What's New in the Treatment of Dementia?

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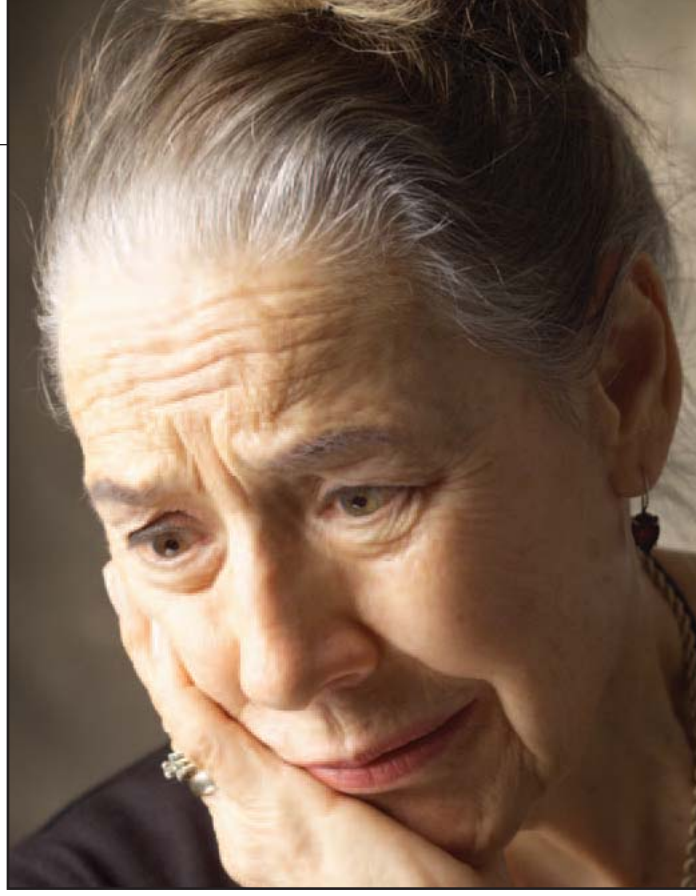

In this article:

1. What are the common symptoms of AD?
2. What medications are available?
3. How do you choose between the various cholinesterase inhibitors?
4. What type of response can you anticipate?

Mrs. Jane's Case

Mrs. Jane, is an 81-year-old widow who lives on her own. You are called by her daughter who expresses concern about her mother's memory and ability to fend for herself. When you see her, Mrs. Jane states that she is fine. Her physical examination is unremarkable, except for a 4 kg weight loss over the last year. On a Mini-Mental State Examination, she scores 19/30. Laboratory investigations are normal. Your diagnosis is Alzheimer's disease.

The daughter asks, "Is there any treatment for her?"

Table 1
Examples of Activities of Daily Living (ADL)

Basic	Instrumental
• Bathing	• Using a telephone
• Dressing	• Traveling outside the neighbourhood
• Toilet	• Shopping
• Transfer	•Preparing meals
• Continence	•Housework
• Feeding	•Taking medicine
	•Managing finances

Many seniors fear dementia more than death.[1] Dementia can steal memories, personality, and independence, and make the person a burden to their loved ones. It is said that with dementia "there is no person, but only a living creature."[2] Dementia becomes increasingly prevalent as we age. By the time we reach 85 years and beyond, a third of us will suffer from dementia.

While there are numerous potential causes of dementia, this article will focus on the most common, Alzheimer's disease (AD).

What are the common symptoms of AD?

AD leads to problems in self-care, cognition, and behaviour. All three areas should be initially assessed and periodically re-evaluated during the course of the illness. Information should be collected from both the patient and someone who knows them well. Both basic and instrumental activities of daily living (ADL) should be examined (Table 1). Standardised scales for assessing ADL are available. An objective test of cognition must be done.[3,4] The Mini-Mental State Examination is the most commonly used (Table 2). Behavioural problems will occur at some time in virtually everyone with AD. Common challenges include agitation, psychotic features, and depression. The Neuropsychiatric Inventory Questionnaire is a validated instrument to assess the behaviours often encountered in patients with AD.[3]

What medications are available?

