



EDUCATIONAL OBJECTIVE: Readers will distinguish Alzheimer disease from the cognitive changes of normal aging

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Alzheimer disease: Time to improve its diagnosis and treatment

ABSTRACT

Basic research is bringing a much-needed infusion of optimism and urgency to the clinical diagnosis and treatment of Alzheimer disease. Some of its risk factors may be modifiable, and although current drugs offer only modest benefit, true disease-modifying drugs are on the horizon. This review is aimed at primary care physicians, who are the first clinicians to see patients with Alzheimer disease and are responsible for their ongoing care throughout the course of their dementia.

KEY POINTS

Interpret screening tests carefully in patients who have very low or very high education levels, who are not tested in their native language, or who have deficits that might limit their performance.

Patients with Alzheimer disease function best in a safe, calm, and predictable environment. Their caregivers require ongoing support and education to develop realistic expectations throughout the course of the illness.

It is important that families be made aware that treatments for Alzheimer disease, such as cholinesterase inhibitors, attenuate decline over time rather than improve cognitive and behavioral symptoms.

Evidence is growing that nutritional factors (eg, dietary restriction, antioxidant intake, and the Mediterranean diet) and lifestyle factors (eg, social and mental activity and exercise) can delay the onset of Alzheimer disease.

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THE NUMBER OF PATIENTS with Alzheimer disease, the most common cause of disability in the elderly, is about to rise dramatically. More than 5 million people in the United States are affected, and by 2050 this figure may rise to between 11 and 16 million.¹ The prevalence doubles every 5 years from ages 65 to 85, so that Alzheimer disease affects 30% to 50% of all people at age 85.^{1,2}

Primary care physicians bear the brunt of diagnosing and treating all these patients,³ requiring that they have the training to meet this critical public health problem.

But diagnosing this disease is not easy. In the early stages, it can be difficult to distinguish between the decline in certain cognitive functions due to normal aging (eg, name recall) and the mild cognitive impairment that often precedes Alzheimer disease.

Once a patient is diagnosed with Alzheimer disease, there needs to be a realistic discussion with the patient and family about what treatment with different drugs can—and cannot—accomplish.

ALZHEIMER DISEASE DIAGNOSIS: THE EARLIER, THE BETTER

While much has been accomplished in Alzheimer disease research in the last 20 years, a

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great deal remains to be done to improve its diagnosis and treatment. There is increasing evidence that early diagnosis of Alzheimer disease will be key to maximizing treatment benefits. But too often, patients are diagnosed in later stages of the disease, when disabling symptoms and neuropathologic changes have become well established.

Mild cognitive impairment: A predementia phase

The pathologic changes of Alzheimer disease typically begin many years before its clinical signs are apparent. Most patients pass through a predementia phase called mild cognitive impairment, with early memory loss but with relatively well-preserved activities of daily living.

From 6% to 25% of patients with mild cognitive impairment progress to dementia annually, a rate far higher than the incidence rate in the general population of 0.3% to 3.9% per year, depending on age.^{4,5} Therefore, patients with mild cognitive impairment are a good population in which to test interventions to prevent dementia.^{6,7}

The concept of mild cognitive impairment is controversial because it is a transitional stage between normal aging and dementia rather than a distinct pathologic entity.⁸ Moreover, in some large community-based studies,^{9,10} a sizeable number of people with mild cognitive impairment reverted to normal cognitive function over 5 years, suggesting that mild cognitive impairment may be unstable over time.

Are other factors causing the dementia?

The *Diagnostic and Statistical Manual IV-Text Revision*¹¹ defines dementia as memory loss and at least one other area of cognitive impairment, not due to delirium, that interferes with social and occupational functioning. Alzheimer disease is the most common cause of dementia in the United States.¹

Still, Alzheimer disease does not typically exist in isolation. For example, while Alzheimer disease was the predominant cause of dementia in a recent postmortem series, 38% of dementia cases featured Alzheimer disease with lacunar infarction.¹² Accordingly, clinicians must consider factors other than Al-

zheimer disease that could contribute to (or even fully account for) the complaints or observed deficits.

