

Diagnostic Evaluation of Elderly Patients with Mild Memory Problems

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This case-based discussion focuses on the clinical presentation and diagnostic assessment of a uniquely challenging group of elderly patients: those with symptoms of mild memory problems. Such patients present a challenge to clinicians because of flux in our understandings of normal, age-related cognitive changes; of cognitive changes due to neurodegenerative illnesses; and of the relationships between depression and cognitive impairment. In addition, symptoms of memory problems may be reported by

an observer rather than by the patient. These challenges warrant stepwise evaluation of elderly patients who present with symptoms of memory loss.

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A 70-year-old man and his son present for an initial visit. The patient says his son made the appointment and insisted he come. The patient's son says that his father has troubles with his memory. At a family reunion 2 months ago, his father could not recall the names of some cousins. The patient laughs and remarks, "It's no worse than for anyone else my age; besides, I haven't seen them in years." His son points out that these are his father's favorite cousins whom he sees at least twice per year.

WHAT ARE THE POTENTIAL CAUSES OF MEMORY PROBLEMS IN ELDERLY PATIENTS?

Memory loss—impairment in the ability to learn new information or to retrieve previously learned information (1)—is among the most common cognitive changes noted by elderly patients or by their families and friends. A patient with clinically meaningful memory loss will almost always show measurable impairment in the ability to recall recently learned information (delayed recall). However, the report of "memory loss" may reflect impairment not in memory but in another cognitive domain that presents as memory loss. For example, trouble finding the right word may actually reflect a language impairment or inattention related to depression, especially if the patient rather than a family member reports the loss (2–8).

In normal aging, decreased ability to retrieve information can cause annoying memory lapses that do not impair the ability to perform activities of daily living (1). These changes are largely the result of declines in frontal lobe function, which is measured as executive function (the ability to organize, plan, and focus on a topic) (9). In contrast, memory loss that impairs the ability to perform activities of daily living strongly suggests neurodegenerative dementia. Dementia is generally defined as a progressive decline in two or more cognitive domains that is severe enough to interfere with the performance of everyday activities (10). Decline in at least two domains suggests a cognitive disorder resulting from damage in more than one brain region. Table 1 summarizes the common causes of cognitive symptoms, the common causes of dementia, their typical historical and clinical features, and key diagnostic

points. The most likely causes of dementia are, in order of likelihood, Alzheimer disease, frontotemporal dementia, and dementia with Lewy bodies.

Typical early features of Alzheimer disease include difficulty retaining new information and a failure of cueing to help jog remembrances. Changes in mood and behavior are initially very mild and may include social withdrawal that can mimic the symptoms of minor depression. Both the behavior and mood changes may simply reflect the patient's difficulty dealing with an environment he or she finds increasingly confusing.

As the illness progresses, most patients begin to exhibit word hesitancy and circumlocutions that progress to a reluctance to initiate conversation and use of phrases loosely connected to a unified thought. However, language comprehension is less impaired than the ability to talk. In addition, patients often retain the ability to interpret and respond to the emotions of those around them.

Another cause of memory loss is *mild cognitive impairment*, a term that describes persons who do not have functional impairments that meet criteria for dementia but whose cognitive function falls between the changes associated with normal aging and dementia. Mild cognitive impairment may represent a prodementia state (14). In the prodromal state of Alzheimer disease, called the amnesic variant of mild cognitive impairment, there are reports of memory loss and subnormal performance on a measure of memory (13). However, mild cognitive impairment can also occur in other domains of cognitive function.

Longitudinal studies suggest that persons with mild cognitive impairment are at increased risk for progressing to Alzheimer disease (12% per year compared with 1% to 2% for matched controls with normal memory) (13). Symptoms may be present for as long as 7 years before they become severe enough to indicate a diagnosis of Alzheimer disease. Intervention trials are under way to determine whether treatments for Alzheimer disease can slow this rate of conversion.

Although affect is not a cognitive domain, the interactions among mood, memory-related symptoms, and cognitive function warrant evaluation of affect as part of a routine assessment of memory problems. Elderly patients with

