Practical Approach to the Use of Cholinesterase Inhibitors in Patients with Early Alzheimer's Disease

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Cholinesterase inhibitors are a treatment option for most people with Alzheimer's disease of mild to moderate severity. This article offers an approach to their use, based on the recommendations of the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. Treatment decisions must be individualized. Monitoring includes evaluating both safety and effectiveness, which entails more than just assessing cognition. Treatment is clinically beneficial when there is evidence of improvement, stabilization, or a slowing of the rate of decline seen prior to the start of treatment without unacceptable side effects.

Key words: *dementia, Alzheimer's disease, cholinesterase inhibitors, safety, effectiveness*

Introduction

There are approximately 60,000 new cases of dementia in Canada each year.[1] About 70% of them are due to Alzheimer's disease (AD), either as the sole cause or in combination with another brain condition (usually cerebrovascular disease).[2] Historically, the detection of dementia has been unreliable in primary care,[3] but an approach for improving the clinical diagnosis of this condition has been described.[4]

The management of dementia is a complex task.[5] This article restricts its focus to the pharmacotherapy of AD that is mild (Mini-Mental State Examination [MMSE] score >18, Global Deterioration Scale [GDS] stage 4) to moderate (MMSE 10–18, GDS 5 or 6). Medications used primarily for the management of the behavioural and psychological symptoms of a dementia, such as agitation, psychosis, depression, and sleep disturbances, are not discussed. This article deals only with the available cholinesterase inhibitors (ChEIs) (donepezil, galantamine, rivastigmine); while memantine can be used for a moderate stage, this agent is not covered. Cholinesterase inhibitors are now the sixth-largest neurological drug class in terms of overall retail spending in Canada. In 2007, the total cost for ChEIs was $162 million.[6]

The first guidelines on drug treatment for AD were published in 1997.[7] This article is based on the recommendations of the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia.[5,8,9] The following questions are addressed: Who should be started on a ChEI? Which ChEI should be used? How should therapy be monitored? When can you decide that treatment has been successful? and, When should you stop therapy?

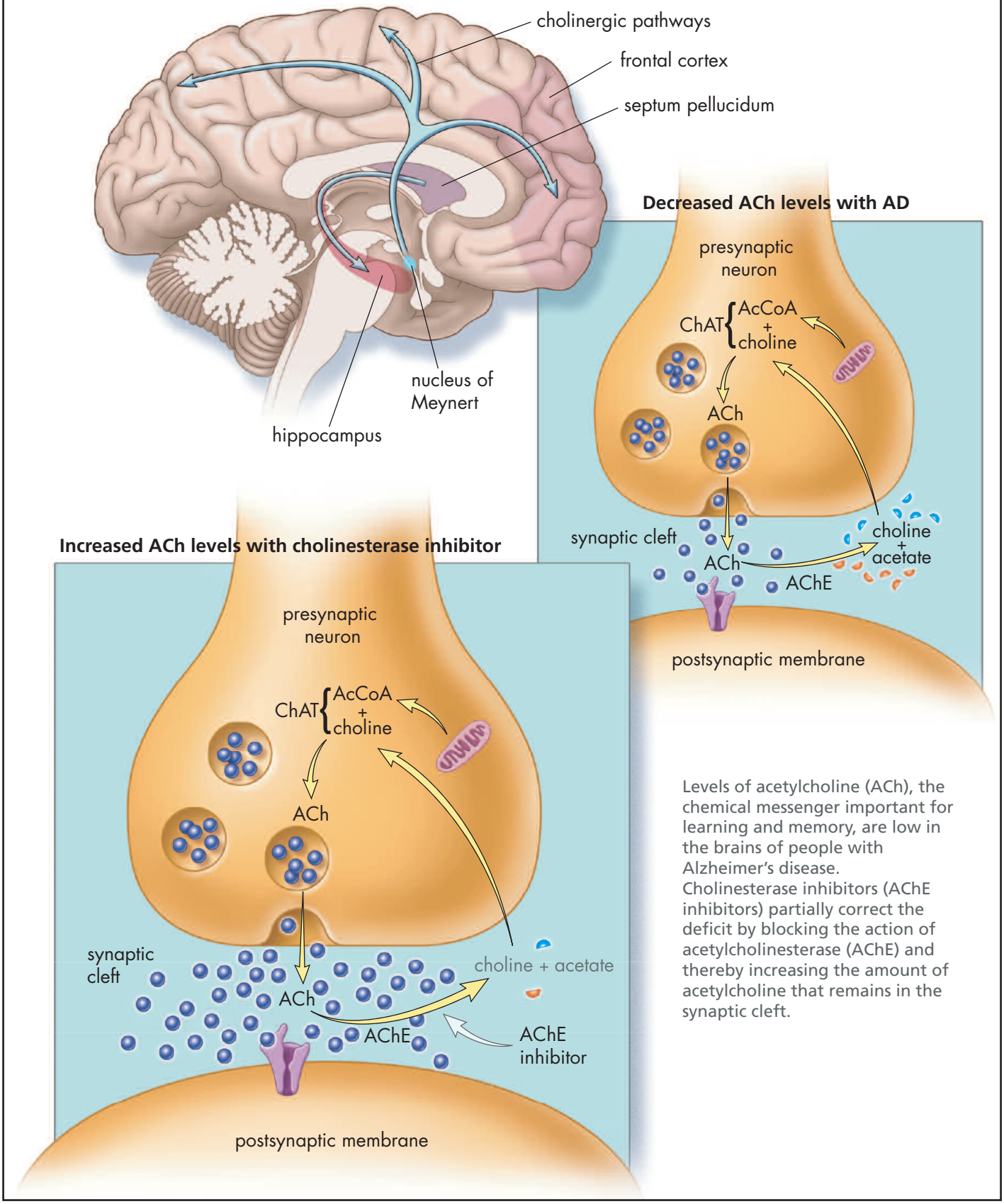
Who Should Be Started on a Cholinesterase Inhibitor?

