Current PSYCHIATRY

Which cholinesterase inhibitor for early dementia?

Consider drug differences, patient factors to find a good match

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Using a cholinesterase inhibitor (ChEI) makes sense for any disorder with a significant cholinergic deficit, such as Alzheimer's disease (AD) and other forms of mild-to-moderate dementia *(Box 1, page 56)*.[1-3] Yet the ChEIs tacrine, donepezil, rivastigmine, and galantamine have pharmacologic differences, and individual patients respond differently to them.

To help you choose the safest, most effective treatment for each patient, we discuss:

- three cases that show how ChEIs differ in mechanism of action, administration, and side effects
- evidence of ChEIs' efficacy in AD—for

Current PSYCHIATRY

Box 1

Is it Alzheimer's? One-third of dementias are something else

Probable Alzheimer's disease (AD) accounts for 64% of all dementias in the United States. Less-common causes include:

- vascular dementia (5%)
- combined vascular dementia and AD (10%)
- probable dementia with Lewy bodies, Parkinson's dementia, or diffuse Lewy body disease (9%)
- Lewy body variant of AD, or AD and dementia with Lewy bodies (6%)
- frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, or Creutzfeldt-Jakob disease (6%).[2,3]

In our experience, many primary care physicians choose to follow their patients with dementia, even when clinical features are atypical or suggest unusual causes. Psychiatrists are asked most often to assist in diagnosis and management of patients with:

- uncommon dementias, including frontotemporal dementia or dementia with Lewy bodies
- rapidly progressive dementia
- dementia in a patient age <60
- dementia with psychiatric comorbidities or severe behavior disturbances.[4]

which they are approved—and in other dementias for which they have been tried
- when to switch agents, and how long to continue treatment.

HOW ChEIs DIFFER

Although dementia remains incurable, recognizing cognitive decline early allows you to start ChEI therapy before substantial neuronal loss occurs *(Box 2, page 57)*.[3,4] The goal of early treatment is to improve or stabilize cognition, behavior, and activities of daily living for as long as possible.

In comparison studies,[5,6] ChEIs have shown differences in tolerability but not consistent differences in efficacy for mild to moderate AD—though these studies had methodologic limitations. Because the agents appear similarly effective, the initial ChEI choice often depends on how their differences might benefit your patient *(Table 1, page 58)*. Consider the following cases:

CASE 1: GRADUAL MEMORY LOSS

Mrs. J, age 76, has experienced a slow, insidious memory decline across 5 years. She has become socially withdrawn and shows some language difficulties. She has had peptic ulcer disease and often does not take medications as prescribed.

Her psychiatrist diagnoses probable AD and chooses donepezil with its easy dosing schedule because of Mrs. J's history of nonadherence. Donepezil's GI tolerability is also a factor in this choice because of the patient's peptic ulcer disease.

CASE 2: DEMENTIA AND MOTOR DEFICITS

Mr. L, age 82, has gradually developed memory loss and parkinsonian symptoms, including slowness of movement and shuffling gait. He has visual hallucinations of people and episodic confusion. His medications include warfarin and digoxin for atrial fibrillation and congestive heart failure.

Mr. L is diagnosed with probable dementia with Lewy bodies. His psychiatrist chooses rivastigmine because it has shown efficacy in this type of dementia and is not known to interact significantly with cardiovascular medications.

CASE 3: STROKE, THEN RAPID DECLINE

Mrs. D, age 68, has a history of hypertension and suffered a stroke in the past. Her family says her memory and behavior—anger outbursts and excessive irritability—have worsened rapidly across 2 years. Examination reveals some focal neurologic deficits.

Her psychiatrist diagnoses probable vascular dementia and chooses galantamine for its efficacy in patients with this dementia type. Mrs. D has no history of GI illness and will likely tolerate the drug's GI side effects. Follow-up care will include monitoring for tolerability.

Mechanism. Donepezil inhibits the enzyme acetylcholinesterase, and rivastigmine inhibits acetylcholinesterase and butyrylcholinesterase. Galantamine inhibits acetylcholinesterase and shows allosteric modulation of the presynaptic nicotinic receptor.

Data indicating that rivastigmine is particularly effective in patients with rapidly progressive illness is consistent with the possible advantage of inhibiting both butyrylcholinesterase and acetylcholinesterase. It has been argued that galantamine's binding to nicotinic receptors modulates their function, which may enhance acetylcholine release.

