

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 man who is still managing investments at a brokerage firm seeks consultation at the urging of his wife for increasing difficulty with memory over the past 2 years. Clients have expressed concern about his occasional lapses in memory. His wife reports that he frequently repeats questions about social appointments and becomes angry when she points this out. The physical examination is normal, but the patient has difficulty remembering elements of a brief story and adding a small amount of change. He has a score of 28 out of 30 on the Mini-Mental State Examination, indicating slightly impaired cognitive function.¹ Early Alzheimer's disease is suspected. How should the patient be further evaluated and treated?

THE CLINICAL PROBLEM

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This article (10.1056/NEJMcp0910236) was updated on September 15, 2010, at NEJM.org.

N Engl J Med 2010;362:2194-201.

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Alzheimer's disease is the most frequent cause of dementia in Western societies, affecting an estimated 5 million people in the United States and 17 million worldwide.² The annual incidence worldwide increases from 1% between the ages of 60 and 70 years to 6 to 8% at the age of 85 years or older.³ In countries in which survival to the age of 80 years or older is not uncommon, the proportion of persons in this age group with Alzheimer's disease now approaches 30% and is expected to continue to increase substantially.⁴ The disease onset is insidious, and manifestations evolve over a period of years from mildly impaired memory to severe cognitive loss. A transitional state, referred to as mild cognitive impairment, often precedes the earliest manifestations of Alzheimer's disease.⁵ The course of Alzheimer's disease is inevitably progressive and terminates in mental and functional incapacity and death. Plateaus sometimes occur in which the degree of cognitive impairment is stable for 1 or 2 years, but progression usually resumes thereafter.

An inability to retain recently acquired information is typically the initial symptom, whereas memory for remote events is relatively spared until later. With disease progression, impairment in other areas of cognition (e.g., language, abstract reasoning, and executive function or decision making) occurs to varying degrees and typically coincides with difficulty at work or in social situations or household activities. Changes in mood and affect often accompany the decline in memory.⁶ Delusions and psychotic behavior are not typically presenting signs but can occur at any time during the disease course.⁷ The occurrence of psychosis during the initial stages of dementia suggests other diagnoses, such as dementia with Lewy bodies.

At autopsy, the most frequent pathological features in the brains of patients with Alzheimer's disease include extracellular beta-amyloid protein in diffuse plaques and in plaques containing elements of degenerating neurons, termed neuritic plaques.⁸ Intracellular changes include deposits of hyperphosphorylated tau protein, a microtubule assembly protein, in the form of neurofibrillary tangles. These pathological lesions first appear in the entorhinal regions of the hippocampus and



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then become widespread. Over time, there is widespread loss of neurons and synapses. The pathogenic mechanisms that are responsible for the development of these changes are unknown.

A family history of dementia is one of the most consistently reported risk factors for Alzheimer's disease.³ There are rare cases of families with autosomal dominant inheritance of Alzheimer's disease that develops between the ages of 30 and 50 years; about half these cases result from mutations in genes encoding amyloid precursor protein, presenilin 1, or presenilin 2.⁹ Studies of these mutated genes have led to the assertion that Alzheimer's disease is caused by the generation and aggregation of beta-amyloid peptide, which then forms neuritic plaques. Although several hundred families carry these mutations, they account for less than 1% of cases.

First-degree relatives of patients with late-onset disease have approximately twice the expected lifetime risk of the disease. The disease is also more often concordant among monozygotic twins than among dizygotic twins.¹⁰ Individuals from families that have many members with late-onset Alzheimer's disease are at increased risk for dementia, but the distribution of cases is rarely consistent with mendelian inheritance.

