CLINICAL PRACTICE

Early Alzheimer's Disease

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 72-year-old, college-educated woman comes in for the evaluation of mild memory loss that has been gradually progressing for the past two years. The patient lives alone, drives her own car, and manages her own finances, although she has recently made some errors in her checkbook. She also forgot the location of her car in a mall parking lot for two hours. Her score on the Mini–Mental State Examination is 26 of a possible 30, but she missed several items pertaining to memory. How should this patient be evaluated and treated?

THE CLINICAL PROBLEM

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At present, 4 million Americans have Alzheimer's disease, and the number of cases is expected to quadruple by the middle of this century.[1] Advancing age is the major risk factor for dementia, with a doubling of risk every five years after the age of 65. Alzheimer's disease accounts for 50 to 75 percent of all cases of dementia. Other frequent causes of dementia include vascular dementia, either alone or in combination with Alzheimer's disease (in 10 to 20 percent of cases), dementia with Lewy bodies (in 10 to 15 percent), and frontotemporal dementia (in 5 to 15 percent). There are no definitive imaging or laboratory tests for the diagnosis of dementia or most of the disorders that cause dementia, including Alzheimer's disease. The evaluation thus depends on careful history taking in interviews with both the patient and a reliable informant, thorough physical and neurologic examinations (including careful testing of mental status), and use of diagnostic criteria for dementia and Alzheimer's disease that have high reliability and validity.

DEFINITIONS OF DEMENTIA, MILD COGNITIVE IMPAIRMENT, AND NORMAL AGING

The criteria for dementia as specified in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (revised)[2] and fourth edition,[3] require that a patient have cognitive loss in two or more domains, such as memory, language, calculations, orientation, and judgment. In addition, the loss must be of sufficient severity to cause social or occupational disability (Table 1). The use of neuropsychological tests and screening instruments, such as the Mini–Mental State Examination (MMSE)[5] and the Blessed Information–Memory–Concentration test (IMC),[6] is recommended to detect and follow cognitive decline.[7,8] The interpretation of scores depends on a person's age and education level, but patients with cognitive losses in two or more domains typically have an MMSE score of less than 24 (the maximal score is 30 and the minimal score 0, with lower scores indicating poorer performance) or an IMC score of more than 8 (the maximal score [number of errors] is 33 and the minimal score 0, with higher scores indicating poorer performance).

Patients with profound memory loss without other cognitive impairments and patients with minor impairments in numerous cognitive domains but no functional im-

pairment at work or home do not meet the criteria for dementia. These patients are generally considered to have mild cognitive impairment. These patients' MMSE scores are typically normal (24 to 28), but they often do poorly on the memory components of the two tests (which require the recollection of three words [on the MMSE] or the recollection of a name and address [on the IMC]). A more detailed evaluation of memory and cognition is generally necessary to confirm this diagnosis, and referral to a neuropsychologist is appropriate. When they are followed longitudinally, each year approximately 15 percent of patients with mild cognitive impairment have progression to dementia, usually Alzheimer's disease.[4]

Persons who are aging normally may also have some mild deficits. For example, mental processing speed and memory for names decline with age, but longitudinal investigations typically show the changes to be less than suggested by cross-sectional studies.[9,10] Moreover, these changes should not materially affect a person's ability to function.

SUBJECTIVE SYMPTOMS RELATED TO MEMORY

With aging, people become increasingly likely to report subjective memory loss; the rate of such reports is 25 to 50 percent in community studies of persons over the age of 65. In most community studies, however, persons with subjective memory loss do not have an increased risk of dementia unless they also have poor objective memory performance (typically defined as a score more than 1.5 SD below age- and education-specific norms on a memory test).[11,12] Highly educated people, however, may report subjective memory difficulties before cognitive deficits can be demonstrated on tests commonly used in the clinic.[13]

Table 1. Criteria for the Diagnoses of Dementia, Probable Alzheimer's Disease, and Mild Cognitive Impairment.