A ChEI is an option for most people with mild to moderate AD (the commonly seen behavioural signs of this phase of AD are shown in Table 1). Physicians prescribing these agents should be aware of their starting dosages, titration regimens, contraindications, precautions, and common adverse effects. Realistic treatment expectations must be communicated to the patients and their family.

An individualized approach is recommended, with the decision about therapy being up to the patients (or their legally appointed representative if they are incapable of making health care decisions, though the patients would still have to "assent" or agree to take the agent) based on the patients' evaluation of the relative benefits and risks of therapy.[8,10,11] Newly diagnosed patients and their families should be told that there is currently no cure for AD and that none of the available therapies will stop its eventual progression. There are medications, though, that might help with the symptoms of a dementia. The impact for most people would be modest and temporary, with not everyone responding.

Cholinesterase inhibitors prevent the breakdown of a chemical messenger (acetylcholine) important for learning and memory (Figure 1). The levels of this chemical are low in the brains of people with AD. The use of these drugs can partially correct the deficit. The three ChEIs now available in Canada (donepezil, galantamine, rivastigmine) are believed to have a similar degree of benefit but do differ in how they work, how they are taken, and in the likelihood of side effects. It is possible that one of these drugs would suit an individual better than another. While most people do not experience side effects, they can occur, with the commonest ones being nausea, loss of appetite, vomiting, and diarrhea. If patients decide to try a ChEI, you need to see them again in about 3 months. You can then decide together whether it is worthwhile to continue taking the drug. They should be encouraged to raise any questions they have now or in the future

Figure 1: The Function of Cholinesterase Inhibitors (ChEIs) in Treating Alzheimer's Disease (AD)



Levels of acetylcholine (ACh), the chemical messenger important for learning and memory, are low in the brains of people with Alzheimer's disease. Cholinesterase inhibitors (AChE inhibitors) partially correct the deficit by blocking the action of acetylcholinesterase (AChE) and thereby increasing the amount of acetylcholine that remains in the synaptic cleft.

Table 1: Commonly Seen Behaviour Signs of Alzheimer's-Associated Executive Dysfunction

Problems	Examples
Stopping	Disinhibited behaviours, such as blurting out socially inappropriate remarks; frontal release signs, such as the grasp and palmomental reflex
Starting	Lack of spontaneous retrieval of previously learned information; needing repeated reminder and monitoring for treatment plans; problems with initiation; lack of motivation; inability to maintain effortful behaviour; mutism is a most extreme example
Switching	Lack of mental flexibility; inability to change strategies for solving problems; difficulty in switching habitual behaviour such as diet and lifestyle; self-management difficulty when there is a change in medical regimen such as dosage and schedule
Socialization	Poor interpretation of social cues; difficulties in socializing due to lack of motivation, personality changes, or uninhibited behaviours
Planning	Inability of volition, multitasking, and organizing; inability to manage polypharmacy and complex dosing regimen; inability to be compliant to suggestions from health care providers; "stubborn" or "uncooperative" patients not compliant with treatment advice
Judgment	Failure to anticipate consequences of behaviour, such as inability to self-monitor blood sugar and obtain hypoglycemia; inability to identify signs of medication adverse effects

with you. It is often helpful to give the patients and their families written educational material.