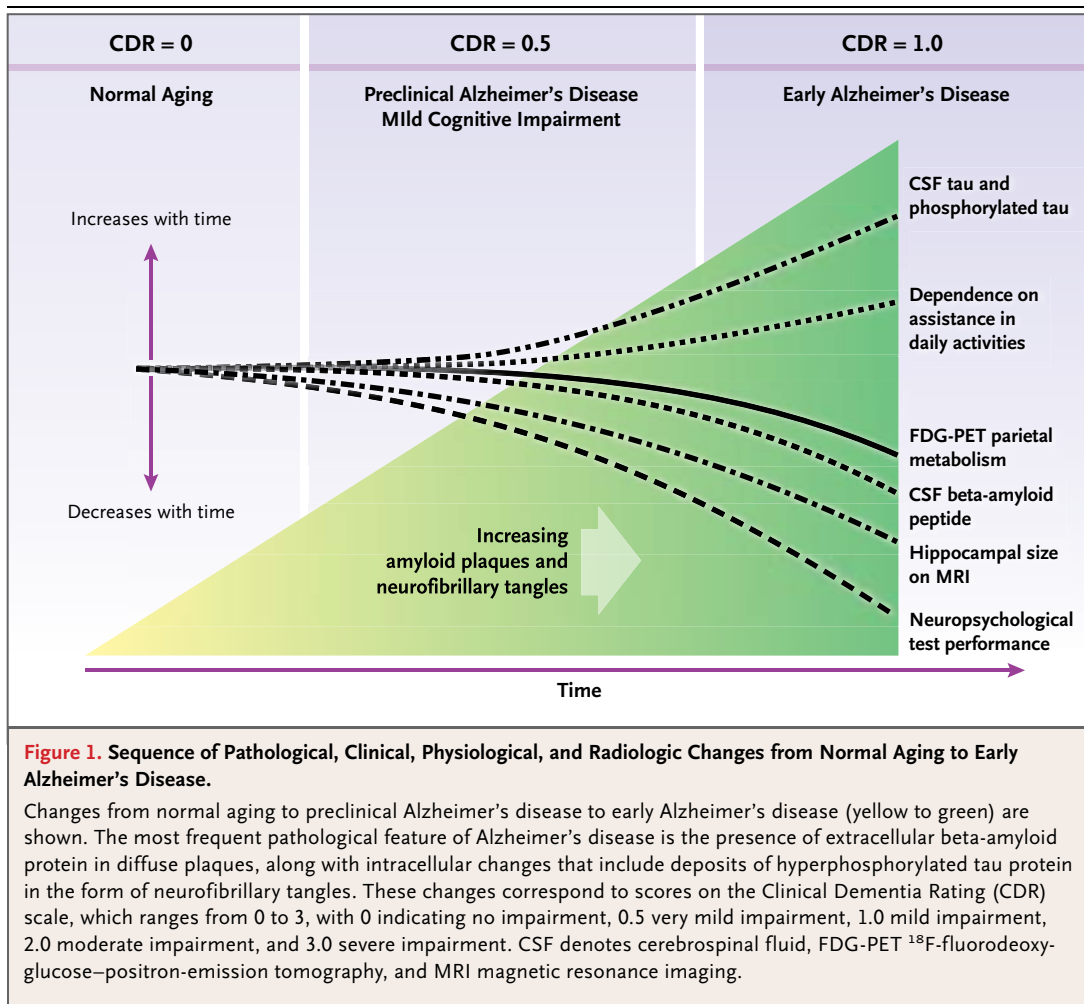
The genetic variant encoding apolipoprotein (APOE) ϵ 4 is the only well-established mutation associated with the late-onset form of Alzheimer's disease.¹¹ Risks that are associated with the APOE ϵ 4 allele peak between the ages of 60 and 80 years. As compared with the absence of the APOE ϵ 4 allele, the presence of one such allele is associated with a doubling or tripling of the lifetime risk of disease, and the presence of two copies is associated with an increase in risk by a factor of five or more. Associations between Alzheimer's disease and variants in sortilin-related receptor 1 (SORL1),¹² clusterin, phosphatidylinositol-binding clathrin assembly protein, and a complement component (3b/4b) receptor have been reported,^{13,14} but mechanisms underlying these associations remain uncertain.

STRATEGIES AND EVIDENCE

Impaired memory is typically one of the first signs of Alzheimer's disease, but difficulty recalling the names of friends or recent events is also common among normal elderly persons. The clinician is thus faced with the difficulty of distinguishing between normal aging and the early stages of

Alzheimer's disease. Mild cognitive impairment is an intermediate state in which persons have more memory problems than would be considered normal for their age, but their symptoms are not as severe as the symptoms of Alzheimer disease and they do not have functional impairment.⁵ Alzheimer's disease develops at a much higher frequency among persons with mild cognitive impairment than among those with normal aging. Determining when patients have reached the very early stage of Alzheimer's disease is not easy, particularly because it is likely that a preclinical stage of Alzheimer's disease exists in which senile plaques, neuritic plaques, and neurofibrillary tangles occur in sufficient numbers to meet standard neuropathological criteria for Alzheimer's disease in the absence of overt symptoms or signs of dementia.¹⁵ Other causes of memory impairment must also be considered, such as cerebrovascular disease, hydrocephalus, hypothyroidism, vitamin B₁₂ deficiency, central nervous system infection, a cognitive disorder related to human immunodeficiency virus infection, adverse effects of prescribed medications, substance abuse, and cancer.