Is it Alzheimer disease or normal aging?

Although cognitive impairment and changes in behavior are common in the elderly, they are not a normal part of aging. Like other chronic disorders associated with aging, Alzheimer disease can be diagnosed and treated. Cognitive impairment may come to light when the patient or a family member reports a problem or the clinician asks about problems or observes signs of impairment in the office. The cognitive difficulties should be taken seriously, and their impact on daily functioning should be evaluated.

Certain cognitive functions such as mental flexibility and speed of processing decline in normal aging,¹³ and many older people report cognitive symptoms. Therefore, it is important to differentiate mild age-associated cognitive changes from the beginning of a cognitive disorder such as Alzheimer disease. This can be difficult because the cognitive complaints of normal aging overlap with the symptoms of early Alzheimer disease, and there are no clear rules for distinguishing the two.¹³

Clues that a more serious problem exists may come from details such as a history of decline in cognitive abilities, involvement of more than one domain, and the extent to which the problem disrupts daily functioning.¹³ When evaluating the nature and severity of a cognitive disorder, one must take into account the patient's level of education, premorbid intellectual and occupational functioning, and concurrent medical and psychiatric conditions. Clinicians must also consider the impact that medications, possible substance abuse, and language and culture of origin have on cognition.

The most common cognitive complaints in the elderly tend to be related to working memory (eg, recalling the name of a recent acquaintance or a telephone number that was just looked up).¹⁴ Other common complaints center on the speed of mental processing (eg, thinking quickly), memory (eg, recalling the name of an old acquaintance, or remembering where objects were placed or why one entered a room), executive function (eg, multitasking

**Aging is the
greatest
risk factor
for Alzheimer
disease**

TABLE 1

Normal aging vs mild cognitive impairment and Alzheimer disease

NORMAL AGING	MILD COGNITIVE IMPAIRMENT	ALZHEIMER DISEASE
Can recall details of events	May forget details; recalls with prompting	May forget entire events
Can use notes, reminders, calendars effectively	Relies more on reminders and derives less benefit	Cannot use reminders effectively
Occasionally misplaces belongings; searches systematically for them	Misplaces things more often; has more trouble finding them	Misplaces items often; cannot find them; may put items in unusual places
Is fully oriented	Makes slight orientation errors	Has trouble keeping track of the date, month, and year
Sometimes cannot find a word	Complains of word-finding problems	Has obvious word-finding problems; may substitute words and use too many words to describe ideas
Follows conversations	Has trouble following complex conversations	May have trouble participating in or initiating conversation
Has intact social judgment	Has intact social judgment	Has impaired social judgment
Shows preserved personality	May show slight changes; eg, irritability, apathy	Is less motivated, more socially withdrawn, depressed, irritable, impulsive
Can perform instrumental activities of daily living (IADLs)	Shows slight impairment in IADLs for complex tasks	Has a clear impairment in IADLs

Alzheimer disease begins many years before its clinical signs

or planning a series of events), attention, and concentration.¹⁴

People with age-related cognitive changes can learn new information and recall previously learned information, although they may do so less rapidly and less efficiently. Furthermore, age-related cognitive change is not substantially progressive and does not significantly impair daily functioning.¹⁴ Nevertheless, complaints of cognitive changes should be monitored, since several studies showed that elderly people with cognitive complaints have an increased risk of developing dementia.^{15,16}

Key warning signs

The Alzheimer's Association¹⁷ lists 10 key warning signs of Alzheimer disease:

- Memory loss
- Difficulty performing familiar tasks
- Problems with language
- Disorientation to time and place
- Poor or decreased judgment
- Problems with abstract thought

- Misplacing things
- Changes in mood or behavior
- Changes in personality
- Loss of initiative.

