



Cognitive enhancers for

John Kasckow, MD, PhD

Director of Geriatric Psychiatry
University of Cincinnati College of Medicine
Cincinnati, Ohio

Three cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—are commonly used to treat Alzheimer's disease. How effective are they in improving or maintaining a patient's cognition, functioning, or behavior? What is their impact on costs and caregiver burden? Read on for answers.

dementia: Do they work?

No psychiatrist likes to see the month-by-month deterioration in an Alzheimer's patient—the losses in cognition, the declining ability to function, the behavioral aberrations that upset family and friends.

The problem will accelerate in the decades ahead as the proportion of elderly in the population increase. More than 4 million people in the United States are afflicted with this disorder. Prevalence rates as high as 10% have been estimated for individuals older than 65. Patients with the disease have estimated direct costs of \$20,000 to \$61,000 per year if the duration lasts 7 to 8 years.¹

Although behavioral and functional deficits account for the high costs associated with Alzheimer's disease (AD), the disorder is defined by cognitive criteria (*Box 1*). The majority of medication trials have been aimed at symptomatic treatment. More recently, studies have been designed to prevent or delay the onset of AD. Early on, initial therapies directed toward AD were aimed at reversing the cholinergic deficit (*Box 2*). Clinical trials utilizing lecithin (25-100 g/d) and choline (<16 g/d) as precursors of acetylcholine did not lead to significant benefit.⁶ Augmenting central cholinergic levels with acetylcholinesterase (AChE) inhibitors has consistently detected symptomatic improvement.

In recent years, the Food and Drug Administration has approved 4 AChE inhibitors—tacrine, donepezil, rivastigmine, and galantamine—for the treatment of AD. I will discuss only the latter 3, since tacrine, the first to

show benefit, has a high rate of adverse effects and is of limited use.⁷ The AChE inhibitors may improve cognition and behavioral symptoms and delay progression of the illness.

Box 1

DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DEMENTIA

- A. The development of multiple cognitive deficits manifested by both:
 1. Memory impairment (impaired ability to learn new information or to recall previously learned information) and
 2. One (or more) of the following cognitive disturbances:
 - a. Aphasia (language disturbance)
 - b. Apraxia (impaired ability to carry out motor activities despite intact motor function)
 - c. Agnosia (failure to recognize or identify objects despite intact sensory function)
 - d. Disturbance in executive functioning (i.e., planning, organization, sequencing, abstracting)
- B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. The course is characterized by gradual onset and continuing cognitive decline.

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington DC: American Psychiatric Press, 1994.



Cognitive enhancers for dementia: Do they work?

They can also have beneficial effects on activities of daily living (ADL) and can reduce costs and improve caregiver burden.⁸

The three AChE inhibitors have unique basic properties (*Box 3*). In order to maximize and prolong positive drug effects, it is important to start early and adjust dosage during the treatment⁹ (*Table 1*). Side effects are tolerable; the most common include nausea, vomiting, and diarrhea. Titrating the dosage slowly can reduce these. The cholinergic quality of these medications dictate that they be prescribed with caution in patients with bradycardic arrhythmias such as sick sinus syndrome, asthma, or chronic obstructive pulmonary disease.¹⁰

Double-blind, placebo-controlled trials have demonstrated improved cognition in patients taking donepezil

Comparison of clinical effects of all 3 agents demonstrates a similar magnitude of improvement. For some drugs, this may represent an upper limit, whereas for others it may still be possible to further increase the benefit.

Results of 4 double-blind, placebo-controlled clinical trials of donepezil, involving more than 1,900 individuals with mild to moderate AD, have been published recently. In all, significant improvements in cognition were observed consistently for both therapeutic doses of donepezil (5 mg/d and 10 mg/d), relative to placebo. Similar benefits were reported for

global functioning.

The long-term clinical efficacy and safety of donepezil versus placebo across 1 year in patients with mild to moderate AD was investigated.¹⁴ The Gottfries-Branc-Steen global assessment for rating dementia symptoms demonstrated the benefit of donepezil over placebo at weeks 24, 36, and 52, and at the study end point. Advantages of donepezil were also observed in cognition and ADL.

Donepezil also appears to work for patients with moderate to severe AD. In a recent 24-week study,¹⁵ patients receiving donepezil showed benefits on the Clinician's Interview-Based Impression of Change with Caregiver Input (CIBIC+), compared with placebo, at all visits up to week 24 and at the study's end point. All other secondary measures showed significant differences between the groups in favor of donepezil at the end of the study. These data suggest that donepezil's benefits extend into more advanced stages of AD than those previously investigated, with good tolerability.

