



Does this patient have Alzheimer disease? Diagnosing and treating dementia

BARBARA J. MESSINGER-RAPPORT, MD, PhD*

Section of Geriatric Medicine, Department of General Internal Medicine,
The Cleveland Clinic

■ ABSTRACT

Alzheimer disease follows a pattern of gradual cognitive, behavioral, and functional decline. Other causes of dementia have overlapping presentations, but with important differences. Most patients with mild to moderate dementia should be treated with cholinesterase inhibitors to temporarily stabilize symptoms and delay clinically important end points. Memantine, an *N*-methyl-D-aspartate antagonist, may soon be available to treat moderate to severe dementia.

Can you be sure
any of these
patients has
Alzheimer
disease—or does
not?

IMAGINE the following three patients come to your office. Can you be sure that any of them has Alzheimer disease—or does *not* have it? What other information would you want before making this diagnosis, and how might you treat them?

Case 1: Singing in the office

Mrs. A, age 74, is brought in by her husband, who reports that her memory has been declining for 20 years, and her function has been decreasing in recent years. Over the past 6 months, she has had more trouble with short-term and long-term memory, has increasing

difficulty finding words, and is sometimes disoriented, not recognizing her husband.

Mrs. A obtained a PhD while in her 50s. At that time she was evaluated for forgetfulness. Neuropsychiatric tests were normal except for subtle memory deficits.

At age 60 she received counseling for anxiety and depression. A few years later, she retired because she was unable to prepare or present lessons.

At 66, she became lost while driving and was prescribed sertraline (Zoloft) for worsening depression.

At age 72, her husband came home to find the house full of smoke—she had left the stove on. Another neuropsychiatric evaluation found significant memory deficits, as well as deficits in language, executive function, and abstraction.

She was started on donepezil (Aricept), which seemed to stabilize her for a while.

Medical history. No history of stroke or cerebral vascular disease. History of concussion in her 40s, which required 2 weeks of hospitalization.

Medications. Sertraline for 8 years, donepezil for 2 years, vitamin E.

Physical examination. Normal. No gait disorder or neurological abnormalities.

Mental status. She appears pleasant, happy, and unconcerned about her problems, and is even singing in the office. Her speech is fluent and her voice strong. She does not know what day it is and cannot provide any details about the World Trade Center tragedy of September 11, 2001. She vaguely remembers Pearl Harbor, but cannot say what war it involved. She can list only three animals in 60 seconds, and she refers to her husband as “this fellow.”

Mini-Mental State Examination. 12/30.

*The author has indicated that she is on the speaker's bureau of the Pfizer corporation. This paper discusses treatments that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.

Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the author but are not peer-reviewed.

Case 2:
'People are stealing my things'

Mrs. B, age 99, has two master's degrees and taught in public schools for 40 years. She now lives in an independent residential facility, and her only complaint is that people are stealing her things.

You contact the facility and are told that Mrs. B has been calling the security department at least weekly for months. The missing items always turn up in her apartment. The staff is concerned about safety and social issues: she has recently left the stove on a few times and can no longer keep up with conversations with her friends.

Medical history. Nothing significant noted.

Mini-Mental State Examination. 30/30.

Case 3:
Sometimes has trouble finding her keys

Mrs. C is an 82-year-old volunteer in the hospital and an avid socialite who expresses concern that she is "developing Alzheimer disease." She says that she thinks more slowly, often can't recall a word, and sometimes has trouble finding her keys and purse.

She is soon to play three rounds of bridge in a tournament and is confident of winning two of them. She says she drives without problems, keeps medical appointments, and fills her own prescriptions.

Medications. Tamoxifen (Nolvadex), aspirin, and supplements that she and her daughter found on an anti-aging website, including melatonin, vitamins C, D, and E, folic acid, dehydroepiandrosterone (DHEA), coenzyme Q, and ginkgo.

Physical examination. Normal.

Mini-Mental State Examination. 30/30.

■ **DEMENTIA: A COMING EPIDEMIC**

Dementia, especially Alzheimer disease, is expected to reach epidemic proportions over the next decades. With the graying of our society, Alzheimer disease is quickly becoming a huge and expensive problem. While only 1% of people have dementia at age 60, as many as 40% are affected by age 85.

In the United States, dementia is the third costliest disease after heart disease and

cancer: \$100 billion a year is spent in direct-care costs, with families spending \$200,000, on average, over the course of caring for a patient.