Table 1. Common Causes of Symptoms of Mild Memory Loss in Elderly Patients*

Cause (Reference)	Typical Historical and Clinical Features	Comments
Alzheimer disease (10)	Insidious onset of losses in memory, language, and visuospatial and executive function with largely normal results on neurologic examination	Patients may appear depressed because of social withdrawal. Extrapyramidal signs may be present, such as rigidity, but they are mild and do not antedate the cognitive symptoms.
Frontotemporal dementia (11)	Two broad patterns of clinical manifestations: 1) profound changes in personality and social conduct and 2) changes in expressive language or in naming and comprehension	The disease category includes Pick disease (pattern 1) and progressive nonfluent aphasia and semantic dementia (pattern 2). Pattern 1 patients show executive function deficits; errors in memory, if any, are the result of inattention.
Lewy body dementia (12)	Pattern of cognitive decline similar to that of Alzheimer disease plus at least two of the following: visual hallucinations, fluctuating cognition, and parkinsonian signs (rigidity, falls, masked face)	Can be confused with Parkinson disease. Parkinsonian signs are usually poorly responsive to L-dopa replacement therapy. Use of phenothiazine-based antipsychotic agents can precipitate marked worsening of parkinsonism.
Mild cognitive impairment (13)	Memory or other cognitive problems in the setting of mild deficits on cognitive testing and relative preservation of other cognitive functions	History will show no clinically meaningful functional impairment as a result of cognitive deficits. Patients may progress to dementia, especially Alzheimer disease.
Depression (major depression, dysthymia, or subsyndromal depression)	Depressed mood plus 2 weeks of at least four of the following: diminished interest in activities of daily living, $\approx 5\%$ change in body weight over 1 month, changes in sleep, psychomotor agitation or retardation, fatigue, feeling of worthlessness or guilt, diminished ability to think or concentrate, recurrent thoughts of death†	Impairments can be found in measures of cognition, but they are typically mild. These generally improve with successful treatment of depression. Patients will report memory loss, but testing of delayed recall will generally show mild if any impairment. Several symptoms of depression can overlap with dementia, such as diminished ability to concentrate, social withdrawal, and sleep disruption.
Cerebrovascular infarcts	Cognitive impairment following the onset of a stroke	With the exception of large strokes and major hemorrhages, the precise contribution to cognitive dysfunction of CT- or MRI-defined infarcts and T2 hyperintensities on MRI remains unclear.
Medications	Cognitive impairment following a medication change or addition	Common causes include medications with anticholinergic or sedative effects.
Medical illnesses that impair brain metabolism	Illnesses that cause hypoxia, hepatic disease, and endocrine disorders such as hypothyroidism and hyperparathyroidism	Thyroid testing is warranted as part of an initial work-up of a patient with documented memory loss.

* Referral to a neurologist is warranted for a patient who has cognitive impairment as well as neurologic signs such as focal muscle atrophy, fasciculations, dysarthria, abnormal voluntary eye movements, or limb weakness that cannot be explained by a stroke. CT = computed tomography; MRI = magnetic resonance imaging.

† These symptoms apply to major depression.

depression may report memory loss (2–6, 8). However, measures of depressed patients' memory are generally not significantly different from those of nondepressed controls (4, 5), and subjective memory symptoms often resolve with treatment of depression (5). Nondemented patients who have both depression and measurable cognitive deficits generally have deficits in speed and attention (for example, spelling the word *world* backward) (15) that manifest as difficulty registering new information (4, 5).

Primary depression was once believed to masquerade as pseudodementia. Clinically significant depressive symptoms are common among patients with dementia. One study found that such symptoms occurred in 40% of patients with dementia versus 12% of nondemented age-matched controls (16), and prevalences of 15% (17) to 49% (18) have been noted in dementia clinics. However, intervention studies of treatment in patients with dementia and minor symptoms of depression show that depressive

symptoms improve with treatment but cognition does not (19, 20). In summary, relationships exist between depression and either reports of cognitive impairment or actual impairments. Thus, a standard work-up of memory loss warrants assessing and treating affective impairments. However, evidence does not support the nosologic status of depression as a cause of dementia (21).

Talking to the patient, you learn that his wife died 4 years ago, he lives alone, and he does not drink alcohol. He completed high school and 1 year of business college, then worked as an insurance agent for 40 years. You note during this history that he has some trouble organizing the sequence of past events, turning to his son for assistance. He admits he may have some problems with memory, but he says it is no worse than what his friends joke about.

The son has noted no problems with his father's ability to perform his instrumental or basic activities of daily living, but

the time together is usually spent at the son's house in the company of other family members. They talk at least weekly by telephone, and the patient visits his son every Sunday.

The medical records provided by the patient's previous personal physician indicate that he has an 8-year history of hypertension that has been treated with hydrochlorothiazide. Eight years ago, while traveling in Arizona, he had a period of confusion diagnosed as a possible "mini-stroke." On direct questioning, he says he has no problems performing his activities of daily living.

IN THE INITIAL EVALUATION OF A PATIENT WHO REPORTS MEMORY PROBLEMS, WHAT HISTORICAL INFORMATION IS NECESSARY AND HOW SHOULD THE CLINICIAN GATHER IT?

In early dementia, impairments in instrumental self-maintenance are among the most sensitive signs of cognitive impairments. Therefore, the history should focus on whether there have been changes in the patient's ability to perform instrumental activities of daily living (22). Instrumental activities are using transportation, managing money, cooking, shopping, housekeeping, doing laundry, using the telephone, and managing medications. People vary in their impressions of what is "normal function." For example, a person may consider it normal to hand a lump sum of money to a clerk and pocket whatever change the clerk returns. Others may require careful calculations of the money owed and returned. Therefore, the clinician should probe reports of normal function. For the assessment of dementia, the earliest changes are seen in the abilities to manage money and medications, use the telephone, and use transportation.

When evaluating a patient with a history of mild memory loss, it is helpful to interview a knowledgeable informant; self-reports of memory problems correlate well with depression and anxiety but not with objective measures of memory impairment (2-8). In addition, dementia that causes mild cognitive symptoms can impair the patient's insight into the presence or severity of the cognitive problem (23, 24). Impairments in frontal lobe function cause many patients with dementia to underestimate the severity of cognitive problems (25). Without a knowledgeable informant, a clinician may underestimate the nature or severity of the patient's cognitive impairments.

