Cognitive Enhancers in Dementia Management

James L. Silvius, BA (Oxon) MD, FRCPC
Presented at the Calgary Therapeutics Course, March 23, 2006.

Cognitive impairment

The biggest challenge with an individual complaining of memory loss is differentiating between an early dementia, most commonly Alzheimer's disease (AD) and mild cognitive impairment. Appropriate diagnosis is required to select appropriate treatment. Treatment is directed towards both affected individuals and their families.

Mild cognitive impairment (MCI)

The predominant change in MCI is memory loss, generally short term memory. Other aspects of cognition are substantially intact (Table 1). Progression of memory loss does occur and is believed that 10% to 15% of individuals may develop AD annually.[1]

AD

AD usually also presents with memory loss, but other deficits are often present. Changes that can occur relatively early may include difficulty finding words in conversation (tip-of-the-tongue phenomenon) and changes in visuo-spatial orientation (demonstrated by clock-drawing). Other changes as it progresses include a decline in:

- learning,
- judgement,
- abstract thought,
- function and
- personality changes.

Later changes may occur in behaviour and mobility. This is a progressive disorder with a fairly consistent decline over time.

Mildred's case

Mildred is a 74-year-old female whose family has noticed her to be more forgetful over the last 18 months

Mildred agrees that she forgets things but disagrees that it is a problem

Her symptoms include being repetitious in conversation

She has recently moved from her home to a lodge where she receives meals and medication reminders at her family's insistence

Physical concerns include gastroesophageal reflux disease and recent depression. Her medications consist of ranitidine and citalopram

- Her Mini-Mental State Examination (MMSE) score was 26/30, clock was normally completed and word generation produced 12 items
- Her family requests cholinesterase inhibitor therapy

Turn to page 22 for more on Mildred.

Treatment of AD

Treatment of AD consists of cholinesterase inhibitors include donepezil, galantamine and rivastigmine. All three agents inhibit acetylcholinesterase. Galantamine is also a nicotinic modulator and rivastigmine also inhibits butyrylcholinesterase. The Health Canada indication for each is the symptomatic treatment of mild-to-moderate AD (Table 2).

Dr. Silvius is Head and Chief, Division of Geriatric Medicine, University of Calgary Medical Leader, Seniors Health (of Seniors Health and Palliative Care), Calgary Health Region, Calgary, Alberta.

Copyright© Not for Sale or Commercial Distribution
Unauthorised use prohibited. Authorised users can download, display, view and print a single copy for personal use

These agents have been recommended by the Canadian Consensus Conference for mild-to-moderate AD.[2] They lead to symptom stabilization for periods of time and are not known to be disease-modifying. Trials with each agent demonstrate similar magnitudes of effect, which are modest, but may be significant for an individual. Most common side-effects are nausea, dyspepsia, anorexia or diarrhea. Other side effects may include insomnia, headache, or syncope. Side effects are less of an issue if at least four weeks elapse between dose adjustments.

The initial choice of a particular agent is guided by the ease of administration and tolerance. Personal opinion around the importance of different mechanisms of action may also affect initial choice. Head-to-head trials have not been conclusive and clinically important differences between the agents have not been demonstrated.

The decision to initiate treatment needs to be made in consultation with the affected individual and their family. Memory, function and behaviour may be affected. Other areas, though less well identified, may include social engagement. With the modest effectiveness of these agents, it is important to identify realistic goals for treatment and to follow-up to determine if the goals are being met.

Table 1

Criteria for Mild Cognitive Impairment (MCI)

- Complaints should be corroborated by others
- Objective memory impairment on testing
- Normal general cognitive functioning
- Essentially intact activities of daily living (early)
- Some loss of executive function (later)

Switching agents

The decision to switch agents depends on patient response. For intolerance or safety issues, a switch should be made once the concern is identified. Assuming the drug is tolerated, switches may be considered if there is failure to achieve the desired effect over a six-month period. This may be challenging to determine though a rule of thumb is that if the decline over the six months on treatment is similar to the decline seen during the six months prior to initiation, the drug is unlikely to be having a significant effect. The decision to switch may also be made on the basis of realistic goals not being attained.