The prognosis for Alzheimer disease is cited in textbooks as between 3 and 20 years, but the time from diagnosis to death is typically 10 years. Family members can usually provide care for a time, but the need for a residential facility becomes likelier as the disease progresses.

Families must often depend on costly services for help: adult day care at \$50 per day, visits from home health care aides at \$61 per visit, assisted living at \$25,000 per year, and nursing homes at \$44,000 per year.

Men and women develop dementia in equal proportions, but more men develop vascular dementia, and women are at greater risk for Alzheimer disease. Women are more likely to face at least the initial stages of dementia on their own. Most women over age 65 are living alone or with someone not related to them, while most men at that age are living with a spouse, who tends to be about 4 years younger. A spouse is more likely to continue home care longer than are other family members.

■ **NORMAL AGING SLOWS THINKING**

Learning and memory should stay intact before age 60 and decline by less than 10% by age 80. It is normal to think more slowly, but elders should be able to recall facts and experiences. Intelligence, organizational skills, and judgment should be preserved and compensate for slower speed of cognition.

■ **MILD COGNITIVE IMPAIRMENT**

We define people with subtle memory deficits but who function normally as having *mild cognitive impairment* (MCI), not dementia. They can still perform activities of daily living and instrumental activities of daily living (TABLE 1).

Another way to gauge impairment (as well as dementia progression) is with the Clinical Dementia Rating Scale, developed at Washington University. Six cognitive-functional categories (memory, orientation, judgment, community affairs, home and hobbies, and personal care) are assessed. The rating sys-

**More than 40%
of people have
Alzheimer
disease by
age 85**

TABLE 1

Activities of daily living and instrumental activities of daily living

Activities of daily living

(Related to personal care)

Bathing or showering
Dressing
Getting in and out of bed
Using toilet
Eating
Continence

Instrumental activities of daily living

(Related to core life activities)

Using telephone
Managing money
Preparing meals
Shopping for groceries and personal items
Doing housework and laundry
Remembering to take medications
Transportation

tem is scored from 0 (normal) to 3 (severe impairment). A score of 1 is defined as mild dementia; 0.5 denotes mild impairment. An algorithm is available for overall scoring. The scale is available on Washington University's web site at <http://www.adrc.wustl.edu/adrc/cdrScale.html>.

Between 6% and 25% of people with mild cognitive impairment progress to dementia annually. Those whose primary deficit involves memory ("amnesic MCI") as opposed to mild but diffuse executive dysfunction are at highest risk.

■ DEMENTIA INVOLVES DECREASED FUNCTION

To diagnose dementia, there must be:

- Short-term and long-term memory loss
- Impairment of at least one other area of cognition: language or motor disturbances, processing of visual and spatial information, abstract thinking, judgment, personality, planning, or organization
- Decreased function involving work, social activities, or relationships.

Dementia cannot be assessed when a person is sick, delirious, or has metabolic abnor-



malities or another brain disease. Furthermore, the functional deficit must constitute a decline from prior ability. Being a lifelong social loner or never being able to balance a checkbook, for example, does not determine dementia.

■ ALZHEIMER DISEASE

The neuropathology of Alzheimer disease is characterized by beta-amyloid deposition in brain parenchyma and blood vessels and by neurofibrillary tangles. Models of Alzheimer disease suggest that increased production of A β peptides, caused by amyloidogenic amyloid precursor protein cleavage, results in A β accumulation in brain tissue, causing neuronal dysfunction. However, it is not certain whether Alzheimer disease is a single entity or is a result of multiple disorders with a common final pathway of dementia. Both genetic and environmental factors play a role.

Risk factors and protective factors

Risk factors have been identified, but old age is the most strongly correlated. Others include:

- Presence of apolipoprotein E4 (the association is stronger for Caucasians than African Americans)
- Cardiovascular disease
- Mild cognitive impairment, especially amnesic type
- A history of head trauma or concussion
- Depression (especially if presenting for the first time at an older age)
- Diabetes (controversial).

Some factors may delay clinical manifestations of Alzheimer disease but are not proven by clinical trials:

- Enriched childhood and higher education
- Exercise
- Sociability
- Anti-inflammatory medications
- Hypertension treatment
- Estrogen therapy when begun in early menopause
- Use of statins.