The management of a patient with AD incorporates both pharmacologic and nonpharmacologic interventions. While drug therapy includes medications to manage behavioural symptoms, in this article we will restrict ourselves to a discussion of agents prescribed for the cognitive deficits. The reader is referred to other sources for more comprehensive reviews of management.[4,5] High doses of vitamin E (2,000 IU per day) may slow the rate of progression seen with AD and should be considered.[4,6] The evidence in support of Ginkgo biloba would have to be graded as insufficient at the present time to lead to a recommendation for its use.[4,7]

Cholinesterase inhibitors (ChEIs) should be considered for all patients with AD.[4,8] They raise acetylcholine levels in the brain by inhibiting its breakdown by cholinesterase. Use of these agents can lead to modest benefits.[8] In the

Table 2

Mini-Mental State Exam (MMSE)

I. Indications

A. Cognitive assessment

B. Documentation of changes from baseline assessment

II. Questions (Total of 30 points)

A. Orientation (10 points)
1. Year, season, month, date, and day of the week.
2. Province, county, town or city hospital or clinic, and floor.

B. Registration (3 points)
1. Name 3 objects: apple, table, penny. Each one is spoken distinctly with a brief pause between them.
2. Then ask the patient to repeat all 3. Give 1 point for each correct answer.
3. Repeat words until the patient learns all 3 (maximum of 3 repetitions). Count number of trials and record.

C. Attention and Calculation (5 points)
1. Ask the patient to spell WORLD backwards.
2. Score is the maximum number of letters in the correct order. For example: DLORW is scored as 4 points.
3. Alternatively ask the patient to substract 7 from 100 and keep subtracting 7 from what is left for a total of 5 subtractions. Each subtraction is scored on its own.

D. Recall (3 points)
1. Ask the patient to recall the 3 objects previously registered. Give 1 point for each correct response.

E. Language (8 points)
1. Show the patient a wristwatch and ask what it is. Do the same for a pencil. (2 points)
2. Ask the patient to repeat "No ifs ands or buts."
3. Ask the patient to follow a three-stage command: "Take the paper in your right hand, fold it in half, and put it on the floor." (3 points)
4. Ask the patient to read and obey the following sentence written on a piece of paper: "Close your eyes." (1 point)
5. Ask the patient to write a sentence. (1 point)

F. Visual Construction
1. Ask the patient to copy a picture of 2 overlapping pentagons. (1 point)

III. Interpretation of MMSE Score

A. Median MMSE score by age and educational level.
1. Zero to Four Years of Education
   a. Ages 18 to 69: Median MMSE score 22-26.
   b. Ages 70 to 79: 21.
   c. Age 80 or greater: 19-20.
2. Five to Eight Years of Education
   a. Ages 18 to 69: 26-28.
   b. Ages 70 to 79: 26.
   c. Ages 80 or greater: 26.
3. Nine to Twelve Years of Education
   a. Ages 18 to 69: 28-29.
   b. Ages 70 to 79: 27-28.
   c. Ages 80 or greater: 26.
4. Twelve and More Years of Education
   a. Ages 18 to 69: 29-30
   b. Ages 70 to 79: 28-29
   c. Ages 80 or greater: 28

References

1. Folstein MF, Folstein SE, and McHugh PR: MMS: A practical method for grading the cognitive state of patients for the clinician. J. Psychiatric Res 1975; 12:189098.
2. Crum RM, Anthony JC, Bassett SS, et al: Population-based norms for the MMSE by age and educational level. JAMA 1993; 269:2386-91.

