Recommendations For the Use of Donepezil

The trial of donepezil in patients with mild to moderate dementia due to probable AD was one recommendation made by the Canadian Consensus Conference on Dementia. Clear guidelines are necessary, as many primary care physicians remain uncertain about administering and monitoring this important treatment.

by William Dalziel, MD, FRCPC and Rémi W. Bouchard, MD, MSc, FRCPC

Alzheimer's disease (AD) is the most common dementing disorder, accounting for approximately 64% of the estimated 350,000 cases of dementia among Canadian seniors. This number is expected to triple over the course of the next 30 years. As a result of its increasing prevalence, AD has become a reality faced by more and more primary care physicians in their everyday practices.

Recognition and assessment of AD have been facilitated significantly by the publication of the conclusions from the Canadian Consensus Conference on Dementia, which recently provided a structured clinical approach to evaluating patients with suspected AD. The objective of the Canadian Consensus Conference on Dementia was to develop evidence-based consensus statements on which to build clinical practice guidelines for primary care physicians. Based on currently available evidence and consultations with experts in the field, consensus statements were developed by a group of experts guided by a steering committee of eight specialists from the areas of neurology, geriatric medicine, psychiatry, family medicine, preventive health care and health care systems. Forty-eight recommendations were made, addressing all diagnostic and therapeutic aspects of dementia care.

One of the treatment recommendations is that, in the absence of contraindications, a trial of donepezil (Aricept) can be prescribed to informed and willing patients with mild to moderate dementia due to probable AD. Donepezil is an acetylcholinesterase inhibitor approved in Canada for the symptomatic treatment of mild to moderate AD. A consistent pathological change in AD is the degeneration of cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. The resulting hypofunction of these pathways is thought to account for some of the clinical effects of AD.

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manifestations of AD. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase.

Donepezil has been on the market in Canada since August 1997. The experimental and clinical experience is now quite comprehensive, with 346 million patient-days worldwide. The efficacy and safety of this medication have been demonstrated conclusively.

Although there is wide experience with donepezil, some primary care physicians remain uncertain about various aspects related to the administration and monitoring of donepezil treatment. These aspects include when to start and stop the medication and how to evaluate treatment benefits in this population of patients.

Assessing the benefits of a symptomatic treatment in AD patients may appear difficult for some clinicians due to the progressive degenerative nature of the disease, its variable course, and the lack of simple, easily administered short-outcome measurement tools. It is important to understand the therapeutic gain of a symptomatic treatment in its right context. Patients are expected to decline at different rates for the various symptoms of the disease and, for most domains, in a non-linear fashion. In such a context, symptoms that improve, stabilize or decline at a lesser pace than would be expected if untreated may considered treatment successes. To facilitate the evaluation of patients treated with donepezil, a group of Canadian specialists was assembled to develop recommendations for its appropriate use in the treatment of AD in a primary care setting. This paper presents the results of this initiative.

Methodology
Development process. The development of the treatment recommendations followed these steps:
1) a preliminary meeting served to establish the outline of the recommendations;
2) based on this outline, a first draft of the treatment recommendations was developed and submitted to an Expert Panel composed of neurologists, geriatric psychiatrists, geriatricians and general practitioners for their input;
3) a final draft was presented to two groups of general practitioners during two different focus group meetings to determine the usefulness and pertinence of the treatment guidelines;
4) the comments from the Expert Panel and focus groups were incorporated into the final recommendations.

Implementation. The present treatment recommendations will be disseminated through various vehicles, such as this publication. Other didactic tools might be developed, based on the formats recommended by the members of the focus groups who participated in the development process.

Recommendations for the Use of Donepezil
The present recommendations are presented as a a step-by-step approach reviewing the various elements to consider in the initial clinical evaluation, and subsequent follow-up visits, of patients with AD in whom treatment with donepezil is indicated.

The following section reviews the various key steps to undertake during each visit. A treatment algorithm (Figure 1) provides a quick reference tool that summarizes the different steps described below. A patient sheet that may be used to record results while following a patient also is included (Figure 2).

1. Baseline Assessment
This step takes place when a diagnosis of AD is established. Diagnosis is established as per recommendations from The Canadian Consensus Conference on Dementia. It is important to mention that baseline assessments may be conducted over the course of several visits.