Dementia*
Loss of memory and one or more other cognitive abilities (aphasia, apraxia, agnosia, or disturbance in executive functioning)†
Substantial impairment in social or occupational functioning (decline from a previous level of functioning)
Deficits that do not occur exclusively during the course of delirium
Probable Alzheimer's disease‡
Typical history of Alzheimer's disease
Insidious onset of symptoms
Gradual progression of symptoms
Cognitive loss documented by neuropsychological tests
No physical signs or neuroimaging or laboratory evidence of other diseases that could cause dementia (such as strokes, Parkinson's disease, subdural hematomas, or tumors)
Mild cognitive impairment§
Report (by the patient or an informant) of memory loss
Abnormal memory performance for age (score >1.5 SD below mean for age)
Normal general cognition
Normal activities of daily living
Criteria for dementia not met

* The criteria are consistent with those of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition (revised) and fourth edition.[2,3]
† Apraxia refers to difficulty in sequencing voluntary motor movements (as in dressing), agnosia to difficulty in processing sensory input (as in recognizing objects by sight), and disturbance in executive functioning to difficulty in planning and organizing activities.
‡ The criteria are consistent with the National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria.
§ The criteria are from Petersen et al.[4]

STRATEGIES AND EVIDENCE

DIAGNOSIS

The first issue is whether the patient has dementia or mild cognitive impairment. If the history and results of cognitive screening tests do not establish the diagnosis, the patient should be referred for more extensive evaluation by a neuropsychologist.

The routine workup for patients with dementia or mild cognitive impairment should include careful history taking and physical and neurologic examinations, including tests of mental status. Medications should be carefully reviewed. Non–contrast-enhanced computed tomographic (CT) scanning or magnetic resonance imaging (MRI) and blood assays (measurement of electrolyte levels, assessment of hepatic, renal, and thyroid function, and measurement of the vitamin B_{12} level) should be performed. Although hypothyroidism or vitamin B_{12} deficiency is rarely the cause of dementia, both are frequent coexisting conditions for which treatment is recommended.[14,15] Screening for depression with the use of a brief instrument, such as the Geriatric Depression Scale,[16] is appropriate, but the clinician should also question the patient (separately from his or her family) and ask family members about any depressive symptoms. Although depression can mimic dementia, it occurs more often as a coexisting condition. Cognitive improvement after the treatment of depression does not rule out an underlying, early dementia.

In patients with dementia, the likelihood of Alzheimer's disease is assessed largely on the basis of the history. According to the National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disor-

ders Association (NINCDS–ADRDA) criteria for probable Alzheimer's disease,[17] the cognitive loss (in two or more domains, including memory) must have an insidious onset and gradual progression. In addition, other causes of dementia must be ruled out by examination, appropriate laboratory testing, and neuroimaging. Table 2 summarizes findings that may suggest a diagnosis other than Alzheimer's disease, although sensitive and specific criteria for identifying these disorders in clinical practice are not available.[18-24]

Additional tests should be considered for patients whose condition seems atypical. An electroencephalogram is warranted if there is a history of seizures, loss of consciousness, episodic confusion, or rapid clinical decline. More extensive neuropsychological evaluation can facilitate diagnosis in patients whose symptoms are very mild or atypical or whose history is unusual. A lumbar puncture should be performed in patients who have a history or signs of infection or cancer.

Apolipoprotein E genotyping and other genetic studies are not routinely indicated.[7] Similarly, positron emission tomography (PET), functional MRI, assays of the cerebrospinal fluid for amyloid and tau proteins, and electrophysiological testing are promising areas of research but are not indicated in the routine clinical care of patients with suspected Alzheimer's disease.

Table 2. Atypical Early Features of Alzheimer's Disease and Other Diagnostic Considerations.

Feature	Diagnostic Consideration
Abrupt onset	Vascular dementia
Stepwise deterioration	Vascular dementia
Prominent behavioral changes	Frontotemporal dementia
Profound apathy	Frontotemporal dementia
Prominent aphasia	Frontotemporal dementia Vascular dementia
Progressive gait disorder	Vascular dementia Hydrocephalus
Prominent fluctuations in level of consciousness or cognitive abilities	Delirium due to infection, medications, or other causes Dementia with Lewy bodies Seizures
Hallucinations or delusions	Delirium due to infection, medications, or other causes Dementia with Lewy bodies
Extrapyramidal signs or gait	Parkinsonian syndromes Vascular dementia
Eye-movement abnormalities	Progressive supranuclear palsy Wernicke's encephalopathy

TREATMENT OF PRIMARY SYMPTOMS

Nonpharmacologic Management, Education, and Support

Since cognitive impairment is frequently exacerbated by medications, medication use should be minimized, with particular attention to the use of prescription sleeping pills, antianxiety medications, and over-the-counter preparations for sleep and cold symptoms.

Safety issues, such as those related to driving, should guide the clinician in determining when a patient can no longer be left unsupervised. Patients with mild Alzheimer's disease will typically become lost while driving before they have difficulty with the process of driving itself. The first clinic visit is the time to begin working with the patient and family to discontinue driving before serious safety risks arise. Other signs that require immediate attention include the patient's wandering or getting lost, leaving stoves or other appliances unattended, or involvement in automobile accidents.