Imaging studies reveal atrophy

Magnetic resonance imaging (MRI) studies of patients with Alzheimer disease may reveal atrophy of the temporal and parietal

lobes, but are not sensitive to the presence of early disease. New magnetic resonance techniques such as diffusion and perfusion imaging, spectroscopy, and functional imaging may evolve as clinical techniques to diagnose Alzheimer disease and differentiate it from other types of dementia.

Chemical imbalances most consistently include a deficit of acetylcholine. Deficits of norepinephrine and serotonin and enhanced excitotoxicity from glutamate may also occur.

Cognitive deficits reflect areas affected

In early Alzheimer disease, neurofibrillary tangles and senile plaques are deposited in specific areas of the brain:

- The parietal lobe, which processes visual information, decodes motion, and helps us name objects. It is important for map reading and calculations
- The temporal lobe, which is also important for identifying or labelling objects and for short-term memory
- The frontal lobe, which manages higher-level functions, motor control, and higher thought
- The hippocampus, which helps consolidate new memories.

Because of this distribution of plaques and tangles, problems with recent memories and naming tend to occur first. Patients typically can't recall what they did on their last birthday or what they had for dinner the night before.

Naming items and people is also a problem, and as the disease progresses, patients forget the names of family members as with Mrs. A. They will, however, typically smile when loved ones enter the room, because emotional memory is retained.

Remote memories are not affected early on, nor are "procedural" memories, which involve a skill such as typing or riding a bike.

Behavioral changes are prominent

Behavioral and psychiatric changes also occur and become more pronounced as the disease progresses. Patients may develop depression, agitation, anxiety, sleep disorders, paranoia, hallucinations, and delusions. As in Mrs. B in Case 2, patients frequently feel others are stealing from them.

Apathy is part of Alzheimer disease and not a matter of volition

TABLE 2

Differential diagnosis of dementia in older adults

| |
|---|
| Alzheimer disease |
| Vascular dementia |
| Dementia with Lewy bodies |
| Frontotemporal dementia |
| Alcoholic dementia (alcohol can complicate any dementia) |
| Infectious agents (eg, HIV, Creutzfeldt-Jakob disease) |
| Huntington dementia |
| Normal pressure hydrocephalus |
| Pugilistic dementia (due to repeated blows to the head) |

Apathy affects more than 90% of patients in the severe stage of Alzheimer disease. It often exasperates family members, who feel that the patient could travel or go out and do things if he or she “really wanted to.” Apathy, however, is part of the disease and not a matter of volition.

Apathy may be confused with depression. Without concomitant dysphoria or other depressive symptoms, it may not respond to typical antidepressives such as sertraline.

Progressive loss of function

After the preclinical phase, which is often unrecognized by the physician, patients start to lose function. At first, complex executive functions are lost, such as keeping appointments, traveling alone, or undertaking multi-step tasks such as shopping and cooking.

Although the risk of motor vehicle accidents in early Alzheimer disease is the same as in age-matched controls, eventually all persons with Alzheimer disease become unsafe drivers. They also find it difficult to manage home appliances such as the stove and washing machine. They may retain the ability to put on clothes but select inappropriate ones or put them on in the wrong order.

Wandering and behavior problems aggravate the later stages. Eventually patients become unable to walk, speak, or feed themselves. The ability to swallow may also be lost.

Families tend to place a loved one in a nursing home when incontinence, wandering, and agitation become barriers to residential care.

LESS COMMON DEMENTIAS

Other causes of dementia should be considered in patients whose symptoms do not fit those of Alzheimer disease (TABLE 2).

Vascular dementia

Vascular dementia and Alzheimer disease have traditionally been considered separate entities, but this concept is in evolution.

Although there are currently four accepted definitions for vascular dementia, the most accepted ones are the Hachinski Ischemic Score as modified by Rosen, and the definition found in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Each definition requires neurologic imaging evidence of ischemic disease (eg, one large or strategically placed infarction, multiple infarcts, or extensive periventricular white matter disease) plus abnormal neurologic findings on physical examination, and a temporal association of the cognitive deficits with the infarction.

Findings of periventricular disease alone on brain imaging are not sufficient for the diagnosis of vascular dementia, and the disease is probably overdiagnosed as the result of nonspecific findings on imaging studies. Some vascular pathology exists in 29% to 41% of all dementia cases in autopsy studies of population-based cohorts, and pure vascular pathology probably accounts for only 10% of dementia cases.¹

The interaction between ischemic cerebrovascular disease and Alzheimer disease is further complicated by multiple shared vasculopathic risk factors such as hypertension, coronary disease, prior transient ischemic attacks, or cerebrovascular accidents.