The clinician should ascertain the nature and extent of the knowledgeable informant's contact with the patient and inquire whether this person has observed changes in the patient's ability to perform instrumental activities of daily living. Open-ended questions can screen for impairments ("How is he doing managing the bills?"). However, because the informant's and clinician's definitions of an impairment may differ, more detailed probing of the particular steps of the task are helpful ("What about the checkbook? Are there any changes in how that is organized and balanced?").

Family members who observe a relative's function

closely can accurately identify patients with dementia (26) and memory loss (2, 7) and assess their degree of physical and functional health (25). However, family members who have high demands and restrictions on their time tend to overreport the degree of patient impairment in instrumental activities of daily living (27).

WHAT COGNITIVE TESTS ARE INDICATED IN THE EVALUATION OF PATIENTS WITH MEMORY SYMPTOMS?

There are two clues that the patient in this case may have clinically significant cognitive impairment. First, although his son could not recount other problems or differences to support his feeling that his father had changed, he had not had the opportunity to observe him closely enough to be a truly knowledgeable informant. Still, he reported that his father did not know family members' names. Between this visit and a follow-up visit, the son will need to pay closer attention to his father's ability to perform activities of daily living.

Second, the clinician structured his informal interview with the patient in a way that required the patient to organize time relationships, recall facts, and reason abstractly. The patient's answers to questions about where he had lived and the order of life events revealed that he may have problems in how well he uses language and executes strategies to figure out details he may not have thought about for years. Patients brought in by concerned family members are often reluctant, but a nonconfrontational interview focused on a life history can build rapport and also allow the clinician to gather useful data in a relaxed and informal manner.

Given this patient's history and the results of the informal interview, it would be reasonable for the clinician to perform brief, standardized cognitive and affective testing at this visit. In the setting of a primary care visit, it is not feasible to perform a full battery of cognitive testing. Table 2 describes a sequence of tests that physicians or office staff can use to assess cognitive function in persons with cognitive symptoms and suspected Alzheimer disease. Table 3 shows the 15-item Geriatric Depression Scale, which clinicians can use to screen for depression in elderly patients (29).

In addition to these tests, the Mini-Mental State Examination (MMSE) is useful as an overall measure of a patient's cognitive function because it measures many domains of cognitive function: memory, executive function, attention, language, praxis, and visuospatial ability (31). Accepted ranges for the stages of Alzheimer disease are as follows: A score of 20 to 24 indicates mild disease, a score of 20 or less or greater than 12 indicates moderate disease, and a score of 12 or less indicates severe disease. However, the relationship between MMSE score and a person's education and age is complicated (32). Because scores decrease with fewer years of formal education and increasing age, a score as low as 23 may be normal for a 75-year-old person who did not complete high school. Thus, the clinician

Table 2. Sequence of Tests for Efficient Office-Based Assessment of Cognition in Persons with Cognitive Symptoms and Suspected Alzheimer Disease*

Domain of Cognition	Clinical Tests That Can Identify Impairment	Administration and Scoring
1. Orientation to date	Recite the month, year, day of the week, date, season. (This can be a useful warm-up for the other cognitive tests.)	At the change of seasons, allow a leeway of 1 week. Marked errors in orientation (i.e., incorrect month or year) strongly suggest cognitive impairment.
2. Registration	Repeat a list of common nouns (e.g., apple, table, penny).	Ask the patient to repeat a list of words after you recite them. Repeat the list up to three times until registration is complete. The need for list repetition suggests errors in language, attention, or working memory. To minimize the effects of education, the words should be common nouns.
3. Visuospatial and executive function	Draw a clock set at 8:20 and make it big enough so that a child can read it. Copy a figure of interlocking pentagons.	The directions should be repeated <i>in full</i> if the patient asks for them. Scoring should consider the positioning of the numbers and the hands and how much effort it takes to accomplish the task. A correct figure should contain 10 angles and four intersecting sides
4. Language	Recite the names of as many animals as possible in 60 seconds. (This test also assesses working memory and executive functioning.)	An abnormal score is naming fewer than 10 animals. Avoid stating the time limit because this can cause performance anxiety. Tell the patient, "I'll tell you when to start and when to stop."
5. Attention and working memory	Spell <i>world</i> backward.	<i>World</i> should be spelled forward and any errors corrected before the patient attempts to spell it backward. Count one error for each letter omission, transposition, insertion, or misplacement.
6. Memory	Recall the list of words used in the registration task.	The interval between registration and recall should include performing cognitive tests 3 through 5.

* Based on reference 28.

must interpret MMSE results in the context of the patient's education, history, and performance on other measure of cognitive function. Referral to a dementia specialist or a neuropsychologist is warranted when the patient's per-

formance on office-based tests and his or her history of cognitive impairment are discrepant (for example, a patient who has normal test scores but a history of changes in the ability to perform activities of daily living).