As annotated on the Alzheimer's Association Web site,¹⁷ the list also highlights key differences between normal aging and more serious symptoms of possible Alzheimer disease. For example, patients with Alzheimer disease are more likely to forget entire experiences and not remember them later, whereas normal elderly may forget parts of events and then recall the missing details later. Also, patients with Alzheimer disease are more likely to lose the ability to complete familiar tasks or to follow written or spoken directions. Additional signs that a more serious cognitive problem exists include misplacing items so often that it interferes with daily activities, frequently losing the thread of conversations, and repeating the same questions, stories, or comments within a short time without being aware of it.¹⁸

The key factor differentiating mild cognitive impairment from dementia is that the former does not significantly disrupt the ability to perform activities of daily living,⁴ although some mild degree of impairment in complex instrumental activities of daily living is likely present.¹⁹ **TABLE 1** highlights some of the considerations discussed here for differentiating normal aging from mild cognitive impairment and Alzheimer disease.

Talk to a family member

Interviewing a reliable informant who knows the patient well is extremely helpful for determining the presence and extent of a cognitive problem. This is particularly important because even patients with mild cognitive impairment may have impaired awareness of their memory problems and may underestimate²⁰ or overestimate²¹ the problem.

Ask the informant about symptoms such as being repetitive, misplacing items, or having trouble with finding words or names, remembering to take medication, managing finances, navigating while driving, or performing multiple tasks or all steps of a task. A change in behavior may be the first sign of a cognitive disorder, so the patient and informant should also be asked about signs of irritability, anxiety, increased social isolation, and decline in motivation.

Screening tests

Memory can be tested with a three- or four-word recall test during the physical examination, with the addition of a clock-drawing task,²² or can be assessed with a composite cognitive measure. For example:

The Mini-Mental State Exam (MMSE)²³ can be given by the clinician or a trained member of the office staff. People with Alzheimer disease show progressive disability and a predictable rate of decline of approximately 2.8 points on the MMSE per year, with slower decline in the milder stages and faster decline in the moderate and severe stages of the illness.

The Montreal Cognitive Assessment Battery (MOCA, www.mocatest.org),²⁴ is a new cognitive screening test with a 30-point format similar to that of the MMSE. It includes a five-word recall, clock-drawing, and executive and visuospatial items that make it more

sensitive for mild cognitive impairment and vascular dementia.

The Alzheimer's Disease 8 (AD8),²⁵ a sensitive eight-question scale developed at Washington University, St. Louis, MO, can be completed by an informant in the waiting room.

New computerized screening measures are being developed that can be completed online or in the waiting room, and some simulate practical tasks such as using an automated teller machine and driving.

Care should be taken when interpreting performance on screening tests in patients who have very low or very high education levels, who are not tested in their native language, or who have physical or sensory deficits that might limit their performance.

Brain imaging and other tests

Patients with evidence of cognitive impairment should undergo a structural brain imaging test such as noncontrast **computed tomography (CT)** or **magnetic resonance imaging (MRI)** to evaluate for changes consistent with Alzheimer disease and to help rule out alternative causes of the cognitive impairment.^{26,27}

Neuropsychologic testing can be done by a dementia specialist, who can also help with diagnosis and treatment.

Positron emission tomography (PET) using fluorodeoxyglucose shows patterns of brain metabolism and can help differentiate Alzheimer disease from non-Alzheimer dementia, as patients with the former typically show hypometabolism in the temporal and parietal cortices.²⁸

Quantitative MRI and PET amyloid imaging are exciting new techniques currently being developed to diagnose Alzheimer disease earlier in clinical practice.^{29,30}

Cerebrospinal fluid markers. A decrease in the amyloid beta 1-42 peptide and an increase in the tau and phosphotau proteins may be the earliest signs of Alzheimer disease.^{31,32} However, before these tests can be widely used in clinical practice, their sensitivity and specificity need to be established, people's reluctance to undergo lumbar puncture will have to be overcome, and third-party reimbursement will have to be obtained.

Genetic factors also play an important role

Take cognitive difficulties seriously; evaluate their impact on function

in the development of Alzheimer disease. The apolipoprotein E4 (ApoE4) allele is a marker for Alzheimer disease. People of European descent who possess one copy of the allele have three times the risk (with onset typically in their 70s), and individuals who are homozygous have 15 times the risk (with typical onset in their 60s), compared with people lacking ApoE4.^{33,34} This test is commercially available but is still considered a research tool.