Studies have shown that the presence of coexisting ischemic lesions worsens the cognitive deficits in Alzheimer disease. Cerebral ischemia may up-regulate the expression of amyloid precursor protein and enhance the cleavage of the A β peptide from amyloid precursor protein. There may also be increased postischemic inflammation with cerebral ischemia as well, also contributing to cerebrovascular dysfunction.² Thus, ischemic cerebrovascular disease may amplify the toxicity of the Alzheimer neuropathology.

Dementia cannot be assessed when the patient is acutely ill



Memory impairment may occur incrementally or, less commonly, in a gradual and progressive fashion. The typical cognitive pattern of vascular dementia includes prominent frontal and executive dysfunction, generally with less language impairment than that observed in Alzheimer disease. Physical signs of vascular disease may include facial masking, rigidity, the Babinski sign, gait disturbances, and urinary incontinence. Although urinary incontinence also occurs in Alzheimer disease, it tends to occur earlier in vascular dementia.

Dementia with Lewy bodies

Dementia with Lewy bodies is the second most common cause of dementia, causing approximately 10% to 15% of cases.

It is characterized by the presence of Lewy bodies in the cortex, not just in the substantia nigra. Alzheimer disease pathology may be present as well.

It is defined by the presence of dementia with the emergence of parkinsonian symptoms, typically rigidity, bradykinesia, and postural changes rather than tremor, within a year of the cognitive findings. Hallucinations and delusions are prominent, and the patient is typically very sensitive to the parkinsonian side effects of traditional antipsychotics. Alertness may fluctuate, resulting in transient lapses of consciousness that may be mistaken for seizures or orthostatic syncope. Cognitive deficits are superficially similar to those in Alzheimer disease. However, neuropsychiatric testing may reveal increased inattention, visual distractibility, impairment in establishing and shifting mental set, incoherent line of thought, confabulation, perseveration, and intrusions more commonly in dementia with Lewy bodies.

Intrusion of the external environment is particularly specific to dementia with Lewy bodies. An example of an intrusion of the external environment would be to respond to a question with a visual cue. For example, the patient who is asked what television program he likes may look at the fire escape and say that he likes fire exits.³

Lewy bodies are a frequent finding on neuropathologic examination of patients with Alzheimer disease, and some 25% to 35% of patients with Alzheimer disease

develop parkinsonian features late in the course of their dementia. The diagnosis of dementia with Lewy bodies is not generally confused with Alzheimer disease when the history of a long progressive cognitive decline is clear and if the neuropsychiatric idiosyncrasies are noted.

Parkinson disease

Parkinson disease is the second most common neurodegenerative disorder in older adults, following Alzheimer disease in prevalence.

Dementia, often similar in appearance to Alzheimer disease, is found late in the course of 30% to 40% of patients with Parkinson disease. Dementia also develops in late stages of neurodegenerative diseases considered to be variants of Parkinson disease (or “Parkinson-plus syndrome”) such as supranuclear palsy, multisystem atrophy, or corticobasal degeneration. The cognitive deficits may resemble frontotemporal dementia (see below) in these situations.

Frontotemporal dementia

Frontotemporal dementia is less common than Alzheimer, vascular, or Lewy-body dementias, particularly in the oldest adults.

Language problems are more common than memory deficits. There is early loss of personal awareness and social awareness; hyperorality may be present; there may be stereotyped, perseverative behavior. Pick disease is a type of frontotemporal dementia, in which patients have difficulty with frontal system tasks, such as verbal fluency, abstraction, and executive function.

Other diseases

Other diseases, such as **alcoholism, normal pressure hydrocephalus, heavy metal or drug toxicity, HIV infection, and prion diseases** may also cause dementia in the older adult, and should be considered in the appropriate setting.

■ DIAGNOSING ALZHEIMER DISEASE

Although Alzheimer disease cannot be diagnosed with certainty without an autopsy, one can be confident of the correct diagnosis from the history and physical examination, and

If the onset of symptoms is rapid, look for a diagnosis other than Alzheimer disease

after seeing expected behavioral changes over time.