Table 3. The Geriatric Depression Scale*

Question	Answer
Choose the best answer for how you felt over the past week.	
1. Are you basically satisfied with your life?	Yes/No
2. Have you dropped many of your activities and interests?	Yes/No
3. Do you feel that your life is empty?	Yes/No
4. Do you often get bored?	Yes/No
5. Are you in good spirits most of the time?	Yes/No
6. Are you afraid that something bad is going to happen to you?	Yes/No
7. Do you feel happy most of the time?	Yes/No
8. Do you often feel helpless?	Yes/No
9. Do you prefer to stay at home, rather than going out and doing new things?	Yes/No
10. Do you feel you have more problems with memory than most?	Yes/No
11. Do you think it is wonderful to be alive now?	Yes/No
12. Do you feel pretty worthless the way you are now?	Yes/No
13. Do you feel full of energy?	Yes/No
14. Do you feel that your situation is hopeless?	Yes/No
15. Do you think that most people are better off than you are?	Yes/No

* Based on reference 29. Affective impairment can affect a person's cognitive function, especially his or her perception of dysfunction. The clinician should routinely assess affect in an elderly patient with memory symptoms. The Geriatric Depression Scale is a useful instrument to quantify the degree of impairment. Each item receives a 0 or 1 score. A "1" indicates an answer that suggests depression, and higher scores indicate greater depressive symptoms. Scores greater than 3 to 5 suggest depression (30).

On his first attempt at a test of registration, the patient registers three objects. On a category verbal fluency test, he names 10 animals. He struggles a bit while drawing a clock to show that the time is 8:20. He initially places the minute hand by the 2 but corrects the error. The hour hand is placed directly on the 8. He correctly spells the word world forward but reverses two letters when spelling it backward. He recalls one out of the three objects he registered earlier. His score on the short version of the Geriatric Depression Scale is 5 out of 15 (29). During the interview, he mentions several times that he would not feel so bored if he were still working and that he misses his wife. He says he has felt this way for a year or so.

This patient's test results suggest that he has depressive symptoms and that at least two cognitive domains may be impaired. He could not recall two out of three words and made errors spelling *world* backward; in addition, his verbal fluency was at the cutoff point of normal. These findings suggest impairments in memory, language, and attention. In addition, he may also have impairments in executive function and constructions. His clock drawing was essentially normal except for a slight malposition of the hour hand, but his performance required more effort than expected given his educational level and employment history. A patient's performance on the clock drawing test,

not simply the final score, contributes information about cognitive function.

HOW CAN CLINICIANS DETERMINE WHETHER DEPRESSION IS THE CAUSE OF A PATIENT'S COGNITIVE SYMPTOMS?

Screening showed that this patient has depressive symptoms. Major depression and dysthymia are potential causes of a depressed mood in persons without psychosis or mania who have not experienced a stressful event, such as a death, within 3 to 6 months and do not report substance abuse (33). The duration, intensity, and number of symptoms describe the differences between these two disorders. Major depression is defined as the daily experience of depressed mood plus at least four of nine possible symptoms for at least 2 consecutive weeks (Table 1). In contrast, dysthymia is defined as 2 years of at least two of the following symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness.

In this case, the patient's symptoms lack the duration and intensity necessary for either diagnosis. Such patients can be labeled as having minor or subsyndromal depression, which remains a research category in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (33). Patients with subsyndromal depression fall between clear categories of "normal" and "disease," but they should provoke clinicians' attention. These patients experience more functional impairment than nondepressed patients (34), equivalent to that of patients with major depression (35–37). Cohort studies suggest that subsyndromal depression precedes as many as half of new cases of major depression (38) and that 10% (39) and 25% (40) of patients with subsyndromal depression develop major depression over 1 year and 2 years, respectively. Treatment of subsyndromal depression, therefore, might improve functional status and reduce the risk for major depression. Furthermore, patients' self-rated quality of life might improve. Among patients with Alzheimer disease, poor self-rated quality of life is associated with depressive symptoms (41).

Many randomized, controlled trials support the benefit of pharmacotherapy for major depression (42). The data to support the benefits of treating elderly patients with subsyndromal or minor depression are less definitive. Only four randomized studies enrolling a total of 831 outpatients have examined the benefit of pharmacotherapy treatment (43–46). Three of these studies enrolled only patients younger than 65 years of age (43, 45, 46). One industry-sponsored study that enrolled 130 elderly patients 60 to 85 years found minaprine to be superior to placebo in the end point of global improvement (improvement was seen in 60% vs. 39% of patients and worsening was seen in 8% vs. 16%) (44). Collectively, these limited data offer little evidence to guide pharmacotherapy for sub-

syndromal depression. The clinician should target pharmacologic or nonpharmacologic therapy for end points such as improved scores on a geriatric depression scale and improved patient symptoms.

Since the available agents generally have similar efficacy (47), the choice of agent should largely depend on potential side effects, cost, convenience, and medication interactions. In general, the clinician treating depressive symptoms in an elderly patient with cognitive impairment should avoid medications with anticholinergic effects (such as tricyclic antidepressants) because they can worsen cognitive function. A low starting dose of one of the older and less expensive serotonergic reuptake inhibitors would be a reasonable choice.

Findings on the patient's physical examination are normal. You note that his errors on the tests and his history raise the concern of the earliest signs of a dementing illness such as Alzheimer disease. You explain that although the patient does not have clear signs of dementia, his symptoms warrant gathering more information. You ask him whether he will allow his son to look at how he is doing handling finances because his memory problems may have caused him to make a costly error. The patient agrees.

WHAT FINDINGS ON PHYSICAL EXAMINATION, LABORATORY TESTS, OR IMAGING STUDIES ARE HELPFUL IN THE EVALUATION OF MEMORY LOSS?