CURRENT AND FUTURE TREATMENTS

Five drugs have been approved for treating Alzheimer disease: four cholinesterase inhibitors approved for mild to moderate disease and a glutamate *N*-methyl *D*-aspartate (NMDA) antagonist approved for moderate to severe disease.

Cholinesterase inhibitors for mild to moderate disease

The cholinesterase inhibitors tend to stabilize memory during the first year of treatment, and they may make the subsequent decline more gradual. The four current drugs have similar efficacy, so the choice is usually based on tolerability and ease of use.

Tacrine (Cognex) is rarely used because it must be taken four times a day, it can cause gastrointestinal adverse effects, and it can raise hepatic enzyme levels.

Donepezil (Aricept) is the drug most often prescribed because it can be taken once daily, a major benefit in older patients with memory loss. Also, its starting dose (5 mg) is a therapeutic dose. Donepezil was also recently approved for the treatment of severe Alzheimer disease on the basis of positive results in trials in patients with moderate to severe disease.^{35,36}

Galantamine (Razadyne) comes in an extended-release formulation that can be taken once daily.

Rivastigmine (Exelon) is taken twice a day with food to reduce the risk of gastrointestinal adverse effects. It is also now available as a daily patch, which has a more favorable adverse-effect profile than oral rivastigmine.³⁷

Memantine for moderate to severe disease

Memantine (Namenda), an NMDA antagonist, is approved for moderate to severe

Alzheimer disease. The approval was based on a trial in which patients with advanced Alzheimer disease who received memantine monotherapy showed less decline in cognition and function after 6 months than those who received placebo,³⁸ and another trial in which patients who received the combination of donepezil plus memantine showed more benefit than with donepezil alone.³⁹

A treatment strategy

Recent guidelines recommend starting treatment with a cholinesterase inhibitor soon after Alzheimer disease is diagnosed and titrating the dose, as tolerated, to the high end of the therapeutic range.⁴⁰ Once patients decline to the moderate stage of the illness, usually with an MMSE score of 10 to 20, memantine should be added and titrated upward to 10 mg twice a day. The medications should be continued as long as they are tolerated and the clinician feels there is some evidence they are helping.

The main benefit of the cholinesterase inhibitors in clinical trials is an attenuation of decline over time rather than an improvement in cognitive or behavioral symptoms. This should be considered when judging whether there has been a positive effect. It is also important to discuss this point with patients and their families, who may expect improvement rather than relative stability. Benefits of these drugs in later stages of the illness usually involve better recognition and engagement with family members and people around them and less severe behavioral disturbances, making care easier.^{36,41-43}

Will drug therapy help in mild cognitive impairment?

Currently, no drugs are approved by the US Food and Drug Administration for patients with mild cognitive impairment, and the use of cholinesterase inhibitors in this population may not be reimbursed.

Six trials of cholinesterase inhibitors for mild cognitive impairment have been completed.⁴⁴⁻⁴⁷ On the whole, donepezil, rivastigmine, and galantamine had no effect on the primary end points in these trials, but they had some effects on some secondary ones.

In the Alzheimer Disease Cooperative

Alzheimer patients drop about 2.8 points on the MMSE per year

Study,⁴⁴ donepezil had no effect on the rate of progression from mild cognitive impairment to Alzheimer disease over the entire 3 years of the study, but it did reduce the rate in the first year of treatment. Moreover, the subgroup with one or two ApoE4 alleles benefitted over the entire 3 years.

A 24-week trial of donepezil in patients with mild cognitive impairment⁴⁵ had negative results with regard to the selected study end points (two standardized tests), but there was evidence of cognitive benefit with donepezil on secondary measures such as the Alzheimer's Disease Cognitive Assessment Scale-Cognitive Subscale,⁴⁸ a widely used cognitive measure in Alzheimer disease trials, and in patients' self-assessment of their memory.

One should discuss the risks and benefits of cholinesterase treatment with patients with mild cognitive impairment in whom underlying Alzheimer disease is strongly suspected.

Addressing behavioral problems

Behavioral problems are often the most disturbing symptoms in dementia, often leading to higher levels of care.