The course of Alzheimer disease is gradual and progressive. The early preclinical phase can be very long, as in Case 1. If a patient has rapid onset of symptoms or the presence of a movement disorder, another diagnosis should be sought.

Specialists, including neurologists, neuropsychologists, and geriatricians, may play a role in making the initial diagnosis and developing a plan of care.

Corroborate the history

It is important to confirm patient complaints of memory deficit and other cognitive symptoms with others. Physicians should find out if problems are more severe than the patient admits or realizes, or if there have been concomitant personality changes, psychiatric issues, or functional losses.

Physicians should check for comorbidity, depression, vitamin B₁₂ deficiency, thyroid disorders, infection, and inflammation.

Structural neuroimaging with either non-contrast computed tomography or MRI is appropriate.

Routine syphilis screening is no longer recommended by the American Academy of Neurology, but testing should be done if the history warrants it.

There are no genetic markers currently recommended for routine diagnostic purposes.

Referral for a full neuropsychiatric evaluation may help confirm the diagnosis. Serial testing (at 6-month to 12-month intervals) may help reveal disease progression (for example, in mild cognitive impairment) if treatment would change based on the findings.

Mini-Mental State Examination

The Folstein Mini-Mental State Examination is a quick office evaluation for dementia, although it takes some time if the patient thinks very slowly. A series of questions and tasks assesses the patient's orientation, attention, calculation, language, visuospatial, executive, and short-term memory abilities.

The cut-off for dementia is generally regarded as 24 out of a possible 30 points, although a normal score may vary with educational level. The test is more useful given seri-

ally to follow disease progression than as a one-time diagnostic tool.

TREATING ALZHEIMER DISEASE

Although dementia cannot be cured, all patients can and should be treated. Intervention may reduce the physical, emotional, and financial burden on the patient and caregivers, as well as on society.

Nurse specialists, speech therapists, occupational and physical therapists, psychologists, and social workers may contribute to the treatment plan.

The Alzheimer's Association (<http://www.alz.org/>) offers innumerable benefits, particularly in the area of caregiver support.

Cholinesterase inhibitors for mild to moderate disease

There are no FDA-approved medications for the two ends of the Alzheimer disease spectrum: mild cognitive impairment (preclinical disease) and severe disease. However, medications are available for the mild and moderate stages of Alzheimer disease: those with a clinical dementia rating of 1 or 2, or whose Mini-Mental State Examination scores fall between 10 and 24.

It is important to reiterate that the Mini-Mental State Examination score is a guideline and not a diagnostic test. A person with a low level of education may score less than 25. A highly educated person may have dementia yet score in the upper 20s or even 30. In this case it would not be appropriate to wait until the score drops to under 25 to diagnose Alzheimer disease. Treatment with cholinesterase inhibitors should begin at the time of diagnosis.

Cholinesterase inhibitors that are FDA-approved for the treatment of Alzheimer disease are donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl), and tacrine (Cognex). They are considered equally effective but differ in biochemical activity and adverse effects. Tacrine is no longer widely used because of hepatotoxicity.

About half of patients clinically improve with a cholinesterase inhibitor, scoring on average 4 points higher on the 70-point Alzheimer Disease Assessment Scale-cognitive subscale after 6 months. Twenty percent

The Mini-Mental score may vary with education level



markedly improve (7-point increase). The number needed to treat for significant improvement is 3 to 7.

Unfortunately, cognitive improvement tends to plateau 6 to 12 months after starting on the medication, then it declines. Additionally, studies show that discontinuation of medication for longer than 6 weeks results in cognitive scores in study patients indistinguishable from those of control patients receiving placebo.

Patients also improve with cholinesterase inhibitors from the perspective of clinicians and caretakers, according to the Clinician's Interview-Based Impression of Change plus Caregiver Input. Additionally, cholinesterase inhibitors reduce neuropsychiatric symptoms, particularly apathy and visual hallucinations.⁴

Studies indicate that the improved behavior and function:

- Allow patients to remain at home longer before being placed in a nursing home
- Enable patients to be maintained longer in a nursing home with less assistance
- May decrease mortality rates when the patient is under nursing home care.

The decision to discontinue a cholinesterase inhibitor depends on the estimates of the family, caregivers, and physician on the benefit of the drug in relation to the burden.