Clinical trials of rivastigmine (1.5-6 mg twice daily PO) have also demonstrated benefits on cognitive and global measures.¹⁶ The efficacy of rivastig-

Effects on cognition and global assessments

Numerous efficacy studies examining cognition and global assessments in AD patients have been performed with the AChE inhibitors. Their major therapeutic effect is to maintain cognitive function at a constant level during a 6- to 12-month period of treatment, as compared to placebo.

Box 2

WHAT IS THE PATHOPHYSIOLOGY OF AD?

The pathophysiologic processes implicated in Alzheimer's disease (AD) include amyloid precursor protein metabolism, tau phosphorylation, apolipoprotein E, inflammation, oxidative stress, and apoptosis. Neuropathological features include amyloid plaques, neurofibrillary tangles, neuronal and synaptic loss, microgliosis, and astrocytosis. The resulting clinical syndrome of dementia is associated with neurotransmitter deficits and intracortical disconnection.

The central cholinergic neurotransmitter system is impaired in AD. This system is involved in learning and memory. The limbic system and neocortex receive projections from the cholinergic system in the septal nuclei and substantia innominata. This includes the medial septal nucleus, diagonal band, and nucleus basalis.² Literature on animals has demonstrated that basal forebrain lesions impair learning and memory. Cholinergic agonists can improve this. Furthermore, cholinergic antagonists such as scopolamine and atropine can impair learning and memory in humans and animals.³ In AD, a 58% to 93% reduction in choline acetyltransferase levels (and other cholinergic markers) in the cortex and hippocampus can be observed and this correlates with dementia severity.⁴ Early AD is characterized by neuronal loss and tangles in the cholinergic nucleus basalis of Meynert.⁵

Box 3

BASIC PROPERTIES
OF THE AChE INHIBITORS

Donepezil is a second-generation, piperidine-class, selective and reversible acetylcholinesterase (AChE) inhibitor. It is structurally dissimilar from other established AChE inhibitors.

Experimentally, donepezil inhibits AChE activity in human erythrocytes and increases extracellular acetylcholine levels in the cerebral cortex and the hippocampus of the rat. Pharmacologically, donepezil has a half-life of approximately 70h, lending itself to once-daily administration.¹¹

Rivastigmine (ENA 713, or carbamoylating) is an AChE inhibitor with brain-region selectivity and a long duration of action. Both preclinical studies and studies in human volunteers have shown that rivastigmine induces substantially greater inhibition of AChE in the central nervous system compartment than it does in the periphery (40% inhibition of central AChE compared with 10% inhibition of plasma butyrylcholinesterase in healthy volunteers). Rivastigmine also preferentially inhibits the G1 enzymatic form of AChE, which predominates in the brains of patients with Alzheimer's disease (AD).

Evidence from animal studies also suggests that rivastigmine is a more potent inhibitor of AChE in the cortex and hippocampus, the brain regions most affected by AD. The principal metabolite of rivastigmine has at least 10-fold lower activity against AChE compared with the parent drug.

Rivastigmine is completely metabolized; the major route of elimination of the metabolites is renal. Rivastigmine is inactivated during the process of interacting with and inhibiting AChE, and, in contrast to other AChE inhibitors, the hepatic cytochrome P-450 (CYP-450) system is not involved in the metabolism of rivastigmine.¹²

Galantamine is an allosterically potentiating ligand that modulates nicotinic cholinergic receptors (nAChR) to increase acetylcholine release as well as acting as an AChE inhibitor. In preclinical experiments, the drug significantly improves learning, reduces AChE levels, and increases nicotinic receptor binding. Action of galantamine is on the most abundant nAChR in the human brain, the α_4/β_2 subtype.¹³

mine tartrate (ENA 713) in patients with mild to moderately severe Alzheimer's disease was evaluated in a 26-week open-label extension of a 26-week, double-blind, placebo-controlled study. By 52 weeks, patients originally treated with rivastigmine 6 to 12 mg/d had significantly better cognitive function than did patients originally treated with placebo.¹⁷⁻¹⁹

Clinical trials of galantamine (4-12 mg/bid PO) have demonstrated similar benefits.²⁰ Following a 4-week placebo run-in, patients were randomized to 1 of 4 treatment arms: placebo or galantamine escalated to final maintenance dosages of 8, 16, or 24 mg/d for a 5-month treatment phase. At study's end, the galantamine-placebo differences on the cognitive subscale of the AD Assessment Scale were 3.3 points for the 16 mg/d group and 3.6 points for the 24 mg/d group. Treatment discontinuations due to adverse events were low in all galantamine groups (6% to 10%) and comparable with that in the placebo group (7%). The incidence of adverse events in the galantamine groups, notably gastrointestinal symptoms, was low and most adverse events were mild.