Among the three agents, only rivastigmine shows a consistent, linear dose-response relationship. It is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite (autohydrolysis). Minimal metabolism occurs via the major cytochrome P (CYP)-450 isoenzymes. Donepezil and galantamine are metabolized by isoenzymes 2D6 and 3A4 and undergo glucuronidation.[7]

Drug interactions. Because rivastigmine avoids hepatic metabolism, interactions with drugs metabolized by CYP-450 isoenzymes have not been reported.[8]

Donepezil interacts with ketoconazole and quinidine, which inhibit donepezil metabolism and increase mean donepezil concentrations. Galantamine interacts with ketoconazole, paroxetine, and erythromycin, which increase mean galantamine concentrations.[9]

Box 2

Dementia diagnosis: Earlier is better

An early dementia diagnosis enables you educate the patient and family (Box 3, page 67) and begin the most effective treatment for the person with cognitive decline. Although dementia remains incurable, early recognition presents the opportunity to start cholinesterase inhibitors before substantial neuronal loss occurs.[3,4]

Patient workup. The Alzheimer's Association offers online information for health care professionals on AD diagnosis and treatment protocols (see Related resources, page 67). A detailed history, physical examination, and Mini-Mental State Examination (MMSE) are necessary if you suspect Alzheimer's or a related dementia.

Also recommended are a comprehensive metabolic screen, complete blood counts with differential, urine analysis, serum B12 and folate studies, homocysteine levels, thyroid studies, chest radiography, ECG, lipid profile, and brain scan (MRI or CT). Perform studies such as the rapid plasma reagin test for syphilis and HIV testing as appropriate.

Administration. Donepezil and extended-release galantamine are given once daily because of their long half-lives, whereas regular galantamine and rivastigmine are taken twice daily with meals to minimize GI effects *(Table 2, page 61)*. Nausea and vomiting can occur with any of the ChEIs but are more common and troublesome with rivastigmine and galantamine.

EFFICACY IN EARLY AD

In controlled clinical trials, all four ChEIs have significantly improved cognition, behavior, and activities of daily living in patients with mild-to-moderate AD.[10-12] Tacrine—the first FDA-approved ChEI—is rarely used because its associated hepatoxicity requires ongoing liver enzyme monitoring.[13] Among the other three:

Donepezil. A review of 16 trials involving 4,365 par-

Table 1

Similarities and differences among cholinesterase inhibitors

	Tacrine	Donepezil	Rivastigmine	Galantamine
Administration	Four times daily	Once daily	Twice daily with full meals	Once daily (extended-release formulation)
AChE inhibitor	Yes	Yes	Yes	Yes
BuChE inhibitor	Yes	No	Yes	No
Allosteric modulation of nicotinic receptor	No	Yes	No	Yes
Pharmacodynamic nicotinic/muscarinic effect	Yes	Yes	Yes	Yes
GI side effects	Present	Present	Present	Present
Hepatotoxicity	Present	Absent	Absent	Absent
Metabolism	CYP-450	CYP-450	Autohydrolysis	CYP-450
Drug–drug interactions	Yes	Yes	None reported	Yes

AChE: acetylcholinesterase
BuChE: butyrylcholinesterase
CYP-450: cytochrome P-450 hepatic isoenzymes

ticipants[10] found significant benefits in cognitive functioning, activities of daily living, and behavior in persons with mild, moderate, or severe AD who were treated with donepezil for 12, 24, or 52 weeks.

Rivastigmine improved or maintained cognitive function, activities of daily living, and behavior for up to 52 weeks in patients with mild to moderate AD, according to a review of studies from 1995 to 2002.[11] GI irritation was the most common adverse effect. Giving rivastigmine for up to 2 years may reduce the cost of caring for patients with AD, mostly by delaying nursing home placement.

Galantamine has beneficial effects on cognition, global function, activities of daily living, and behavior in patients with AD, vascular dementia, and AD with cerebrovascular components, according to a review of clinical studies.[12] Adverse events are generally mild to moderate, transient, and gastrointestinal.

EFFICACY IN OTHER DEMENTIAS

In addition to their FDA-approved use for mild-to-moderate AD, ChEIs also have been studied in persons with other types of dementia and mild cognitive impairment (MCI).

