded to treatment should continue as long as possible.
- Strategies for switching may optimize response and minimize the risk of abrupt deterioration.

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