Memantine on the horizon for severe Alzheimer disease

Memantine, a derivative of amantadine, is a noncompetitive, highly voltage-dependent *N*-methyl-D-aspartate (NMDA) inhibitor. The NMDA receptor is a postsynaptic receptor implicated in memory processes and in the pathogenesis of Alzheimer disease. Overstimulation of the NMDA receptors by glutamate leads to neuronal calcium overload and degeneration.

Memantine (marketed as Axura) has been used in the treatment of dementia for over 10 years in Germany. Marketed as Ebixa, the drug was approved for the treatment of moderate to severe Alzheimer dementia in May 2002 in the European Union.

Studies have demonstrated a modest improvement in cognition with memantine used alone or in combination with a cholinesterase inhibitor. Adverse effects have been minimal and include dizziness,

headache, fatigue, and somnolence, in rates similar to those with placebo. Drug interactions in doses of 10 to 20 mg/day were minimal as well. A phase 3 trial is ongoing in the United States.

Treating behavior and mood disorders

Depression can be treated with antidepressant medications and may improve quality of life.

Psychotic symptoms, typically visual hallucinations or paranoid delusions, should be treated with atypical antipsychotic medications if the patient functions poorly because of disturbing psychotic features.

Apathy can be extremely difficult for patients and families. Anticholinesterase inhibitors often help.

Behavioral symptoms such as agitation or an abnormal sleep/wake cycle may be improved with medications, but all have side effects.

Benzodiazepine use is discouraged in dementia because of risks of sedation, falls, inhibition of learning and memory, and paradoxical excitation.

Anticonvulsive agents such as divalproic acid and carbamazepine have been used to treat paroxysmal and aggressive behavior without concomitant psychosis, but supporting data are limited in this population, and side effects include drug-drug interactions and excessive sedation.

Atypical antipsychotics, particularly risperidone, quetiapine, and olanzapine, have been used for agitation as well as psychosis in elderly patients with dementia. Improvement is modest; they are not FDA-approved for this indication, and long-term effects are unknown. The manufacturer of risperidone recently added a warning to the label of a possibly increased risk of ischemic cerebrovascular disease.

Trazodone, an antidepressant, has hypnotic and anxiolytic features at low doses (50–100 mg) and may help with agitation and sleep. Adverse drug effects include lethargy, orthostatic hypotension, and falls.

No medication eliminates the wandering or repetitive activity that demented patients may exhibit. We advise families to organize the household so the patient can wander and explore safely.

No medication eliminates wandering or repetitive activity in dementia

Other treatments for Alzheimer disease

Vitamin E is recommended for mild-moderate dementia in a dosage of 1,000 IU twice daily (lower if the patient is on warfarin or has a bleeding disorder). Evidence for risk and benefit is equivocal.⁵

Ginkgo. Evidence of benefit is weak.

Social engagement appears to prevent cognitive decline in community-dwelling elders. Physicians may be helpful in encouraging older adults at risk of isolation to attend senior programs and, if appropriate, adult day care centers.

Estrogen therapy (hormone replacement), begun in late menopause, may increase the risk of developing dementia, and does not improve cognition.

Nonsteroidal anti-inflammatory drugs (NSAIDs). A meta-analysis of NSAID trials to prevent Alzheimer disease (not to treat it) found a relative risk reduction of 73% in those taking the drugs for 2 or more years. Studies (such as the Alzheimer Disease Anti-inflammatory Prevention Trial) are examining the ability of selective and nonselective NSAIDs to prevent or treat Alzheimer disease. However, adverse effects may limit the usefulness of these drugs.

Statins appear to reduce the risk of developing dementia in cohort studies. Interventional studies are ongoing in subjects with mild Alzheimer disease.

Folic acid supplements to lower homocysteine levels are being considered in trials to prevent or treat Alzheimer disease.

Vaccines. A phase 2 trial of the vaccine AN1792 in 360 human subjects was intended to stimulate the immune system against beta amyloid. This trial was discontinued in January 2002 when 6% of subjects developed brain inflammation. Antibodies specific for the target were successfully induced, however, and it is possible that a revised form of the vaccine may be tested in the future.

Early treatment. Studies of treatment of amnesic mild cognitive impairment (which is thought to be the preclinical stage of Alzheimer disease) are ongoing and include the cholinesterase inhibitors. They are not approved for treatment of mild cognitive impairment at this time.

Late treatment. Studies of severe Alzheimer disease are ongoing. Cholinesterase inhibitors are not approved for treatment of severe Alzheimer disease at this time.