A substantial decline in verbal memory and executive function (e.g., the ability to perform sequential tasks) typically occurs at the onset of Alzheimer's disease but may be difficult to document without formal neuropsychological testing (Fig. 1). Reduced independence in daily activities (often recognized by the patient's family) is one of the strongest predictors of disease.¹⁶ Functional status can be measured by the Clinical Dementia Rating (CDR) scale, which evaluates cognitive and functional performance on a scale ranging from 0 to 3, with higher scores indicating a greater severity of impairment.¹⁷ This assessment requires a collateral source of information gathering concerning the patient's ability to function independently but can be performed in the primary care setting and is particularly useful for clinicians who do not have ready access to formal neuropsychological testing. The assessment requires 30 to 45 minutes to administer, and training is provided online. (Additional details are available in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The CDR score was the strongest predictor of Alzheimer's disease in a study involving community volunteers without dementia, and scores on a functional rating scale that is based on the CDR effectively identified patients in the early stages of Alzheimer's disease in a clinical setting.¹⁸ Formal neuropsychological



testing that shows a substantial decline in verbal memory and executive function supports the diagnosis of Alzheimer's disease^{18,19} but requires a trained professional for administration and interpretation.

Occasionally, patients with early Alzheimer's disease present with impaired language or perceptual dysfunction rather than memory loss.²⁰ Over time, both memory impairment and functional decline become apparent in such patients.

Patients with early disease are at increased risk for motor vehicle accidents. The American Academy of Neurology²¹ recommends that clinicians perform a careful assessment of driving ability, including asking the caregiver to rate the patient's driving ability and reviewing any traffic citations and accidents. Cognitive assessments that include visual perception and sequential-task performance may also be helpful in assessing the capacity to

drive.²² Many state motor vehicle agencies have simulated driving laboratories or are willing to assess driving ability for a nominal fee. Information regarding resources for evaluating potentially impaired drivers is available through the National Highway Traffic Safety Administration (www.nhtsa.dot.gov).

TREATMENT OPTIONS

DRUG THERAPIES

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the *N*-methyl-*D*-aspartate receptor antagonist memantine are the only treatments for Alzheimer's disease that have been approved by the Food and Drug Administration²³ (Table 1). Randomized, placebo-controlled clinical trials of cholinesterase inhibitors have included patients with mainly mild-to-moderate Alz-

Table 1. Drug Therapy for Alzheimer's Disease.

Medication	Dose	Common Adverse Side Effects	Comments
Donepezil (Aricept)	5 mg/day at bedtime with or without food for 4 to 6 weeks; 10 mg/day thereafter, if tolerated	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams	Available in a single daily dose
Rivastigmine (Exelon)	3 mg daily, split into morning and evening doses with meals; dose increased by 3 mg/day every 4 weeks as tolerated, with a maximum daily dose of 12 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, indigestion, dizziness, drowsiness, headache, diaphoresis, weakness	Available as a patch
Galantamine (Razadyne)	8 mg daily, split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks, as tolerated, with a maximum daily dose of 16 to 24 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue	Available as an extended-release capsule
Memantine (Namenda)	5 mg/day with or without food; dose increased by 5 mg every week, with a maximum daily dose of 20 mg	Constipation, dizziness, headache, pain (nonspecific)	Often used as an adjunct to cholinesterase inhibitors; not recommended alone for treatment of early disease

heimer's disease and have shown significant but clinically marginal benefits with respect to cognition, daily function, and behavior.²⁴⁻²⁶ The condition of patients who are taking these drugs remains stable for a year or more and then may decline, though at a rate that is slower than that among untreated patients.