Advance directives, durable power of attorney, and stress on the part of caregivers must be addressed. Training for caregivers in strategies to manage daily activities, and referrals to day care, respite care (short-duration residential care to relieve the caregiver temporarily), home support services, counseling, and support groups can be very helpful, although such services are generally not covered by Medicare or other insurance carriers. Several local and national organizations are excellent sources of information that may be useful to clinicians and families, including the Alzheimer's Association (http://www.alz.org or 800-272-3900) and the Alzheimer's Disease Education and Referral Center (http://www.alzheimers.org or 800-438-4380). Although the available data are not consistent, there is evidence that these nonpharmacologic interventions can help prolong the period before admission to a nursing home[25,26] and reduce depression, burden, anger, and fatigue on the part of caregivers.[27-30]

Pharmacologic Management

Cholinesterase inhibitors are the drugs that have proven most effective for the primary treatment of Alzheimer's disease, and four — tacrine, donepezil, rivastigmine, and galantamine — are currently approved by the Food and Drug Administration (FDA) for this indication (Table 3). These drugs presum-

ably act by increasing the availability of acetylcholine, the loss of which is the primary neurotransmitter deficit in Alzheimer's disease.

Cholinesterase inhibitors typically result in a small improvement in symptoms, followed by an eventual decline to a level below base line — a pattern that corresponds to a two-to-seven-month delay in symptomatic progression. Virtually all studies of cholinesterase inhibitors to date have involved patients with mild-to-moderate Alzheimer's disease (range in MMSE score, 10 to 26). Patients treated with these agents may appear more alert and attentive and may have moderate improvements in memory, language, and the activities of daily living, such as dressing. In addition, cholinesterase inhibitors may reduce behavioral disturbances, such as aggressiveness and agitation.[31-33] Patients who are treated have a decline that parallels that of patients who receive placebo, although performance generally remains better with treatment than without treatment for at least one year.[34-37]

If side effects develop, a switch in medications can be accomplished relatively quickly; the use of the new medication can generally be initiated 24 hours after the discontinuation of the first one. Data are lacking on the benefit of switching to a different agent in a given class if one such agent appears ineffective. There are also limited data on the efficacy of cholinesterase inhibitors in patients with severe dementia or dementias other than Alzheimer's disease (such as vascular dementia or dementia with Lewy bodies). Some studies, however, have suggest-

Table 3. Medications Useful for the Treatment of Symptoms of Dementia.

Symptom and Drug	Initial Dosage	Recommended Final Daily Dose	Common Side Effects
Cognitive loss			
Tacrine (Cognex)*†	10 mg four times a day for 4 wk; increase by 10 mg per dose every 4 wk	20–40 mg four times a day	Elevated aminotransferase levels, nausea, vomiting
Donepezil (Aricept)*	5 mg daily for 4–6 wk; increase to 10 mg daily	10 mg daily	Nausea, diarrhea, insomnia, vomiting
Rivastigmine (Exelon)*‡	1.5 mg twice a day (with food); increase by 1.5 mg per dose every 2 wk	3–6 mg twice a day (with food)	Nausea, diarrhea, vomiting, weight loss
Galantamine (Reminyl)*‡	4 mg twice a day (with food); increase by 4 mg per dose every 4 wk	8–12 mg twice a day (with food)	Nausea, vomiting, weight loss
Depression			
Paroxetine (Paxil)*‡	10–20 mg daily; increase by 10–20 mg per day every wk	20–50 mg daily	Nausea, somnolence
Sertraline (Zoloft)*‡	25–50 mg daily; increase by 25–50 mg per day every wk	50–200 mg daily	Nausea, headache, insomnia
Agitation, delusions, or hallucinations			
Haloperidol (Haldol)§	0.5 mg daily; increase by 0.5 mg per day	0.5–2.0 mg twice a day	Extrapyramidal effects, tardive dyskinesia
Risperidone (Risperdal)*‡¶	0.5 mg daily at bedtime; increase by 0.25–0.5 mg per dose every 2–7 days	0.5–2.0 mg twice a day	Insomnia, agitation, extrapyramidal effects
Quetiapine (Seroquel)*	25 mg twice a day (by mouth); increase by 25 mg per day every 2 days	25–250 mg three times a day	Headache, somnolence, hyperlipidemia

* This agent is contraindicated in patients with known hypersensitivity to it. It should be used with caution in patients with cardiac-conduction disease, hepatic or renal disease, asthma, peptic ulcer disease, or seizure disorders.
† Serum levels of hepatic enzymes (e.g., alanine aminotransferase) should be checked every 2 weeks for 16 weeks and then once every 3 months.
‡ This agent is available as an oral solution.
§ This agent is contraindicated in patients with Parkinson's disease.
¶ This agent has been associated with an increased risk of stroke.