Dementia with Lewy bodies. Rivastigmine given with flexible titration from 6 to 12 mg/d improved behavior in 120 patients with Lewy body dementia.[14] In the double-blind, multicenter study, patients taking rivastigmine, mean 9.7 mg/d for 20 weeks, were less apathetic and anxious and had fewer delusions and hallucinations than did those

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Table 2

How to use cholinesterase inhibitors for patients with dementia

Drug	Recommended dosing	Possible side effects	Titration	Administration
Tacrine	Initial: 40 mg/d Maximum: 160 mg/d	Liver damage causing increase in ALT levels, GI effects (nausea, indigestion, vomiting, diarrhea, abdominal pain), skin rash	Dosage can be increased every 4 weeks	Divide into four doses; take on empty stomach
Donepezil	Initial: 5 mg/d Maximum: 10 mg/d	GI effects (nausea, diarrhea, vomiting, loss of appetite), insomnia, muscle cramps, fatigue	Increase dosage after 4 weeks	Once daily in morning or at bedtime
Rivastigmine	Initial: 3 mg/d Maximum: 12 mg/d	GI effects (nausea, vomiting, loss of appetite, weight loss, diarrhea, heartburn)	Increase dosage every 4 weeks	Twice daily after meals
Galantamine (regular, ER)	Initial: 8 mg/d Maximum: 24 mg/d	GI effects (nausea, vomiting, diarrhea, weight loss), possible increased mortality risk in patients with MCI	Increase dosage every 4 weeks	Regular: Twice daily after meals ER: Once daily after a meal

ALT: alanine transferase
ER: extended-release formulation
MCI: mild cognitive impairment

taking placebo. The drug was judged to be safe and well tolerated.

Vascular dementia. Patients with vascular dementia showed improved cognition and global function when treated with donepezil, 5 or 10 mg/d, for up to 24 weeks. Donepezil was well tolerated in this combined analysis of two randomized, placebo-controlled trials.[15]

Kumar et al[16] compared two rivastigmine dosages in patients with mild-to-moderate AD, some of whom also had vascular dementia risk factors. Patients were randomly assigned to placebo, low-dose rivastigmine (1 to 4 mg/d), or high-dose rivastigmine (6 to 12 mg/d) for 26 weeks. Cognition, activities of daily living, and disease severity improved with rivastigmine in patients with or without vascular risk factors. Greater benefit was seen with high-dose than low-dose rivastigmine and in patients with AD plus vascular risk factors than in those with AD alone.

In a multicenter, double-blind trial,[17] patients with vascular dementia or AD with vascular risk factors received galantamine, up to 24 mg/d, or placebo for 6 months. Compared with controls, those taking galantamine showed improved cognition, behavior, and function. The drug overall was well tolerated, with nausea and vomiting the most common side effects.

Parkinson's dementia. Emre et al[18] evaluated rivastigmine's efficacy and safety in patients whose

Box 3

Information for patients and families about cholinesterase inhibitors

- Cholinesterase inhibitors may help improve or stabilize cognition, behavior, and/or activities of daily living
- Persons receiving these agents may decline more slowly than those who have not been treated
- Common side effects include nausea, vomiting, diarrhea, and loss of appetite
- Other less-common side effects are muscle cramps, slowed heart rate, dizziness, and fainting
- Because of differences in these agents, it may make sense to switch to another cholinesterase inhibitor if the patient has intolerable side effects or does not improve with the first one tried

mild-to-moderate dementia developed at least 2 years after a clinical diagnosis of Parkinson's disease (PD). Patients were randomly assigned to placebo or rivastigmine, 3 to 12 mg/d, for 24 weeks, and 410 of 541 enrollees completed the study. Compared with placebo, rivastigmine was associated with statistically significant improvements in cognition and global measures in dementia associated with PD but also with higher rates of nausea, vomiting, and tremor. PD's motor symptoms did not change significantly in either group.