Although there are few studies directly comparing the three cholinesterase inhibitors, a systematic review and meta-analysis of data from 27 randomized trials concluded that there were no significant differences in effects on cognitive performance among these medications.²⁷ During the study period (usually, 3 to 6 months), the use of each of these drugs as prescribed at a standard dose resulted in a mean improvement of 2 to 3 points on the Alzheimer's Disease Assessment Scale for cognition (a scale ranging from 0 to 70, with higher scores indicating worse cognition) or a decreased rate of decline, as compared with the placebo group (approximately a 3-point difference, with a minimal clinically important difference of 4 points).

On the basis of 14 studies that measured daily function, donepezil was modestly but significantly more effective than rivastigmine. Donepezil was likewise modestly but significantly better than rivastigmine and galantamine with regard to behavior, as measured by the Neuropsychiatric In-

ventory (on a scale ranging from 1 to 144, with higher scores indicating a greater severity of disease). Patients receiving donepezil had a mean reduction of 4.3 points in the baseline score, as compared with a reduction of 1.4 for those receiving the other agents. The likelihood of an overall improvement in score was 1.9 times as great with donepezil as with placebo, 1.2 times as great with rivastigmine as with placebo, and 1.6 times as great with galantamine as with placebo. Adverse effects (including nausea, vomiting, diarrhea, dizziness, and weight loss) were frequent with all three medications, although slightly less frequent with donepezil than with the other medications.

Initial randomized trials of memantine involving patients with moderate-to-severe disease showed a small but significant reduction in cognitive deterioration.²⁸ Subsequent randomized trials involving patients with mild-to-moderate disease showed that memantine resulted in marginal benefits over a period of 6 months, with absolute changes in cognitive and functional measures of 1 percentage point.²⁹ However, studies that were limited to patients with mild or early-stage disease have shown no significant benefit of memantine therapy.³⁰ Memantine has also been used in patients with late-stage disease in combination with cholinesterase inhibitors, such as donepezil,

with modest improvements (a relative change in score of 2 to 5%) on the Severe Impairment Battery and the activities of daily living inventory of the Alzheimer's Disease Cooperative Study.³¹

More data are needed to guide the optimal timing of treatment of early Alzheimer's disease. In a small, randomized, placebo-controlled trial of donepezil, patients in whom Alzheimer's disease had been diagnosed within the preceding year showed improvement in cognitive performance over a period of 24 weeks.³² In an open-label study, patients who were treated early in the disease course had improvement that was only slightly greater than that of patients who began treatment later.²⁶ In another observational study, a duration of treatment with cholinesterase inhibitors or memantine of at least 3 years was associated with a significantly slower rate of decline in cognitive ability and daily function.³³

In practice, subjective reports of improvement in patients receiving cholinesterase inhibitors or memantine are common, but objective improvements are modest, if detectable at all. A rational approach is to try a cholinesterase inhibitor first, switching to another agent in the same class if the initial agent is ineffective or if intolerable side effects emerge.²³ Memantine may be added to any of the cholinesterase inhibitors in patients who have little or no improvement with cholinesterase inhibitor monotherapy.

OTHER STRATEGIES

The use of nonsteroidal antiinflammatory drugs, estrogen therapy, antioxidant vitamins, or statins has been proposed for the prevention of Alzheimer's disease, but the results of randomized trials have been inconsistent or negative.³⁴⁻³⁷ Similarly, the efficacy of commonly used complementary therapies (e.g., ginkgo biloba, acetyl-L-carnitine, lecithin, huperzine A, piracetam, curcumin, periwinkle, and phosphatidylserine) has not been shown in randomized trials.³⁸ A review of nine randomized clinical trials of cognitive training and rehabilitation therapies that were used to address loss of memory and other intellectual functions showed no significant effects.³⁹

MANAGEMENT OF PSYCHIATRIC SYMPTOMS

Behavioral and psychiatric symptoms typically increase with disease progression. However, depression and anxiety are frequent even in the early

stage of Alzheimer's disease. In one study, 25% of patients with Alzheimer's disease were reported to have received the diagnosis of depression at the time of or just before the onset of symptoms of the disease.⁴⁰ In patients in whom pharmacotherapy is considered appropriate, selective serotonin-reuptake inhibitors are commonly used; tricyclic antidepressants are generally avoided, since their anticholinergic effects can cause or exacerbate confusion.⁴¹

Psychosis that is characterized by hallucinations and delusions may occur infrequently in patients with early Alzheimer's disease. The occurrence of agitation, delusions, hallucinations, and irritability early in the disease course also raises the possibility of an alternative diagnosis, such as dementia with Lewy bodies. Treatment with conventional or atypical antipsychotic agents may be helpful, but such drugs should be used with caution because of the potential adverse effects (e.g., parkinsonism, extrapyramidal signs, sedation, and confusion).⁴²

CAREGIVER SUPPORT

Persons who live with and provide care for patients with Alzheimer's disease, even in the early phases of the disease, often report emotional stress, in part related to the need to give up vacations, hobbies, or even work to care for the patient. Caregivers should routinely be offered counseling and support. Resources for caregivers and patients are available through the Alzheimer's Association (www.alz.org).