ed that cholinesterase inhibitors may also improve cognition and behavior in these patients.[38,39]

The use of antioxidants is another approach to treatment. Antioxidants presumably work by reducing free-radical production and oxidative injury to the brain. The results of a randomized, double-blind, two-year clinical trial involving 341 patients[40] suggested that either vitamin E (alpha-tocopherol at a dose of 1000 IU twice a day) or selegiline (a selective monoamine oxidase inhibitor) was beneficial for patients with moderately severe Alzheimer's disease; both of these medications delayed the time to clinically meaningful end points, including institutionalization and deficits in activities of daily living, such as the ability to bathe and dress. On average, treated subjects reached these end points six to nine months later than those given placebo.[40] There was no improvement in cognition, and the combination of these agents offered no additive benefit. Vitamin E is recommended more frequently than selegiline because it is less expensive and has fewer side effects.

Studies have suggested that antiglutamatergic therapy may be useful for treating Alzheimer's disease and vascular dementia by limiting the neuronal damage that may result from excessive release of glutamate.[41,42] In one recent study,[41] patients with Alzheimer's disease who had moderate-to-severe dementia (MMSE score, <8) and were treated with memantine, a noncompetitive N-methyl-D-aspartate–receptor antagonist, for a seven-month period had improvements in ratings of severe impairment, scales of clinical impression, and activities of daily living.[41] Memantine, as compared with placebo, delayed symptomatic progression by approximately two months, and there were no significant differences between the two groups in the overall rate of adverse events. At present, this treatment remains experimental in the United States, although it is available in some other countries. No data are yet available on its use for milder dementias.

Data on the efficacy of *Ginkgo biloba* for treating dementia are limited and come largely from small or open-label studies. The effect size in the few randomized trials that are available is generally less than the effect size associated with acetylcholinesterase inhibitors,[43-45] but ginkgo remains a possible treatment option. As with all dietary supplements, the purity and potency of the preparations used may not be known.

Several large trials have failed to show that estrogen (alone or in combination with progesterone), nonsteroidal antiinflammatory drugs, and prednisone offer benefit in the treatment of Alzheimer's disease.[46-49] Recent data from the Women's Health Initiative Memory Study[50] indicate that therapy with a combination of estrogen and progesterone may increase the risk of dementia, including Alzheimer's disease.

TREATMENT OF SECONDARY SYMPTOMS

For virtually all patients with Alzheimer's disease, the symptoms extend beyond cognitive loss. Depression occurs in 25 to 50 percent of patients, agitation in 50 to 70 percent, and psychotic symptoms such as paranoid delusions and hallucinations in 30 to 60 percent. Treatment of these symptoms can improve the quality of life for both the patient and the caregiver. In addition to nonpharmacologic management, the use of medications should be considered, although drugs for these symptoms have not been approved by the FDA specifically for treatment in patients with dementia.

In randomized clinical trials,[51-57] haloperidol and the atypical antipsychotic agents risperidone and olanzapine, when compared with placebo, reduced the rates of agitation, delusions, and hallucinations by about 20 to 30 percent. Atypical antipsychotic agents may be better tolerated than the older, traditional antipsychotic drugs, such as haloperidol. Side-effect profiles should guide the choice of agents (Table 3).[44] Similarly, antidepressant agents (including sertraline, citalopram, and fluoxetine) have improved depressive symptoms and irritability in persons with dementia.[58-60] Sedative antidepressants (e.g., paroxetine) or antipsychotic medications (e.g., quetiapine) frequently improve sleep disorders and nocturnal agitation, thereby circumventing the need for sleep medications, which may further compromise cognition.

AREAS OF UNCERTAINTY

The response to medications for the treatment of primary and secondary symptoms of Alzheimer's disease is not predictable, and the choice of dosage and the duration of treatment rely on clinical judgment. Definitive diagnostic tests remain to be developed. Appropriate therapy for patients with mild cognitive impairment is unclear, although studies are in progress. For the primary prevention of Alzheimer's disease, data from randomized clinical trials are necessary to evaluate putative protective factors identified in observational studies.[61] Pro-

tective factors may include diet and exercise and the use of estrogen (preparations without progesterone), nonsteroidal antiinflammatory drugs, antioxidants, cholesterol-lowering agents, and ginkgo.