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Practice pointer

ChEIs differ in their pharmacologic effects, dosing intervals and side effect profiles. Choices are generally made on these characteristics.

short-term, there can be improvements on cognitive measures. There can be stabilisation or slowing in the rate of cognitive and functional decline. Behavioural problems may improve or be prevented from occurring.[9] In Canada, there are now three ChEIs available: donepezil, rivastigmine, and galantamine (Table 4).[8]

These drugs are felt to provide symptomatic relief. It remains unproven whether they modify the course of the disease and provide long-term benefits. Open-label extension studies cannot prove long-term efficacy, let alone show conclusively that these drugs are disease modifying. Extension studies are unblinded, and have a high likelihood of yielding false positive results.[10] As a comparator, a projected placebo group response is generated, which in itself leads to uncertainty. Another problem is the high dropout rates. Studies become suspect when dropout rates are 20% or higher.[11] This figure is exceeded in the extension studies of ChEIs. For example, in the galantamine six-month extension study, the 268 subjects completing the study represented only 42% of the 636 individuals initially randomised, and 61% of the 438 who completed the initial six-month double-blind phase.[12]

Potential new therapies within the foreseeable future include mamantine (an N-methyl-D-aspartate antagonist), secretase inhibitors, and immunotherapy.[13]

Table 3

When Should You Stop ChEI Treatment?

ChEIs should be stopped after an adequate trial if:

- The patient (or proxy decision-maker) decides to stop.
- The patient is nonadherent.
- Intolerable side effects occur.
- The patient deteriorates at the same or at an accelerated rate compared to before initiating therapy.
- The patient progresses to a stage where no clinically meaningful benefit occurs for the patient with continued therapy (based on an individualised assessment of the relative benefits and costs of therapy).

Table 4
Comparison of Donepezil, Rivastigmine, and Galantamine

	Donepezil	Rivastigmine	Galantamine
Mechanism	Reversible AChE[1] inhibitor	Pseudo-irreversible AChE/BuChE[2]	Reversible AChE inhibitor and allosteric modulator of nicotinic receptors
Pharmacokinetics	Rapidly absorbed; highly bound to plasma proteins; liver metabolism (P450 Isozymes 2D6 and 3A4)	Rapidly absorbed; food delays; hydrolysed by esterases; duration of ChEI in the CNS is 10 hours	Rapidly absorbed; food delays; liver metabolism (P450 Isoenzymes 2D6 and 3A4)
Half-Life	70 hours	1 to 2 hours	5 to 7 hours
Drug Interactions	Might interact with drugs metabolised by P450 isoenzymes; drugs which affect cholinergic system	Drugs which affect cholinergic system	Might interact with drugs metabolised by P450 isoenzymes; drugs which affect cholinergic system
Starting Dose	5 mg OD	1.5 mg BID	4 mg BID
Escalation	To 10 mg OD in 4 weeks as tolerated.	To 3.0 mg BID in 4 weeks, with option to go to 4.5 mg BID in 4 weeks, with option to go to 6.0 mg BID in 4 weeks, as tolerated	To 8 mg BID in 4 weeks with option to go to 12 mg BID in 4 weeks, as tolerated
Maximum Dose	10 mg OD	6.0 mg BID	12 mg BID
Common Adverse Effects	Nausea, diarrhea, vomiting, insomnia, muscle cramps, anorexia	Nausea, vomiting, diarrhea, abdominal pain, anorexia, weight loss	Nausea, vomiting, dizziness, diarrhea, anorexia, weight loss

AChE = Acetylcholinesterase, BuChE = Butyrylcholinesterase, CNS = Central nervous system, ChEI = cholinesterase inhibitors, OD = every day, BID = Twice a day

How do you choose between the various ChEIs?