No laboratory investigations in addition to what would be done as part of the diagnostic work-up are needed before initiating therapy, other than possibly an electrocardiogram (ECG). Some recommend routinely getting an ECG in order to identify potentially important conduction abnormalities,[12] but abnormal ECGs did not predict cardiovascular events in the randomized controlled trials (RCTs) of ChEIs. The frequency of adverse cardiovascular adverse events has been low in practice. An alternate appropriate approach would be based on the patient's pulse and history.[13] If a patient's pulse is <50 beats per minute, don't prescribe a ChEI but review them for the underlying cause of the bradycardia. For those with a pulse 50+ but symptoms of presyncope/syncope, evaluate for the etiology of these complaints before prescribing a ChEI. If their pulse is 50+ and there are no symptoms suggestive of presyncope/syncope, you can prescribe a ChEI without an ECG, but check the patient's pulse and inquire about presyncope/syncope during follow-up visits.[13]

Currently we have no way of reliably predicting who will have a clinically important beneficial response to ChEI therapy[10]; however, a lower baseline MMSE score and a faster rate of progression pretreatment have been associated with a greater likelihood of showing short-term benefits as measured by the MMSE.[14]

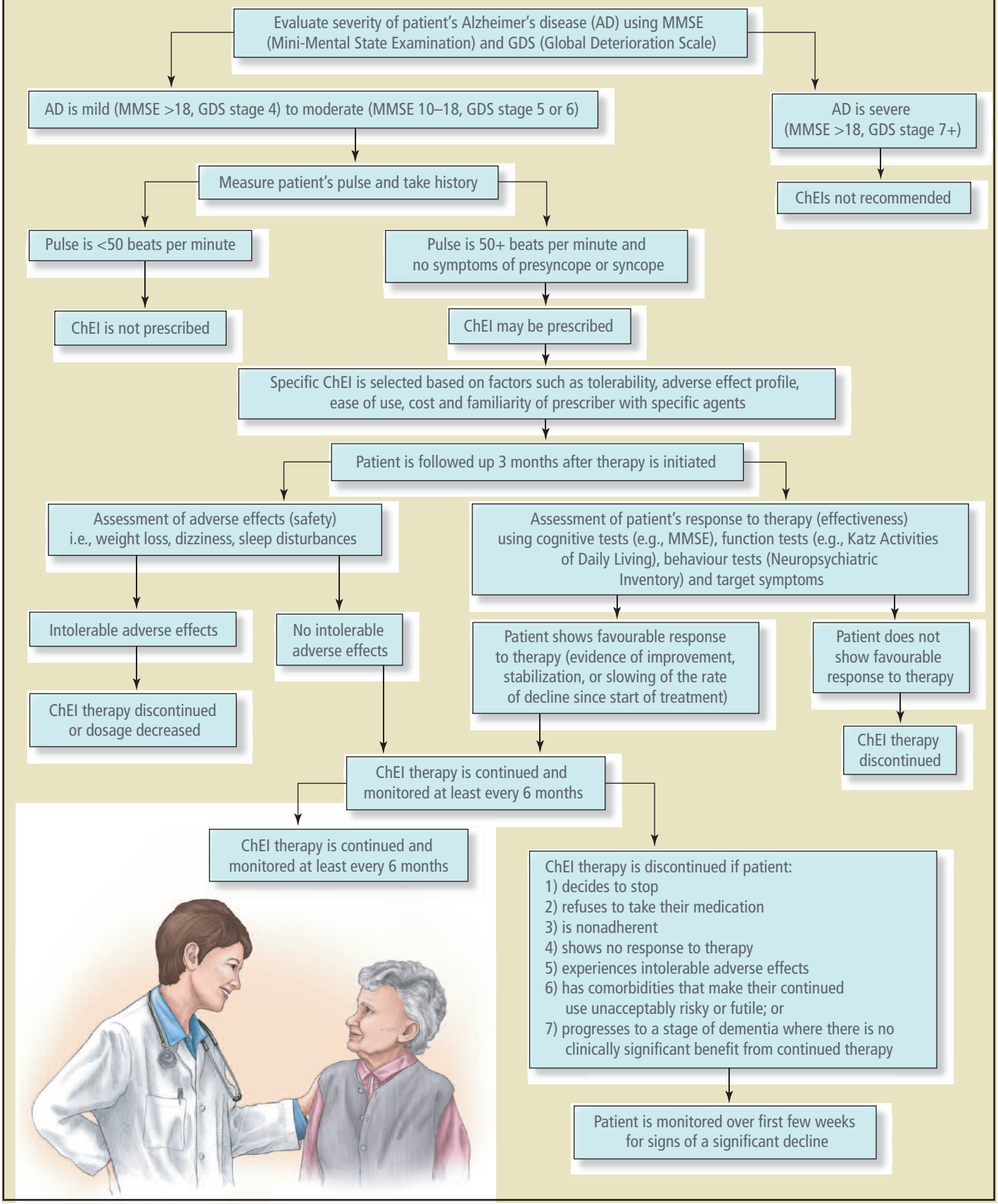
Figure 2 presents an algorithm for decision-making in treating mild-to-moderate AD with ChEIs.