For the treatment of dementia, several other strategies are currently under investigation, including the use of glutamate antagonists other than memantine, calcium-channel blockers, cholesterol-lowering agents, antioxidants other than vitamin E, and combination therapy (cholinesterase inhibitors and antiglutamatergic agents). Clinical trials of immunotherapy with beta amyloid (so-called vaccination) were halted last year after encephalitic reactions developed in several patients,[62] but new formulations may soon be available for clinical investigation.

GUIDELINES

Guidelines for the diagnosis and management of Alzheimer's disease have been developed by many organizations, including the American Academy of Neurology (summarized in Table 4) (http://www.aan.com/professionals/practice/guidelines.cfm),[7,14,44] the American Psychiatric Association (http://www.psych.org/clin_res/pg_dementia.cfm),[63] the American Academy of Family Physicians,[64,65] and a consortium of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society (http://www.americangeriatrics.org/products/positionpapers/aan_dementia.shtml).[66] All endorse the use of cholinesterase inhibitors and the treatment of coexisting conditions, if clinically indicated. They also emphasize nonpharmacologic approaches for patient care.

Table 4. Guidelines for the Diagnosis and Management of Dementia.*

Diagnosis of dementia

Recommended definitions
- National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria.
- *Diagnostic and Statistical Manual of Mental Disorders,* third edition (revised).

Tests
- Either computed tomography or magnetic resonance imaging is recommended for the initial evaluation; no other imaging procedure is recommended.
- Currently, no test for genetic markers is recommended.
- Screening for depression, vitamin B_{12} deficiency, and hypothyroidism should be performed.
- Screening for syphilis is not justified unless there is a clinical suspicion of neurosyphilis.

Management of dementia

Standards
- Use of cholinesterase inhibitors should be considered in patients with mild-to-moderate Alzheimer's disease, although the average benefit is limited.
- Estrogen should not be prescribed to treat Alzheimer's disease.
- Antipsychotic agents should be used to treat agitation and psychosis when environmental manipulations fail.
- Behavior modification and scheduled toileting are helpful to reduce urinary incontinence.

Guidelines
- Use of vitamin E should be considered in an attempt to slow the progression of Alzheimer's disease.
- Use of antidepressant medications should be considered for patients with depression.
- Educational programs can be supportive for caregivers and nursing-home staff.

* The guidelines are based on those of the Quality Standards Subcommittee of the American Academy of Neurology.[14,44]

CONCLUSIONS AND RECOMMENDATIONS

The diagnosis and management of memory loss are clinical challenges that require considerable time from busy health care providers. There are no biologic markers for Alzheimer's disease or most other dementias, but with careful evaluation and the application of well-defined, reliable clinical criteria, diagnosis can be made with a high level of accuracy.

A crucial component of the workup is careful testing of mental status, to distinguish among dementia, mild cognitive impairment, and normal aging. With regard to the patient in the vignette, normal aging is an unlikely possibility, given the history of checkbook errors and forgetfulness about the location of the car. For some patients, examination of global mental status (e.g., with the MMSE) is adequate for ascertaining the presence or progression of dementia. However, patients with mild disease and with a high level of functioning at base line (such as the woman in the vignette), as well as younger patients or those with atypical symptoms, may require referral to a neuropsychologist for more extensive psychometric testing.

Forms for reliable instruments such as the MMSE, the Geriatric Depression Scale, and the Instrumental Activities of Daily Living tool can be downloaded from links on the Alzheimer's Association Web site (http://www.alz.org/resourcecenter/resourcecenter.htm). Norms specific for age and level of education for the MMSE are available at http://www.nemc.org/psych/mmse.asp.[8] Nurses and other trained personnel can perform the cognitive examinations, the costs of which are frequently reimbursable.

If testing confirms the presence of dementia, I would prescribe a cholinesterase inhibitor (Table 4), as I do for most patients with Alzheimer's disease at the time of diagnosis, with the expectation of moderate improvements in memory, thinking, and general alertness and a delay in the progression of symptoms. The benefit of vitamin E is less clear; I discuss the data with patients and families and leave the decision to them. Perhaps the most important intervention is the identification and treatment of other disabling symptoms, such as depression, agitation, delusions, and sleep disorders. Overall, I try to minimize the use of medications.

A caregiver should be encouraged to come to all of the patient's appointments to ensure the safe arrival of the patient, who perhaps should not be driving, and to facilitate the accurate assessment of symptoms. In addition, the caregiver's own level of stress can be assessed. Follow-up visits at which informants are interviewed and the patient is given brief cognitive tests should take place every three to six months, at a minimum, and more frequently when there are behavioral problems or sudden changes or when medications are being adjusted.

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