■ TREATING OTHER DEMENTIAS

Mild to moderate vascular dementia can be treated with cholinesterase inhibitors, with benefits comparable with those observed with Alzheimer disease. Memantine, when available, may also be of benefit. Treatment to prevent further strokes is essential.

Cholinesterase inhibitors may also improve memory in patients with dementia with Lewy bodies and do not aggravate movement. Levodopa may help the movement disorder.

No medications specifically treat frontotemporal disease. Counseling and symptom management are the mainstays of treatment.

■ CASES REVISITED

Case 1: Discuss prognosis and home safety with her husband

The singing patient with declining function has Alzheimer disease with a long preclinical phase prior to manifestation of symptoms. She is already taking donepezil and vitamin E. They should be continued in the hope that they will help her maintain enough function to stay at home and delay nursing home placement.

The most important issues to discuss with her husband surround prognosis and safety. Her husband can still care for her at home, but she should not be left alone in the house. He should look into adult day care, not only for respite for himself, but so that his wife can socialize with others.

Case 2: Begin transition to assisted living

The 99-year-old woman who scored perfectly on the Mini-Mental State Examination but worried about people stealing from her was diagnosed with mild Alzheimer disease and was started on donepezil. The phone calls to security to report missing items stopped within 1 week of starting the medication. Six months later, she was still misplacing things, but she no longer felt they were stolen.

Social engagement appears to prevent cognitive decline



Because of the continued safety and social issues, the staff at her facility began to prepare her to move to assisted living.

When I saw her at age 100, her Mini-Mental State Examination score was still 30/30. She had a satisfactory move to assisted living. I saw her recently at age 101, and her score had dropped to 28. She again felt that people were stealing from her, but didn't worry about it. I had no changes to recommend at that time and will see her again in a few months.

Case 3: 'Worried well' or preclinical phase?

The 82-year-old bridge champion who loses her keys is the type of patient whom, a few

years ago, I would have dismissed as one of the "worried well." Now I'm not so confident that she doesn't have mild cognitive impairment or early Alzheimer disease.

I encourage people like her to keep up their social life and exercise. Hypertension and other risk factors for vascular disease should be treated if present.

I would prefer delaying the diagnosis in this patient until she comes in with a family member or close friend who can confirm that she is doing as well as she says she is. Is her bridge game still as competitive as before, for example? Is she still managing her affairs well? I don't really know just because she says so.

REFERENCES

1. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; 56:1143–1153.
2. Iadecola C, Gorelick P. Converging pathogenic mechanisms in vascular and neurodegenerative dementia. *Stroke* 2003; 34:335–337.
3. Doubleday E, Snowden J, Varma A, Neary D. Qualitative performance characteristics differentiate dementia with Lewy bodies and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2002; 72:602–607.
4. Cummings JL. Cholinesterase inhibitors: a new class of psychotropic compounds. *Am J Psychiatry* 2000; 157:4–15.
5. Sano M, Ernesto C, Thomas R, et al. A controlled trial of selegiline, alpha-tocopherol, or both as a treatment for Alzheimer's disease. *N Engl J Med* 1997; 336:1215–1222.

SUGGESTED READING

- Clark CM, Karlawish JH. Alzheimer disease: current concepts and emerging diagnostic and therapeutic strategies. *Ann Intern Med* 2003; 138:400–410.
- Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. *Neurology* 2000; 54:295–301.
- Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000; 356:1627–1631.

Karlawish JH, Clark CM. Diagnostic evaluation of elderly patients with mild memory problems. *Ann Intern Med* 2003; 138:411–419.

Mega S, Masterman D, O'Connor S, Barclay T, Cummings J. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. *Arch Neurol* 1999; 56:1388–1393.

Mulnard R, Cotman C, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000; 283:1007–1015.

Petersen R, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001; 58:1985–1992.

Snowdon D, Greiner L, Mortimer J, Riley K, Greiner P, Markesbery W. Brain infarction and the clinical expression of Alzheimer disease. The Nun study. *JAMA* 1997; 277:813–817.

Winbland B, 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 Geriatr Psychiatry* 1999; 14:135–146.

Wolozin B, Kellman W, Rousseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 2000; 57:1439–1443.

ADDRESS: Barbara J. Messinger-Rapport, MD, PhD, Section of Geriatric Medicine, Department of Internal Medicine, A91, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.