Other studies examining galantamine have demonstrated similar clinical benefits.^{8,21}

When using AChE inhibitors, the slope of cognitive decline is similar in treated and untreated patients after the initial improvement. These drugs essentially do not reverse the disorder's course but shift upward the curve describing the time course of cognitive decline. This applies also to behavioral and functional benefits. Thus the benefit obtained is symptomatic and not neuroprotective, and is lost after discontinuing the medications.

Effects on functioning and behavior

In a 24-week multinational clinical trial, patients receiving donepezil (10 mg/d) were more able than placebo-treated patients to perform complex daily functioning tasks.²² Similar effects have been observed with rivastigmine and galantamine.^{16,20}

All 3 AChE inhibitors have demonstrated improvements in the behavioral changes associated with AD. Cummings et al²³ tested the hypothesis that behavioral disturbances are reported at significantly lower rates by caregivers of AD patients receiving donepezil, compared with a group of patients not



Cognitive enhancers for dementia: Do they work?

Table 1

COMPARING THE AChE INHIBITORS

	Donepezil	Rivastigmine	Galantamine
Chemical class	Piperidine	Carbamate	Phenanthrene alkaloid
AChE inhibitor	Yes	Yes	Yes
BuChE inhibitor	Small	Yes	Small
Nicotinic modulation	No	No	Yes
Elimination half-life	50-70 h	0.6-2 h	5-7 h
Administration	Once daily	Twice daily	Twice daily
Starting dosage	5 mg/d	1.5 mg bid	4 mg bid
Total recommended dosage	5-10 mg/d	6-12 mg/d	16-24 mg/d

Adapted from Conn DK. Cholinesterase inhibitors: Comparing the options for mild-to-moderate dementia. *Geriatrics* 56: 56-57, 2001.

receiving a drug for treatment of dementia. Donepezil patients were described as significantly less likely to be threatening, destroy property, and talk loudly, and significantly fewer were treated with sedatives.

An open-label study by Weiner et al²⁴ examined the effects of donepezil on emotional and behavioral symptoms using the CERAD Behavior Rating Scale for Dementia and its subscales. In a group of 25 AD patients treated with donepezil, scores returned to baseline levels at 12 months. In contrast, the scores of the reference group worsened minimally.

Galantamine has also proved effective in treating behavioral symptoms associated with AD. In the Tariot et al²⁰ study, galantamine at 16 mg/d and 24 mg/d had a significantly better outcome on CIBIC+, ADL, and behavioral symptoms versus placebo.

Rosler et al²⁵ assessed the ability of rivastigmine to improve behavioral symptoms in AD. Using the behavioral component of the CIBIC+, results showed that long-term

treatment with rivastigmine could slow the progression of symptoms. Symptoms showing stabilization included aggressiveness, activity disturbances, hallucinations, and paranoid features. The results also suggest that patients treated earlier with rivastigmine may attain a greater benefit than those whose treatment is delayed 6 months.

Rivastigmine also has significant effects on controlling behavioral symptoms in patients with Lewy body dementia.²⁶ A placebo-controlled, double-blind, multicenter study was performed in 120 patients with Lewy body dementia. Individuals were given up to 12 mg/d rivastigmine or placebo for 20 weeks, followed by 3 weeks rest. Assessment by neuropsychiatric inventory was made at baseline, and again at weeks 12, 20, and 23.

Patients taking rivastigmine were significantly less apathetic and anxious than those on placebo, and had fewer delusions and hallucinations. Almost twice as many patients on rivastigmine as on placebo (37, 63% versus 18, 30%) showed at least a 30% improvement from baseline. In a computerized cognitive assessment system and neuropsychological tests, patients were significantly faster and better than those on placebo, particularly when performing tasks with a substantial attentional component.