Discontinuation

No literature supported-guidelines are available to guide discontinuation. It has been suggested that the criteria for discontinuation may include intolerance to several agents:

- no obvious benefit after a "good" trial,
- non-compliance with therapy,
- deterioration after an initial benefit, or
- a decision to discontinue.

While not shown in the literature, a taper is recommended for donepezil because of the risk for a significant deterioration with abrupt discontinuation.

Table 2

Available medications

Drug	Donepezil	Galantamine	Rivastigmine	Memantine
Formulation	Tablet	Extended release tablet	Immediate release capsule Oral solution (2 mg/ml)	Tablet
Initial dose	5 mg q.d.	8 mg q.d.	1.5 mg b.i.d.	5 mg q.a.m.
Maximum dose	10 mg q.d.	24 mg q.d.	6 mg b.i.d.	10 mg b.i.d.

The biggest challenge with an individual complaining of memory loss is differentiating between early dementia, most commonly AD and mild cognitive impairment.

Mildred's case cont'd

- Mildred's assessment revealed a most likely diagnosis of MCI
- She was not prescribed a cholinesterase inhibitor as benefit has not been shown with MCI. The reasons for this were discussed with her and her family
- A commitment was made for a repeat assessment in six months with a request to call for an earlier appointment if things changed

Take-home message

1. Cholinesterase inhibitors have a stabilizing role in mild to moderate Alzheimer's disease.
2. Cholinesterase inhibitors have a modest effect and individualizing desired goals is important for patients and their families.
3. Switching agents may be done for intolerance or lack of effect over six months. but not otherwise as there is no demonstrated clinical difference between drugs
4. Discontinuation may be considered, but should be done in consultation with patients and/or family members
5. MCI should not be treated with cholinesterase inhibitors as benefit is unclear and in one trial, potential risks were noted.

Memantine

Memantine is indicated for monotherapy or combination therapy in moderate-to-severe AD. It is a glutamate modulator and has been studied in several trials with more severely affected individuals, both alone and with donepezil. The primary effect studied has been behaviour and the conclusion was that there is a modest, but clinically significant effect on behaviour.[3-5]

Treatment of MCI

Cholinesterase inhibitors are not indicated for treatment of MCI. Of the two available studies, the donepezil trial in MCI demonstrated a delay in progression from MCI to AD in the donepezil-treated group over the first year, but by the end of the third year, no differences were seen between the donepezil and placebo groups.[6] The galantamine trial found no difference in conversion rate to AD or improvement in cognition over 24 months and there was an excess mortality in the galantamine treated group that has not been seen in studies with AD.[7] Therefore, cholinesterase inhibitor therapy is not recommended in MCI.

cme

References:
1. Petersen RC, Doody R, Kurz A, et al: Current concepts in mild cognitive impairment. Arch Neurol 2001; 58(12):1985-92.
2. Patterson CJ, Gauthier S, Bergman H, et al: Management of dementing disorders: Conclusions from the Canadian Consensus Conference on Dementia. CMAJ 1999;160:(12suppl).
3. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. NEJM 2003;348(14):1333-41.
4. Tariot PN, et al: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: A randomized controlled trial. JAMA 2003;291(3):317-2.
5. Winblad B and Poritis N. Memantine in severe dementia: Results of the 9m-best study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriat Psych 1999;14(2):135-46.
6. Petersen RC, Thomas RG, Grundman et al: Vitamin E and donepezil for the treatment of mild cognitive impairment. NEJM 2005;352(23):2379-88.
7. www.clinicalstudyresults.org/documents/company-study_96_1.pdf Accessed July 7, 2006.