In this case, the history and the interview are starting to narrow the list of potential causes of the patient's cognitive symptoms. The patient has a history of hypertension and may have had a transient ischemic attack in the past. His examination suggested impairments in mood, memory, language, and executive function. These findings suggest subsyndromal depression and either mild cognitive impairment or dementia. If he has dementia, the most likely causes are Alzheimer disease, a combination of Alzheimer disease and vascular dementia, or vascular dementia. Vascular dementia alone is the least likely cause because he showed no evidence of a focal neurologic deficit that could be attributed to a stroke.

Other causes of dementia are very unlikely because his neurologic examination lacked findings of other types of neurodegenerative dementia. In particular, he lacked parkinsonism, a gait disorder, or altered levels of alertness and visual hallucinations, which would suggest dementia with Lewy bodies, or frontal motor and behavioral signs, which would suggest frontotemporal dementia.

There is suspicion that the patient has dementia, but there is not enough evidence to show whether he has progressed from mild cognitive impairment to dementia. Until it is clear that he has dementia, it is prudent to defer ordering any neuroimaging. Instead, the next step would be to obtain more history to determine whether day-to-day function has worsened as a result of cognitive impairments. If subsequent history shows changes in function, structural

neuroimaging (magnetic resonance imaging [MRI] and computed tomography) would be recommended because it can add clinically useful information to the diagnostic assessment of patients with mild dementia (48, 49).

Standard laboratory tests for a work-up of dementia are directed toward identifying medical illnesses that can cause or contribute to cognitive symptoms (50, 51). The consensus of many reviews supports the performance of a complete blood count, basic blood chemistries, thyroid function tests, and a vitamin B₁₂ level (49, 52). The companion piece to this review, available on pages 400-410, describes potential diagnostic tests that may become part of clinical practice.

Because of the patient's history of hypertension, and to evaluate for medical causes of cognitive symptoms, you recommend tests to evaluate his blood count, lipid levels, vitamin B₁₂ level, and kidney and thyroid functions. You recommend treatment with an antidepressant. You ask the patient to call you in 3 weeks so you can see how he is doing and to plan on follow-up after that. With the patient's permission, you also ask his son to call you with his observations.

At the 3-week telephone call, the patient reports some improvement in his mood. You increase the dose of his antidepressant. A telephone conversation with the patient's son reveals that the patient's garden is less organized than usual and that he forgot a scheduled visit to a neighbor's house. The patient's checkbook is in order, but he has not balanced it in 3 months and several bills are unpaid and misfiled. The patient's son reports that this is not characteristic of his father, who once ran an insurance office.

You tell the son that you are concerned about these changes because they suggest that his father has dementia. You recommend a brain MRI. You urge the son to make sure his father is taking the new dose of the antidepressant and to look for changes in his father's mood.

At the 6-week follow-up visit, the patient says his mood is "OK." You readminister the tests performed at the initial visit, and the results are within the ranges of normal. His Geriatric Depression Scale score is 3 out of 15, and he says things don't seem as bad as he thought. His MMSE score is 26 out of 30, with three errors in delayed recall and one error on the reverse spelling of world. It is still difficult for him to complete the clock drawing, but he makes no errors. Verbal fluency is 10. The MRI radiology report reads "mild atrophy consistent with age, periventricular white-matter hyperintensities, and one lacuna in the centrum semiovale."

HOW DO THE PATIENT'S INCREASINGLY IMPAIRED ABILITY IN ACTIVITIES OF DAILY LIVING AND THE MRI FINDINGS NARROW THE DIFFERENTIAL DIAGNOSIS?

The history and examination showed an insidious progression of changes in cognitive function that had impaired the patient's ability to perform activities of daily living and an improvement in his subsyndromal depression. This information, together with the results of his cognitive testing,

supported a diagnosis of dementia. Therefore, MRI imaging was warranted. The lacuna provided evidence of cerebrovascular disease but was not in a location that could explain the patient's cognitive problems. These data support the diagnosis of Alzheimer disease and suggest that vascular disease may also have contributed to this patient's cognitive impairments.

The degree to which vascular disease contributes to cognitive dysfunction is controversial. The five diagnostic criteria of vascular dementia are based on expert consensus (33, 53-56) and have substantial interrater and intercriteria variability in case definition (57). Despite these problems, evidence shows that both lacunar and cortical stroke increase the prevalence and severity of cognitive impairment among patients with (58) and without (59) the neuropathic changes of Alzheimer disease. These data suggest that treating the causes of vascular disease can affect the progression and severity of dementia.

This patient's MRI also showed "mild atrophy consistent with age" and periventricular white-matter hyperintensities. At present, the clinical significance of subjectively rated cortical atrophy is uncertain. The companion article on pages 400-410 describes the potential for MRI to quantify atrophy as a means of diagnosing dementia. Areas of periventricular white-matter hyperintensities are a common neuroradiographic finding among elderly persons. However, their precise contribution to cognitive dysfunction remains unclear. One study has shown no difference in grade and location of white-matter findings between patients with Alzheimer disease and cognitively normal age-matched controls (60). However, among community dwelling, nondemented elderly persons, these areas of hyperintensity are associated with slowed motor skills and lower scores on cognitive tests of attention (61). In summary, infarcts and white-matter changes are associated with worse cognitive dysfunction. Therefore, clinicians should focus on describing all of the MRI abnormalities that might contribute to a patient's cognitive impairment instead of using summary diagnostic labels that might neglect a contribution.