Which Cholinesterase Inhibitor Should Be Used?

The available data are insufficient to allow direct comparisons about the effectiveness of the ChEIs. The selection of which one to use should be based on factors such as tolerability, adverse effect profile, ease of use, cost, and the familiarity of the prescriber with the specific agents and the prescriber's beliefs about the importance of the differences between the ChEIs in their pharmacokinetics and other mechanisms of action.[8,10]

Treated patients may be switched to another ChEI. This is generally done because of either intolerable side effects or an inadequate response to the initial agent. When changing to another ChEI, you should seek to avoid symptomatic deterioration (from stopping the first agent, especially if there is a prolonged washout period) and the emergence (or worsening) of adverse effects.[15] If a switch is being made because of adverse effects (AEs), you should stop the first agent and wait until the AEs have cleared for at least 48–72 hours before initiating therapy with the second ChEI. When a change is being done because of an inadequate response, an immediate switch (i.e., the first dose of the second ChEI is taken 24–36 hours after the last dose of the first ChEI) has been found to be safe and well tolerated. Notwithstanding this, others recommend a short washout period (e.g., 2 days for galantamine and rivastigmine or 5–7 days for donepezil) before starting the new ChEI. Either approach is reasonable. The second ChEI should be commenced at its usual starting dose, with subsequent increases as per the recommended titration regimen for the agent. Unfortunately, the methodological weaknesses of the studies that have

Figure 2: Decision Making in the Treatment of Alzheimer's Disease Using Cholinesterase Inhibitors (ChEIs)



been published do not permit us to draw any conclusions about the likelihood of benefit for patients when switching is done because of an inadequate response to the first agent.

How Should Therapy Be Monitored?

The RCTs of the ChEIs have shown consistent (albeit modest and of debatable clinical significance) benefits with treatment with regard to cognition and global clinical state.[8,10,16] About 15% more patients taking ChEIs stabilize or improve on a global assessment scale compared with those on placebo. The number needed to treat in order to have one additional patient meet the criteria of a cognitive responder (i.e., defined in this meta-analysis as a 4+ point improvement on the cognitive portion of the Alzheimer's Disease Assessment Scale) was 10. The equivalent figure for a global responder (i.e., at least a minimal improvement on the global assessment scale) was 12.[17]

After initiating therapy, patients must be followed up for the development of AEs (safety) and patients' response to therapy (effectiveness). A reasonable initial trial is 3–6 months as long as the patients have no intolerable AEs. After this first follow-up visit, they should be seen at least every 6 months—sooner if the need arises.

The most common AEs encountered with ChEIs are gastrointestinal (e.g., anorexia, nausea, vomiting, diarrhea), which are more likely to occur at the commencement of therapy or when the dosage is increased; they are dosage related and tend to be transient. As weight loss occurred during the clinical trials of all three ChEIs, weight should be monitored. Dizziness is another common AE. It is generally mild, transient, and unrelated to cardiovascular problems. Syncope (while rare) has been reported with these agents. Donepezil has been associated with sleep disturbances, vivid dreams/nightmares, and hypnopompic hallucinations. The number needed to harm (i.e., the number needed to cause one additional adverse event of any severity) has been estimated as 12 (95% confidence interval 10–18).[17] If intolerable AEs occur, generally the ChEI should be discontinued (if the side effects are judged to be disabling or dangerous) or the dosage decreased.