Apathy is the most common behavioral symptom in Alzheimer disease, increasing with disease severity.⁴⁹ There is no approved treatment for these apathetic symptoms, though methylphenidate (Ritalin) and modafanil (Provigil) are being tested in small clinical trials.

Depression and irritability are common and may respond well to low doses of serotonin reuptake inhibitors.

Agitation and psychosis are distressing and are likely to overwhelm the caregiver's ability to cope. Recent studies have raised concern about the safety and efficacy of atypical neuroleptics in patients with dementia and suggest that these drugs be used with careful monitoring.⁵⁰

A safe, calm, predictable environment

Patients with Alzheimer disease function best in an environment that is safe, calm, and predictable, and their caregivers require ongoing support and education to develop realistic expectations throughout the course of the illness.

Behavioral treatments for problematic be-

haviors for which supportive evidence exists include reduction of environmental stressors and behavioral management of problematic behaviors.⁵¹⁻⁵³ Such interventions typically include carefully observing and recording the problematic behavior, including its antecedents and situations under which it is most likely to occur, and then modifying the physical and interpersonal environment and schedule to reduce its occurrence.⁵¹

A challenge to the use of behavioral interventions in dementia is that the patient's cognitive functioning is gradually declining, and this may require adjustments of interventions with time and in response to new behaviors that emerge.⁵¹ Referral to a behavioral specialist such as a geriatric psychiatrist may be helpful in managing disruptive and hard-to-treat behavioral problems.

Amyloid-lowering drugs are being tested

The cholinesterase inhibitors and memantine are symptomatic therapies that help maintain neuronal function but do not have a significant impact on the underlying disease process. Their benefits are mild, and treatments that modify the disease course are urgently needed.^{54,55}

New disease-modifying agents are being tested to see if they delay disability, promote independence, and improve quality of life. Chief among these are compounds that reduce brain amyloid.

The amyloid cascade hypothesis is the current prevailing view of the pathogenesis of Alzheimer disease.⁵⁶ Small molecules of extracellular amyloid are deposited in the brain early in the course of the disease. These oligomers of beta-amyloid gradually coalesce into fibrillar sheets that form the core of amyloid plaques. Amyloid invokes an immune response and stimulates the hyperphosphorylation of tau into intraneuronal neurofibrillary tangles. The accumulation of these tangles contributes to neuronal and synaptic loss, which correlates with dementia and disability.

The current disease-modifying strategies are designed to decrease the production of amyloid, inhibit fibrillogenesis, and promote clearance of the toxic amyloid beta 1-42 fragment. We should note, however, that the correlation between amyloid burden and clinical

TABLE 2

Experimental agents to slow the progression of Alzheimer disease

THERAPY	MECHANISM
Amyloid-based therapies	
Beta and gamma secretase inhibitors and modulators	Decrease the cleavage of amyloid beta 1-42 from the amyloid precursor protein
Anti-aggregation agents	Decrease formation of fibrillar amyloid plaque formation and promote clearance of oligomeric forms of amyloid
Active and passive amyloid vaccines	Promote clearance of amyloid plaques and clearance of oligomeric forms of amyloid
Statins	Promote metabolism of amyloid
Insulin sensitizers	Promote metabolism of amyloid
RAGE (receptor for advanced glycation end-products) inhibitors	Decrease inflammation, amyloid beta 1-42 deposition, and amyloid beta transport into brain
Tau-based and neuroprotective approaches	
Kinase inhibitors	Decrease development of hyperphosphorylated tau tangles
Anti-inflammatory medications	Reduce inflammation-related injury
Nerve growth-factor-like agents	Preserve synaptic function
Antioxidants	Reduce oxidative injury

decline is not strong, and that lowering brain amyloid may not produce a measurable clinical benefit.⁵⁷

Large-scale trials are being conducted with agents that modulate and inhibit gamma secretase, an enzyme involved in cleaving the amyloid precursor protein into the toxic fragment of beta amyloid.⁵⁸ Early results show improvement in cognition and decreased amyloid levels in transgenic animals treated with these agents.