You tell the patient and his son that you are pleased that his depressive symptoms have improved but remain concerned that he has troubles with memory and keeping his house and finances organized. You explain that the most likely cause of this problem is early Alzheimer disease complicated by the single small stroke shown on the MRI. You reassure the patient that this is very mild Alzheimer disease and that the goal is to keep it that way for as long as possible.

WHAT IMMEDIATE NONPHARMACOLOGIC INTERVENTIONS ARE INDICATED ONCE A PATIENT RECEIVES A DIAGNOSIS OF DEMENTIA?

In addition to pharmacologic treatment (62), nonpharmacologic treatment should address the impact of dementia on this patient's ability to perform activities of daily

4. Additional Information on Alzheimer Disease Diagnosis and Care for Health Care Practitioners, Family, Caregivers, and Patients

Category (Reference)	Description
Guidelines for the diagnosis and treatment of dementia Knopman et al. (49) Doody et al. (62)	These articles present the American Academy of Neurology's recently updated evidence-based guidelines.
Organizations and services Adult day care	Day care designed for persons with at least late-mild to moderate dementia can provide structured and safe daily activities that reduce patient boredom and anxiety as well as caregiver distress. Local chapters of the Alzheimer's Association, agencies on aging, or social work services can provide locations and information.
Alzheimer's Disease and Related Disorders Association	This national association (www.alz.org ; telephone, 800-272-3900) has regional chapters across the United States. It offers information on disease progression and management, and caregiver support groups. Patient support groups are a recent service.
Alzheimer's Disease Education and Referral (ADEAR) Center	This center (www.alzheimers.org), funded by the National Institute on Aging, offers a variety of information resources, including a clinical trials data bank.
Safe Return bracelet	These bracelets for both patient and caregiver have a toll-free number that is linked to a nationwide identification database. This service is available through the Alzheimer's Association. It is very useful for identifying patients who become separated from family.

living. Specifically, the patient should have his driving skills formally reassessed and, depending on state law, the clinician will report the diagnosis to a driving authority. The family should arrange financial management that addresses the patient's impairments. Finally, the family must begin thinking about possible future living arrangements, medical advance directives, and estate planning while the patient can still participate in a meaningful way. Table 4 lists useful informational resources for patients and their families.

You urge the patient and his son to discuss who would make decisions for him if he could not and how he wants to be cared for. You tell the patient that you are concerned about the errors he is making with his finances and the potential for problems with his driving. You recommend he have a driving test at a facility with expertise in evaluating elderly people with impairments and, if he passes this test, to repeat it in 6 months to 1 year.

You recommend vitamin E, 1000 IU twice per day, to slow the progression of Alzheimer disease; a cholinesterase inhibitor to treat the symptoms of memory loss; and aspirin, 81 mg per day, to prevent stroke. You urge the patient to continue to take his hydrochlorothiazide and reassure him that his blood cholesterol level is good.

AT FUTURE VISITS, WHAT GENERAL ISSUES NEED TO BE ADDRESSED?

The physician will need to assess the son's affect and distress because these psychiatric comorbid conditions are common in caregivers (63) and influence assessments of patient quality of life (41, 64), as well as decisions about treatment (65) and placement in a long-term care facility (66–68). As the disease progresses, the clinician should educate the caregiver in the management of problematic

behaviors, signs of progression, and adult day care because these interventions can minimize caregiver distress and delay nursing home placement for a clinically significant interval (69).

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References

1. Squire LR. *Memory and Brain*. New York: Oxford Univ Pr; 1987.
2. McGlone J, Gupta S, Humphrey D, Oppenheimer S, Misen T, Evans DR. Screening for early dementia using memory complaints from patients and relatives. *Arch Neurol*. 1990;47:1189-93. [PMID: 2241616]
3. Hänninen T, Reinikainen KJ, Heikala EI, Koivisto K, Mykkänen L, Laakso M, et al. Subjective memory complaints and personality traits in normal elderly subjects. *J Am Geriatr Soc*. 1994;42:1-4. [PMID: 8277103]
4. O'Hara MW, Hinrichs JV, Kohout FJ, Wallace RB, Lenke JH. Memory complaint and memory performance in the depressed elderly. *Psychol Aging*. 1986;1:208-14. [PMID: 3267400]