Cognitive and global functioning. Once a diagnosis is made, evaluate cognitive and global functioning, activities of daily living and behavioral symptoms (e.g., apathy, agitation, irritability). Interview the patient and caregiver to evaluate problem areas and potential treatment
Baseline assessment after diagnosis is made

- Evaluate cognition, global functioning, ADLs and behavior
- Evaluate health status, treat concomitant illnesses and evaluate concomitant drug usage
- Discuss potential treatment benefits/expectations, side effects and compliance

Baseline assessments may be done in several visits

• Initiate donepezil 5 mg/day at bedtime
  • Ask patient/caregiver to contact you if any side effects
  • If side effects are severe, persist or worsen rapidly, withdraw treatment

2 weeks

• Discuss and evaluate tolerability and compliance during a visit or by phone
• Adjust drug regimen if appropriate (e.g., switch to morning regimen if sleep disturbance)

4 to 6 weeks

- Assess compliance, check vital signs (heart rate and blood pressure)
- Even if too early to determine treatment benefit, discuss first impression of change with patient/caregiver

• Increase dose to 10 mg/day unless there are some concerns

3 to 6 months

- Evaluate benefits by comparing performance from this visit to that of baseline visit

Is there evidence of improvement, stabilization or some slowing of losses?

No

- Caregiver and physician feel there is continued deterioration at pre-treatment rate
- Discuss stopping therapy with patient and caregiver
- Monitor patient closely; consider restarting medication within 2-3 weeks at previous dose if patient clearly is worse and no other reasons are found

Yes

Continue therapy and reassess every 6 months using the performance level from the previous evaluation

If worsening is observed, consider the following before withdrawing donepezil therapy:
- worsening may be disease-related (e.g., onset or aggravation of behavioral manifestations, consider non-pharmacologic treatments or introduction of psychotropic medications
- deterioration may be due to superimposed health or compliance problems

If benefits are still observed, the following are not necessarily grounds for discontinuation:
- patient has an MMSE score of < 10
- patient has been placed in a nursing home
- patient scores fall below initial baseline level
benefits. In particular, ask the patient and caregiver to identify three to five target symptoms they would hope to see improved or stabilized as a result of donepezil treatment.

**Health status and co-morbidity.** Evaluate health status (i.e., measure blood pressure and vital signs), verify potential precautions to take or contraindications to drug treatment, treat co-morbid illnesses (e.g., depression), and evaluate concomitant drug usage (e.g., drugs to be avoided). Discuss the following topics with the patient and caregiver:

**Potential treatment benefits and expectations.** The safety and efficacy of donepezil have been studied in several double-blind, placebo controlled studies with durations of six months and one year, and in open-label studies spanning more than two years.3-6 Treatment benefits, defined as an improvement, stabilization or some slowing of losses (i.e., decline is less than expected based on the rate of deterioration in the six to 12 months prior to initiation of donepezil therapy) in performance levels, have been observed in global and cognitive functioning, activities of daily living and neuropsychiatric symptoms.7-9 Benefits usually are observed after six to 12 weeks of continuous treatment. It also is known that these benefits are lost six weeks after withdrawal.

**Potential side effects and how to handle them.** The most common adverse clinical events (occurring in at least 5% of patients) associated with donepezil are predictable consequences of its pharmacologic properties, and include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia.10 These events often are mild and transient, resolving with continued treatment without the need for dose modification. Treatment with the 5 mg/day dose for over four to six weeks prior to initiating treatment with the 10 mg/day dose is associated with a lower incidence of gastrointestinal intolerance.

**Compliance.** As for all medications, maximum therapeutic benefits are observed when the medication is taken as recommended. A pill count at each visit may help assess compliance. The available blister pack also may be useful in this regard. Stress the fact that compliance increases possible treatment benefits.

**Precautions.** It is important to initiate donepezil therapy, at 5 mg/day, for four to six weeks at night to minimize gastrointestinal side effects. Instruct patients to switch to morning administration if insomnia develops. Ask the patient and/or caregiver to contact you if any side effects appear.

**Evaluate perception of benefit.** Although it is too early to expect significant therapeutic benefits, it may be useful to ask the patient and/or caregiver for their first impressions of treatment benefits.

3. At Four to Six Weeks

**Increase dosage.** After four to six weeks of treatment, the dose of donepezil should be increased to 10 mg/day, unless there are specific concerns (e.g., in low-weight patients).

**Check compliance.** Again at this stage, a pill count can be performed to determine how closely the patient has been following the prescribed drug regimen.

**Assess vital signs.** This should include measurements of heart rate and blood pressure in all patients.

**Evaluate perception of benefit.** Although it is too early to expect significant therapeutic benefits, it may be useful to ask the patient and/or caregiver for their first impressions of treatment benefits.

4. At Three to Six Months

Evaluate benefits by comparing the performance from this visit to that of the baseline visit.