Mixed dementia states. As mentioned, galantamine improved cognitive and noncognitive abilities in patients with vascular dementia or AD with vascular risk factors in a 6-month, double-blind trial.[17] Patients who received galantamine or placebo could then continue open-label galantamine, 24 mg/d, for another 6 months. In patients treated the full 12 months, galantamine continued to improve or maintain:

- cognition, based on Alzheimer's Disease Assessment Scale-cognitive subscale scores
- functional ability, measured by the 40-item Disability Assessment for Dementia
- behavior, measured by the Neuropsychiatric Inventory.[19]

Frontotemporal dementia. No placebo-controlled trials have evaluated cholinesterase inhibitors in patients with frontotemporal dementia, although an open-label trial suggests that rivastigmine may benefit these patients and their caregivers. Moretti et al[20] used rivastigmine, 3 to 9 mg/d, in 20 patients ages 60 to 75 with probable frontotemporal dementia. A group of matched patients received antipsychotics, benzodiazepines, or selegiline.

After 12 months, the rivastigmine-treated patients were less behaviorally impaired than the matched patients, and their caregivers reported reduced stress. Rivastigmine did not prevent cognitive deterioration, as assessed with the Mini-Mental State Examination (MMSE).

Mild cognitive impairment. Persons with MCI have objective psychometric evidence of memory loss compared with their peers, but they are not significantly impaired in activities of daily living or other cognitive functions (language, abstract thinking, or problem-solving).

At this time, we do not recommend using ChEIs to treat MCI. These agents have shown little benefit and potential risk in patients who do not meet diagnostic criteria for dementia:

- Salloway et al[21] tested donepezil's efficacy and safety in 270 patients with MCI in a 24-week, double-blind, placebo-controlled trial. Donepezil was started at 5 mg/d for 42 days, then escalated to 10 mg/d. Compared with placebo, donepezil showed no significant effects on recall, but some improvements were seen in attention and psychomotor speed.
- In two unpublished placebo-controlled trials, galantamine did not improve memory when given for 2 years to elderly patients with MCI. A

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Related resources

- Alzheimer's Association. Information for health care professionals:
  - Diagnosing Alzheimer's
    www.alz.org/Health/Diagnose/overview.asp
  - Treating cognitive symptoms
    www.alz.org/Health/Treating/symptoms.asp
- American Association for Geriatric Psychiatry. Information for older patients and their families on Alzheimer's disease, other dementias.
  www.gmhfonline.org/gmhf/consumer/alzheimers.html.

DRUG BRAND NAMES

Tacrine • Cognex
Donepezil • Aricept
Rivastigmine • Exelon
Galantamine • Razadyne (was Reminyl)

DISCLOSURES

Drs. Kamat and LeFevre report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Grossberg receives grant/research support from Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Cyberonics, Eli Lilly and Co., Eunoe, Forest Pharmaceuticals, Novartis Pharmaceuticals Corp., Pfizer, and Wyeth Pharmaceuticals. He is a consultant to AstraZeneca Pharmaceuticals, Forest Pharmaceuticals, Janssen Pharmaceutica, KV Pharma, Novartis Pharmaceuticals Corp., Organon International, and Sanofi-Synthelabo.

ACKNOWLEDGMENT

The authors thank Anjali Baliga, MD, for her contribution and help in preparing this article

precaution was added to the drug's prescribing information because 13 of the 1,026 patients taking galantamine died, compared with 1 of 1,022 taking placebo. Vascular disease caused one-half of the galantamine group deaths. No evidence of increased mortality risk has been seen in studies of galantamine in patients with mild-to-moderate AD, for which it is indicated.

GETTING THE GREATEST RESPONSE

To gauge response to ChEI therapy, family reports about the patient are helpful—such as that cognition has improved or cognitive decline has not progressed as rapidly as before. Assessment tools such as the MMSE can document improvement or stabilization.

We recommend trying an initial ChEI for at least 6 months to determine its efficacy. If your

patient cannot tolerate one ChEI or fails to respond to initial treatment, two consensus panels[22,23] recommend that you consider changing ChEIs:

- If switching because of intolerable side effects, wait at least 2 to 3 days after stopping the first ChEI before starting another.
- If switching because of poor response, you can start a different ChEI immediately after the first one is stopped.

Long-term therapy. If ChEI therapy is effective and well tolerated, encourage patients and their families to continue it indefinitely (*Box 3, page 62*). Withdraw the medication when the patient progresses to dementia's terminal phases and no longer has a meaningful quality of life.

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Bottom Line

Cholinesterase inhibitors (ChEIs) can improve and stabilize cognition and function in elderly patients with Alzheimer's disease and other dementias. Switch to another ChEI if one is not effective because the agents' mechanisms differ and response varies among patients. Educate the family and patient not to discontinue these drugs if effective.