AREAS OF UNCERTAINTY

Further study of brain-imaging methods and biomarkers that may facilitate the identification of patients with early Alzheimer's disease is needed. Focal atrophy on magnetic resonance imaging (MRI) of the inferior temporal region, particularly the hippocampus, has been shown to predict the conversion from mild cognitive impairment to Alzheimer's disease.⁴³ However, there is no standard technique to quantify atrophy in the clinical setting, and the diagnostic sensitivity and specificity of MRI are unclear.

Studies have shown that evidence of decreased metabolism and perfusion in the parietal lobes on ¹⁸F-fluorodeoxyglucose-positron-emission tomography (FDG-PET) is as accurate as evidence

of focal atrophy on MRI in predicting progression from mild cognitive impairment to Alzheimer's disease.^{43,44} However, PET scanning is costly and not widely available at present, and its role in diagnosis remains uncertain. PET imaging with the use of amyloid-binding compounds, such as carbon 11-labeled Pittsburgh compound B (PIB),⁴⁵ has been reported to identify patients with early Alzheimer's disease.⁴⁶ Some normal elderly persons without dementia have PIB retention similar to that observed in patients with Alzheimer's disease, but progression to Alzheimer's disease occurs more rapidly in persons with mild cognitive impairment who have PIB retention than in those without retention, indicating that amyloid deposition may be an early biomarker of incipient disease.^{47,48}

Measurement of markers in cerebrospinal fluid has also been proposed to identify early Alzheimer's disease. Among persons with mild cognitive impairment, reduced levels of beta-amyloid peptide and increased levels of total tau and tau phosphorylated at threonine 181 have predicted the diagnosis of Alzheimer's disease.^{49,50} Assessment requires lumbar puncture, and the threshold diagnostic levels of these markers have varied across studies.^{51,52} These measures are now commercially available with clinical interpretation, but their role in practice remains unclear.

GUIDELINES

The European Federation of Neurological Societies has published recommendations for the diagnosis and management of Alzheimer's disease.⁵³ On the basis of available randomized trials, treatment with cholinesterase inhibitors is recommended even for mild or early disease; no specific cholinesterase inhibitor is recommended over another. The American Academy of Neurology published practice recommendations in 2001⁵⁴ that have not yet been updated. In 2006, the American Association for Geriatric Psychiatry published

practice recommendations that also emphasize treatment with approved medications for cognitive symptoms, as well as symptomatic treatment for neuropsychiatric manifestations, such as depression and psychosis, and attention to issues related to safety, such as driving, living alone, and medication administration.⁵⁵

CONCLUSIONS AND RECOMMENDATIONS

The 72-year-old patient who is described in the vignette has a history of memory and functional impairment, with a relatively high Mini-Mental State Examination¹ score and a normal neurologic examination. Basic blood chemical analysis and measures of thyrotropin should be performed, along with additional laboratory studies as deemed clinically relevant. Brain MRI to rule out other brain diseases and assess atrophy and a detailed neuropsychological assessment are warranted to make a preliminary diagnosis. If the diagnosis of Alzheimer's disease is established, I would discuss with the patient and caregiver potential safety issues, including the current living situation and driving, and I would initiate treatment with one of the cholinesterase inhibitors, probably donepezil (starting at 5 mg each night at bedtime). I would plan a follow-up visit in 4 to 6 weeks to assess the side effects and efficacy of the medication (both subjective and objective) by repeating the Mini-Mental State Examination. At that time, the dose of the cholinesterase inhibitor could be increased to 10 mg daily if the drug has been well tolerated. The patient should be closely followed clinically, with repeated neuropsychological assessment within 2 years.

Dr. Mayeux reports receiving an honorarium from Quintiles for serving on a data and safety monitoring board for a trial of a product manufactured by Eli Lilly. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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