All the ChEIs seem to produce the same degree of improvement.[8,13] They do differ in their other pharmacologic effects, dosing intervals, and side effect profiles. Choices are generally made based on these characteristics.[8]

Head-to-head trials have been done, but with methodologic limitations. Another concern is that all of these studies have been done with industry sponsorship. Not surprisingly, the sponsor's medication tends to come out looking better than the competition. Industry

sponsorship has been found elsewhere to be associated with a greater likelihood of pro-industry conclusions and restrictions on publication.[14]

Switching to a second ChEI can be done at the request of the patient or in the face of either an inadequate response or the development of intolerable side effects from the first ChEI.[8] Switching regimens have been developed which are easy to use.[8] It must be emphasised, though, that we currently don't know if individual patients truly do respond better to one ChEI compared to the others. Also, adverse effects can occur while switching.[15]

What type of response can you anticipate?

A beneficial response can be improvement, stabilisation, or a slowed rate of decline. Gauging response is generally determined by the physicians' global assessment of the patient, collateral information provided by a caregiver, and/or the patient's score on standardised measures of cognition, function, and behaviour. Treatment for six to 12 months is often required to assess potential benefit (Table 3). Dx

References
1. Kleinfield NR: More than death, many elderly fear dementia. *New York Times* November 11, 2002.
2. Jackson JH: The factors of insanities. In: Adams LB, ed: *Selected writings of John Hughlings Jackson.* Gryphon Editions (Birmingham, AL), 1985, pp.411-21.
3. Cummings JL, Frank JC, Cherry D, et al: Guidelines for managing Alzheimer's Disease: Part I. Assessment. Am Fam Physician 2002, 65:2263-72.
4. Patterson C, Gauthier S, Bergman H, et al: The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. Can J Neurol Sci 2001; 28 (Suppl 1):S3-S16.
5. Cummings JL, Frank JC, Cherry D, et al: Guidelines for managing Alzheimer's Disease: Part II. Treatment. Am Fam Physician 2002, 65:2525-34.
6. Sano M, Ernesto C, Thomas RG, et al: A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997, 336:1216-22.
7. Gold PE, Cahill L, Wenk GL: The lowdown on Ginkgo biloba. Scientific American 2003, 288(3):86-91.
8. Hogan DB, Patterson C: Progress in Clinical Neurosciences: Treatment of Alzheimer's disease and other dementias – review and comparison of the cholinesterase inhibitors. Can J Neurol Sci 2002, 29:306-14.

Take-home message

Common symptoms of AD: Problems in cognition, self-care, and behaviour.

Diagnosing AD: Problems in cognition, self-care and behaviour should be initially assessed and periodically re-evaluated. Information should be collected from both the patient and someone who knows them. The Mini-Mental State Examination and the Neuropsychiatric Inventory Questionnaire are useful instruments for assessment.

Medications available: High doses of vitamin E (2,000 IU per day), and cholinesterase inhibitors (ChEIs) (such as donepezil, rivastigmine or galantamine).

Choosing a ChEI: ChEIs differ in pharmacologic effects, dosing intervals and side effect profiles. Choices are generally made based on these characteristics.

9. Trinh N-H, Hoblyn J, Mohanty S, Yaffe K: Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease. JAMA 2003, 289:210-16.
10. Spilker B: Guide to Clinical Trials. Raven Press (New York), 1991, pp. 15-20,508-9.
11. Unnebrink K, Windeler J: Intention-to-treat: methods for dealing with missing values in clinical trials of progressively deteriorating diseases. Statist Med 2001, 20:3931-46.
12. Raskind MA, Peskind ER, Wessel T, et al: Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. Neurology 2000, 54:2261-68.
13. Clark CM, Karlawish JHT: Alzheimer disease:current concepts and emerging diagnostic and therapeutic strategies. Ann Intern Med 2003, 138:400-10.
14. Bekelman JE, Li Y, Gross CP: Scope and impact of financial conflicts of interest in biomedical research – a systematic review. JAMA 2003, 289:454-65.
15. Taylor AM, Hoehms JD, Anderson DM, Tobert DG: Fatal aspiration pneumonia during transition from donepezil to rivastigmine. Ann Pharmacotherapy 2002, 36:1550-53.

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