In evaluating effectiveness, you must administer and interpret brief standardized cognitive tests (e.g., MMSE); but, these cannot be used as the sole method of monitoring patients. The MMSE, for example, is too insensitive to detect the modest cognitive benefits seen with ChEIs[18] and does not evaluate other important areas. However, as the results do inform clinical judgment, they are still worth doing. Function and behaviour also have to be assessed. Input from caregivers about these areas as well as caregiver burden, patients' global status, and caregivers' perceptions of patients' response to therapy should be obtained whenever possible.[8,19] Standardized instruments can be helpful in assessing function (e.g., Katz Activities of Daily Living, Lawton Instrumental Activities of Daily Living) and behaviour (e.g., Neuropsychiatric Inventory). The GDS, a measure of overall severity, can be used in combination with the MMSE to monitor disease progression.[9] An attractive way of evaluating response to therapy is with target symptoms, which are personally meaningful manifestations of dementia that are measurable and potentially responsive to therapy. When revisited at follow-up appointments, they can be used to assess the effects of therapy.[20] Caregivers can obtain assistance in developing a symptom profile specific to the person they care for that can then be used to track and communicate changes by joining a service offered by a Halifax-based company, DementiaGuide,[21] at a cost of $20 for 1 month, $45 for 3 months, or $120 for a full-year's subscription.

When assessing effectiveness, you have to be able to validly and reliably determine if there has been a favourable response (i.e., evidence of improvement, stabilization, or a slowing of the rate of decline seen prior to the start of treatment).[22] This is a challenge in light of the limited time available and the relatively insensitive nature of the instruments available. All sources of data have to be utilized, but often a degree of uncertainty about the effectiveness of these agents in a given patient remains. As all Canadian provinces pay for these agents when used to treat mild to moderate AD, you should also be aware of the specific regulations for coverage in your jurisdiction and help your patients obtain coverage when appropriate.

Key Points

- Decisions about treatment with a cholinesterase inhibitor should be individualized and based on the informed consent/assent of the patient.
- At follow-up visits the patient has to be assessed for both safety (e.g., open and targeted questioning, pulse, weight, physical examination/laboratory indications as indicated by history) and the effectiveness of therapy.
- The evaluation of effectiveness is more than just the assessment of cognition (you also have to examine function, behaviour, and global state) and should include questioning the patient's caregiver.
- Identifying and monitoring target symptoms specific to the patient offer a way of monitoring response to therapy that is personally meaningful to the patient and the caregivers.
- Once "on" doesn't always mean "on"—there are rational reasons for discontinuing pharmacotherapy.

Clinical Pearls

Deciding whether to take a cholinesterase inhibitor should be made by an informed patient (or legally appointed representative) based on their evaluation of the relative benefits and risks of therapy.

Monitoring treatment entails looking at both effectiveness (i.e., evaluating cognition, behaviour, function, and/or target symptoms with input sought from both the patient and their caregiver) and safety (i.e., asking about adverse effects as well as checking weight and pulse).

When Can You Decide That Treatment Has Been Successful?

If the patient has shown a favourable response without unacceptable side effects, treatment can be judged as clinically beneficial. Deciding whether to persist with therapy is a shared responsibility involving the patients and/or their substitute decision-makers.

When Should You Stop Therapy?

Pharmacotherapy should be discontinued if patients (1) decide to stop (or their substitute decision-makers, if present, decide therapy should be stopped); (2) refuse to take the medication; (3) are nonadherent and it is not possible to set up a system that would rectify the problem; (4) show no response to therapy (i.e., no evidence of improvement or failure to either postpone or slow the rate of decline seen prior to the start of treatment) after a reasonable trial (at least 3–6 months); (5) experience intolerable AEs; (6) have comorbidities that make continued use either unacceptably risky or futile (e.g., terminally ill); or, (7) progress to a stage of dementia where there is no clinically significant benefit from continued therapy.[8] If stopped, patients should be monitored over the first few weeks for signs of a significant decline. If this occurs, consider reinstating therapy. Gradual dose reduction when discontinuing a ChEI might decrease the likelihood of a clinically significant decline occurring.[23]

Dr. Hogan has received honoraria from Pfizer and Janssen-Ortho for continuing medical education presentations.

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