Cost effectiveness

Numerous studies have demonstrated that AChE inhibitors are cost savers in AD treatment. Fillit et al²⁷ examined the impact of donepezil in a multisite managed care organization for 2 years using claims data for 70 individuals with AD and related dementias. The median per diem medical costs were \$1.22 lower post treatment than they were in the pretreatment phase. Moreover, posttreatment costs were reduced in 6 of 7 service settings, with median per

John Kasckow, MD, PhD



diem savings of \$0.77 in outpatient care and \$0.65 in office visits.

Neumann et al²⁸ utilized cost-effectiveness analysis to predict that for mild AD, donepezil would pay for itself in cost offsets if the drug's effect exceeds 2 years. Donepezil costs were partially offset by a reduction in the costs of care due to enhanced cognitive functioning and the delay in placing the patient in more costly disease stages and settings.

One study used the disease-progression model to estimate potential per-patient savings resulting from the treatment of AD in Canada.²⁹ Rivastigmine was estimated to delay the transition to more severe stages of AD by up to 188 days for patients with mild AD after 2 years of treatment. For patients with mild-to-moderate and moderate disease, this delay was estimated to be 106 and 44 days, respectively.

The Assessment of Health Economics in Alzheimer's Disease model uses algorithms to predict the time until patients with AD require full-time care. A study, performed in Canada, compared treatment with galantamine to treatment without pharmacological interventions.³⁰ Galantamine was predicted to reduce the duration of full-time care by almost 10%. Approximately 5.6 patients with mild-to-moderate disease must be placed on treatment to avoid 1 year of full-time care, resulting in savings averaging \$528 per patient. For patients with moderate disease, 3.9 patients must be placed on treatment to avoid 1 year of full-time care, with savings predicted at \$2,533 per patient.

Caregiving burden

Fillit et al addressed caregiver well-being in a self-administered, nationwide survey of AD caregivers. Caregivers of patients treated with donepezil ($n = 274$) were compared with caregivers of patients not treated with donepezil ($n = 274$).³¹ The Caregiver Burden Scale measured time demands and distress linked to commonly performed caregiving tasks. Donepezil caregivers reported significantly lower scores on difficulty of caregiving. Similar findings have been observed with galantamine.³²

Numerous studies have demonstrated that AChE inhibitors are cost savers in AD treatment

References

1. Irizarry M, Hyman B. Alzheimer's disease. In: *Principles of neuroepidemiology*. Batchelor T, Cudkowicz M, eds. Boston: Butterworth-Heinemann, 2001:69-98.
2. Mesulam MM, Mufson EJ, Levey AI, Warner BH. Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol*. 1983a;214:170-197.
3. Drachman DA, Leavitt J. Human memory and the cholinergic system. A relationship to aging? *Arch Neurol*. 1974;30:113-121.
4. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet*. 1976;2:1403.
5. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol*. 1981; 10:122-126.
6. Higgins JPT, Flicker L. Lecithin and cognitive impairment. *The Cochrane Database of Systematic Reviews*. 2001.
7. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. *JAMA*. 1994;271:985-991.
8. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology*. 2000;54:2262-2268.
9. Giacobini E. Cholinesterase inhibitors stabilize Alzheimer's disease. *Methods Find Exp Clin Pharmacol*. 2000;22:609-613.
10. Irizarry MC, Hyman BT. Alzheimer Disease Therapeutics. *J Neuropathology Exp Neurol*. 2001;60:923-928.
11. Wilkinson DG. The pharmacology of donepezil: a new treatment of Alzheimer's disease. *Expert Opin Pharmacother*. 1999;1:121-135.
12. Polinsky RJ. Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. *Clin Ther*. 1998;20:634-647.
13. Samochocki M, Zerlin M, Jostock R, et al. Galantamine is an allosterically potentiating ligand of the human $\alpha 4/\beta 2$ nAChR. *Acta Neurol Scand*. 2000(Suppl);176:68-73.
14. Winblad B, Engedal K, Soininen H, Verhey F, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*. 2001;57:489-495.
15. Feldman H, Gauthier S, Hecker J, et al. Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology*. 2001;57:613-620.
16. Farlow M, Anand R, Messina J Jr, Hartman R, Veatch J. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. *Eur Neurol*. 2000;44:236-241.
17. Rogers S, Friedhoff L. Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease. *Dementia*. 1996;7:293-303.
18. Rogers S, Farlow M, Doody R, Morris R, Friedhoff L. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology*. 1998;50:136-145.
19. Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, DalBianco P, Stahelin HB, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: International randomized controlled trial. *BMJ*. 1999;318:633-638.