**Improvement, stabilization or slowing of decline.** Continue therapy and reassess in three to six months if the patient is better, the same or demonstrates some slowing of losses (i.e., decline is less than expected based on the rate of deterioration in the six to 12 months prior to initiating treatment with the 10 mg/day dose is associated with a lower incidence of gastrointestinal intolerance.)
Figure 2
DONEPEZIL PATIENT FOLLOW-UP SHEET

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accompanied by / Relationship:</td>
<td>Date of birth:</td>
</tr>
<tr>
<td></td>
<td>Age:</td>
</tr>
</tbody>
</table>

**Medical history:** From patient and reliable informant (onset, duration, evolution of symptoms, precipitating factors and family history).

**Physical exam:** Rule out adverse drug effects, depression, metabolic or systemic illness.

**Medication:**

**Laboratory:**
- CBC
- Electrolytes
- Calcium
- TSH
- Glucose
- Scan

**Alzheimer’s disease diagnosis date:**

**Issues to address with patient/caregivers:**
- Diagnosis and prognosis
- Information about the disease process
- Driving competencies
- Power of attorney and legal issues
- Support organizations/Alzheimer Society
- Offer TriAd Disease Management Program

**Before initiating treatment, discuss with patient and caregiver:**
- Potential treatment benefits
- Potential side effects
- Compliance

**Donepezil starting date:**

<table>
<thead>
<tr>
<th>Psychometric testing</th>
<th>Baseline</th>
<th>3-6 months Follow-up date:</th>
<th>Follow-up date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition: (e.g., memory, aphasia, apraxia, executive function)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function: Instrumental activities of daily living (e.g., shopping, housekeeping, money management) Basic activities of daily living (e.g., bathing, feeding, grooming) FAQ/PSMS score:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior: (e.g., hallucinations, agitation, depression, anxiety, disinhibition)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver input: (specify problem areas)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global clinical impression of severity/change:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**When using donepezil:**

**Contraindications:** Hypersensitivity to cholinesterase inhibitors.

**Precautions:** Anesthesia, cardiovascular, gastrointestinal, genitourinary, neurological and pulmonary conditions; renal and hepatical impairment.

**Medication not recommended, or to be used with caution:** Anticholinergics, antipsychotics with strong anticholinergic effects, cholinomimetics, MAO inhibitors, neuromuscular blocking agents, other cholinesterase inhibitors, tricyclic.
months prior to initiation of donepezil therapy).

Rapid decline. Faced with a rapid decline, consider the following before withdrawing the medication: superimposed depression, acute infection, delirium, drug reaction/interaction or stroke. Moreover, if the worsening is related to the onset of new or aggravated behavioral manifestations, consider non-pharmacologic treatment or introduction of psychotropic medications before withdrawing donepezil.

Continued deterioration. If the caregiver and physician feel there is continued deterioration at pretreatment rate, discuss the option of discontinuing therapy with the patient and caregiver. If a decision is made to discontinue the medication, provide information to caregivers about potential outcomes and monitor the patient closely. Due to its long half-life, gradual tapering of donepezil is not necessary.

Consider re-starting the medication within two to three weeks, at the previous dose, if the patient clearly is worse and no other reasons can explain the deterioration. Make sure the patient has medication to re-start treatment if necessary, or that the patient is seen during a follow-up visit.

The following should not necessarily be considered grounds for discontinuing medication:
- MMSE < 10 or psychometric test scores below baseline
- nursing home placement
- new or aggravated behavioral symptoms

If the clinician, patient and caregiver still note benefits, continuation of therapy is recommended.

Referral. Consider referral to a specialist if difficulties are encountered in assessing treatment benefits, or for a second opinion. Physicians also may refer patients to specialized dementia clinics to give patients access to new drug trials.

Caregiver. Interview the caregiver for possible depression and/or to assess the stress and burden associated with caring for the patient.

5. Every Three to Six Months (Follow-up Visits)
Assess treatment benefits using the treatment assessment measures. Evaluate benefits by comparing the performances from this visit to those of the evaluation performed three to six months ago.

Conclusion
The development of these treatment recommendations required that a great wealth of information derived from the scientific literature and physician interviews be adapted in a concise fashion.

The participants (specialists and primary care physicians alike) felt any effort to make the management of AD patients simpler would improve care. The only way to ensure that more patients with AD are identified and treated adequately is to simplify the management of these patients.

It is our hope that these treatment recommendations will facilitate the practice of primary care physicians, improve the quality of life of AD patients, and alleviate caregiver burden and stress.

References
2. IMS Global Services, August 1997-December 1999.
10. Aricept Product Monograph, May 2000, Pfizer Canada Inc.