5. Popkin SJ, Gallagher D, Thompson LW, Moore M. Memory complaint and performance in normal and depressed older adults. *Exp Aging Res.* 1982;8:141-5. [PMID: 7169071]
6. Bassett SS, Folstein MF. Memory complaint, memory performance, and psychiatric diagnosis: a community study. *J Geriatr Psychiatry Neurol.* 1993;6:105-11. [PMID: 8512626]
7. Tierney MC, Szalai JP, Snow WG, Fisher RH. The prediction of Alzheimer disease. The role of patient and informant perceptions of cognitive deficits. *Arch Neurol.* 1996;53:423-7. [PMID: 8624217]
8. Turvey CL, Schultz S, Armit S, Wallace RB, Herzog R. Memory complaint in a community sample aged 70 and older. *J Am Geriatr Soc.* 2000;48:1435-41. [PMID: 11083320]
9. Schaacter DL. *Stories of Elders. Searching for Memory: The Brain, the Mind, and the Past.* New York: Basic Books; 1997:280-308.
10. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-44. [PMID: 6610841]
11. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology.* 1998;51:1546-54. [PMID: 9855500]
12. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology.* 1996;47:1113-24. [PMID: 8909416]
13. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol.* 1999;56:303-8. [PMID: 10190820]
14. Ritchie K, Touchon J. Mild cognitive impairment: conceptual basis and current nosological status. *Lancet.* 2000;355:225-8. [PMID: 10675135]
15. Christensen H, Griffiths K, Mackinnon A, Jacomb P. A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *J Int Neuropsychol Soc.* 1997;3:631-51. [PMID: 9448376]
16. Lazarus LW, Newton N, Cöhler B, Lesser J, Schwenn C. Frequency and presentation of depressive symptoms in patients with primary degenerative dementia. *Am J Psychiatry.* 1987;144:41-5. [PMID: 3799838]
17. Reding M, Haycox J, Blass J. Depression in patients referred to a dementia clinic. A three-year prospective study. *Arch Neurol.* 1985;42:894-6. [PMID: 4026634]
18. Lyketsos CG, Steele C, Baker L, Galik E, Kopinck S, Steinberg M, et al. Major and minor depression in Alzheimer's disease: prevalence and impact. *J Neuropsychiatry Clin Neurosci.* 1997;9:556-61. [PMID: 9447496]
19. Petracca G, Tesón A, Chemerinski E, Leiguarda R, Starkstein SE. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci.* 1996;8:270-5. [PMID: 8854297]
20. Reifler BV, Teri L, Raskind M, Veith R, Barnes R, White E, et al. Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. *Am J Psychiatry.* 1989;146:45-9. [PMID: 2643356]
21. Reifler BV. Arguments for abandoning the term pseudodementia. *J Am Geriatr Soc.* 1982;30:665-8. [PMID: 7119335]
22. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9:179-86. [PMID: 5349366]
23. McGlynn SM, Kaszniak AW. Unawareness of deficits in dementia and schizophrenia. In: Prigatano GP, Schaacter DL, eds. *Awareness of Deficit after Brain Injury: Clinical and Theoretical Issues.* New York: Oxford Univ Pr; 1991: 84-110.
24. Feher EP, Iarrabee GJ, Sudilovsky A, Crook TH 3rd. Memory self-report in Alzheimer's disease and in age-associated memory impairment. *J Geriatr Psychiatry Neurol.* 1994;7:58-65. [PMID: 8192832]
25. Kiyak HA, Teri L, Borson S. Physical and functional health assessment in normal aging and in Alzheimer's disease: self-reports vs family reports. *Gerontologist.* 1994;34:324-30. [PMID: 8076873]
26. Koss E, Patterson MB, Ownby R, Stuckey JC, Whitehouse PJ. Memory evaluation in Alzheimer's disease. Caregivers' appraisals and objective testing. *Arch Neurol.* 1993;50:92-7. [PMID: 8418807]
27. Zanetti O, Geroldi C, Frisoni GB, Bianchetti A, Trabucchi M. Contrasting results between caregiver's report and direct assessment of activities of daily living in patients affected by mild and very mild dementia: the contribution of the caregiver's personal characteristics. *J Am Geriatr Soc.* 1999;47:196-202. [PMID: 9988291]
28. Weintraub S. Neuropsychological assessment of mental state. In: Mesulam M, ed. *Principles of Behavioral and Cognitive Neurology.* 2nd ed. New York: Oxford Univ Pr; 2000:121-73.
29. Yesavage JA, Brink TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* 1982;17:37-49. [PMID: 7183759]
30. Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med.* 1997;157:449-54. [PMID: 9046897]
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-98. [PMID: 1202204]
32. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA.* 1993;269:2386-91. [PMID: 8479064]
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV.* 4th ed. Washington, DC: American Psychiatric Assoc; 1994.
34. Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA.* 1989;262:914-9. [PMID: 2754791]
35. Lyness JM, King DA, Cox C, Yonedono Z, Caine ED. The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. *J Am Geriatr Soc.* 1999;47:647-52. [PMID: 10366161]
36. Williams JW Jr, Kerber CA, Mulrow CD, Medina A, Aguilar C. Depressive disorders in primary care: prevalence, functional disability, and identification. *J Gen Intern Med.* 1995;10:7-12. [PMID: 7699487]
37. Roy-Byrne P, Katon W, Broadhead WE, Lepine JP, Richards J, et al. Subsyndromal ("mixed") anxiety-depression in primary care. *Gen Intern Med.* 1994;9:507-12. [PMID: 7996294]
38. Hurwath E, Johnson J, Klerman GL, Weissman MM. Depressive symptoms as relative and attributable risk factors for first-onset major depression. *Arch Gen Psychiatry.* 1992;49:817-23. [PMID: 1417435]
39. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA.* 1990;264:2524-8. [PMID: 2146410]
40. Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpatients. Results from the Medical Outcomes Study. *Arch Gen Psychiatry.* 1992;49:788-94. [PMID: 1417431]
41. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Quality of life in Alzheimer's disease: patient and caregiver reports. *Journal of Mental Health and Aging.* 1999;5:21-32.
42. Snow V, Lascher S, Mottur-Pilson C. Pharmacologic treatment of acute major depression and dysthymia. American College of Physicians-American Society of Internal Medicine. *Ann Intern Med.* 2000;132:738-42. [PMID: 10787369]
43. Szegedi A, Wenzel H, Angersbach D, Dunbar GC, Schwarze H, Philipp M, et al. A double-blind study comparing paroxetine and mirtazapine in depressed outpatients. *Pharmacopsychiatry.* 1997;30:97-105. [PMID: 9211571]
44. Parnetti L, Sommacal S, Labate AMM, Senin U. Multicentre controlled randomised double-blind placebo study of mirtazapine in elderly patients suffering from prolonged depressive reaction. *Drug Investigations.* 1993;6:181-8.
45. VanMuffaert M, Vogels C, Beckers G, Vereecken A, Dermaux P, Wolfrum C. Moclobemide versus amitriptyline in the treatment of depression: two double-blind multicenter studies in Belgium. *New Trends In Experimental and Clinical Psychiatry.* 1989;3:167-77.
46. Stewart JW, McGrath PJ, Quitkin FM. Can mildly depressed outpatients with atypical depression benefit from antidepressants? *Am J Psychiatry.* 1998;149:615-9. [PMID: 1575250]
47. Song E, Freemantle N, Sheldon TA, Hrusa A, Watson P, Long A, et al. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability.