The AChE inhibitors donepezil, rivastigmine, and galantamine can modestly delay cognitive impairment, functioning, and behavioral agitation associated with Alzheimer's disease. As a result, there are reductions in costs as well as in the burden that caregivers must bear.

BottomLine



Cognitive enhancers for dementia: Do they work?

Related resources

- ▶ Bullock R. New drugs for Alzheimer's disease and other dementias. *Br J Psychiatry*. 2002;180(2):135-139.
- ▶ Brodaty H, Ames D, et al. Pharmacological treatment of cognitive deficits in Alzheimer's disease. *Med J Aust*. 2001;175(6):324-329.
- ▶ Ahmed MB. Alzheimer's disease: recent advances in etiology, diagnosis, and management. *Tex Med*. 2001;97(12):50-58.
- ▶ Frisoni GB. Treatment of Alzheimer's disease with acetylcholinesterase inhibitors: bridging the gap between evidence and practice. *J Neurol*. 2001;248(7):551-7.

DRUG BRAND NAMES

Tacrine • Cognex
Donepezil • Aricept

Rivastigmine • Exelon
Galantamine • Reminyl

DISCLOSURE

The author reports that he receives grant/research support from, serves as a consultant to, and is on the speaker's bureau of Janssen Pharmaceutica and Pfizer Inc., and serves as consultant to and is on the speaker's bureau of Novartis Pharmaceuticals Corp.

20. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology*. 2000;54:2269-2276.
21. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: Multicentre randomized controlled trial. Galantamine International - 1 Study Group. *BMJ*. 2000;321:1445-1449.
22. Knopman DS. Management of cognition and function: new results from the clinical trials programme of Aricept (R) (donepezil Hcl). *Int J Neuropsychopharmacol*. 2000;3:13-20.
23. Cummings JL, Donohue JA, Brooks RL. The relationship between donepezil and behavioral disturbances in patients with Alzheimer's disease. *Am J Geriatr Psychiatry*. 2000;8:134-140.
24. Weiner MF, Martin-Cook K, Foster BM, Saine K, et al. Effects of donepezil on emotional/behavioral symptoms in Alzheimer's disease patients. *J Clin Psychiatry*. 2000;487-492.
25. Rosler M, Retz W, Retz-Junginger P, Dennler HJ. Effects of two-year treatment with the cholinesterase inhibitor rivastigmine on behavioural symptoms in Alzheimer's disease. *Behav Neurol*. 1998;11:211-216.
26. McKeith I, Del Ser T, Spano P, Emre M, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet*. 2000;356(9247):2031-2036.
27. Fillit H, Gutterman EM, Lewis B. Donepezil use in managed Medicare: effect on health care costs and utilization. *Clin Ther*. 1999;21:2173-2185.
28. Neumann PJ, Hermann RC, Kuntz KM, Araki SS, Duff SB, Leon J, Berenbaum PA, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology*. 1999;52:1115-1116.
29. Hauber AB, Gnanasakthy A, Mauskopf JA. Savings in the cost of caring for patients with Alzheimer's disease in Canada: an analysis of treatment with rivastigmine. *Clin Ther*. 2000;22:439-451.
30. Getsios D, Caro JJ, Caro G, Ishak K; The AHEAD Study Group. Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. *Neurology*. 2001;57:972-978.
31. Fillit HM, Gutterman EM, Brooks RL. Impact of donepezil on caregiving burden for patients with Alzheimer's disease. *Int Psychogeriatr*. 2000;12(3):389-401.
32. Blesa R. Galantamine: therapeutic effects beyond cognition. *Dement Geriatr Cogn Disord*. 2000;11(Suppl 1):28-34.



Keep up a jump ahead of your colleagues!

The editors of *Current Psychiatry* invite you to be a member of our Practicing Psychiatry Review Panel.

Three or four times a year, we will e-mail you a manuscript submitted for publication, to get your reactions prior to editing. You can tell us whether it's relevant to your practice, and raise questions that the authors has not answered satisfactorily.

You'll be contributing to the excellence of *Current Psychiatry* for your colleagues—and at the same time—you'll be among the first to learn what's new!

To be considered for the panel, send your name, address, phone number and e-mail address, with a brief description of your practice, to **Senior Editor Pete Kelly**, pete.kelly@dowdenhealth.com