- BMJ. 1997;315:306-307. [PMID: 8471919]
48. Chui H, Zhang Q. Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's practice parameters. *Neurology*. 1997;49:925-35. [PMID: 9339669]
 49. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, 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;56:1143-53. [PMID: 11342678]
 50. Freter S, Bergman H, Gold S, Chertkow H, Clarfield AM. Prevalence of potentially reversible dementias and actual reversibility in a memory clinic cohort. *CMAJ*. 1998;159:657-62. [PMID: 9780965]
 51. Clarfield AM. The reversible dementias: do they reverse? *Ann Intern Med*. 1988;109:476-86. [PMID: 3046450]
 52. Small GW, Rabins PV, Barry PP, Buckholz NS, DeKosky ST, Ferris SH, et al. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA*. 1997;278:1363-71. [PMID: 9343469]
 53. Chui HC, Victoroff JJ, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology*. 1992;42:473-80. [PMID: 1549205]
 54. Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. *Lancet*. 1974;2:207-10. [PMID: 4135618]
 55. Román GC, Tatavich TK, Erkinjuntti T, Cummings JL, Masden JC, García JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-60. [PMID: 8094895]
 56. The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research. Geneva: World Health Organization; 1993.
 57. Chui HC, Mack W, Jackson JE, Mungas D, Reed BR, Tinklenberg J, et al. Diagnostic criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. *Arch Neurol*. 2000;57:191-6. [PMID: 10681076]
 58. Snowden DA, Greiner LH, Murriner JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA*. 1997;277:813-7. [PMID: 9052711]
 59. Bowler JV, Hachinski VC. Vascular cognitive impairment: a new approach to vascular dementia. In: Hachinski VC, ed. *Cerebrovascular Disease*. Volume 4. London: Baillière Tindall; 1995:357-76.
 60. Erkinjuntti T, Gao F, Lee DH, Eliasziw M, Merskey H, Hachinski VC. Lack of difference in brain hyperintensities between patients with early Alzheimer's disease and control subjects. *Arch Neurol*. 1994;51:260-8. [PMID: 8129637]
 61. Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Raininko R, Tilvis R. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. *Arch Neurol*. 1993;50:818-24. [PMID: 8352667]
 62. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56:1154-66. [PMID: 11342679]
 63. Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist*. 1995;35:771-91. [PMID: 8557205]
 64. Karlawish JH, Casarett D, Klocinski J, Clark CM. The relationship between caregivers' global ratings of Alzheimer's disease patients' quality of life, disease severity, and the caregiving experience. *J Am Geriatr Soc*. 2001;49:1066-70. [PMID: 11555068]
 65. Karlawish JH, Klocinski JL, Merz J, Clark CM, Asch DA. Caregivers' preferences for the treatment of patients with Alzheimer's disease. *Neurology*. 2000;55:1008-14. [PMID: 11061260]
 66. Lieberman MA, Kramer JH. Factors affecting decisions to institutionalize demented elderly. *Gerontologist*. 1991;31:371-4. [PMID: 1879712]
 67. Cohen CA, Gold DP, Shulman KI, Wortley JT, McDonald G, Wargon M. Factors determining the decision to institutionalize dementing individuals: a prospective study. *Gerontologist*. 1993;33:714-20. [PMID: 8314097]
 68. Aneshensel CS, Pearlin LI, Schuler RH. Stress, role captivity, and the cessation of caregiving. *J Health Soc Behav*. 1993;34:54-70. [PMID: 8463635]
 69. Mittelman MS, Ferris SH, Shulman E, Steinberg G, Levin B. A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. *JAMA*. 1996;276:1725-31. [PMID: 8940320]