A recently completed phase III trial of tramiprosate, a glycosaminoglycan receptor inhibitor that interferes with fibrillization of amyloid, did not show positive results, but other antifibrillization agents are currently being tested.^{59,60}

Exciting immunotherapeutic approaches that target the toxic fragment of beta amyloid have been developed. In the active vaccine approach, a small fragment of beta amyloid is injected to stimulate the production of beta amyloid antibodies to lower brain amyloid levels. However, although active vaccines are designed primarily to stimulate a B-cell re-

sponse, they can cause adverse effects through unplanned stimulation of T cells.

Passive immunization with a monoclonal antibody against beta amyloid may be a safer strategy, and a number of compounds are undergoing clinical trials.⁶¹⁻⁶³ Intravenous immune globulin contains anti-amyloid antibodies and other immunomodulatory factors that may be useful in treating Alzheimer disease, and a phase III trial is being planned in view of positive results from earlier-phase studies.⁶⁴

Future disease-modifying treatments

Treatments designed to prevent hyperphosphorylation of tau are also being pursued. Currently approved compounds such as lithium (Eskalith) and valproic acid (Depakene) have been shown to decrease the formation of neurofibrillary tangles in laboratory models. There is some retrospective epidemiologic evidence that statin treatment is associated with a lower incidence of Alzheimer disease and decreased amyloid deposition in in vitro preparations, and two large phase III trials of

Continue Alzheimer drugs as long as you think they are helping

TABLE 3

Factors that may increase or decrease the risk of Alzheimer disease

Increase risk

Age
Female sex
Apolipoprotein E4
Family history of dementia
Stroke
Obesity
Elevated blood pressure and cholesterol
Diabetes

Decrease risk

Education
Physical exercise
Social activities and hobbies
Nutritional factors
Curcumin
Green tea
Mediterranean diet
Omega-3 fatty acids
Red wine (modest use)

No drugs are yet approved for mild cognitive impairment

statins in addition to cholinesterase inhibitors are nearing completion.^{65,66}

Aging is the strongest risk factor for Alzheimer disease, and future treatment targets will be derived from new insights into the biology of neuronal aging and senescence. Two recent phase III trials of xaliproden, a neurotrophin enhancer, were negative in patients with mild to moderate Alzheimer disease.⁶⁷

Future mechanism-based treatments will be directed at reducing oxidative stress, promoting neurorestoration, and genetic modification. A summary of the disease-modifying strategies now being tested has recently been published (TABLE 3).⁶⁸

SOME RISK FACTORS ARE MODIFIABLE

Evidence is growing that nutritional factors (eg, dietary restriction, antioxidant intake,

and the Mediterranean diet) and lifestyle factors (eg, social and mental activity and exercise) can promote healthy brain aging and delay the onset of Alzheimer disease.^{69,70}

Animals on low-calorie diets live longer, and some epidemiologic studies have shown that people who consume fewer calories have a lower incidence of Alzheimer disease.⁶⁹

Consuming fish two to three times per week appears to lower the incidence of Alzheimer disease, and a recent report in 2,254 elderly people followed for 4 years found that a Mediterranean diet of fish, olive oil, vegetables, and fruit had a protective effect.⁷¹

Resveratrol, a chemical found in red wine, is associated with longevity. A clinical trial of resveratrol to prevent Alzheimer disease is being planned.⁷²⁻⁷⁴ Compounds such as docosahexaenoic acid (an omega-3 fatty acid), a flavanoid found in green tea, and curcumin (a component of many curry dishes) are also associated with lowering levels of amyloid.⁷⁵⁻⁷⁷

Foods high in antioxidants may reduce the risk of Alzheimer disease.^{69,78} Daily folate supplements may have a protective effect, but antioxidants such as vitamin E and anti-inflammatory medications have shown disappointing results in preventing or treating Alzheimer disease and may have significant adverse effects.^{44,59,79,80}

Evidence is also increasing that education, learning new skills, frequent socializing, and regularly engaging in physical exercise and mentally stimulating activities delay the onset of Alzheimer disease, and these pursuits should be encouraged.⁸¹⁻⁸³ Also, treatment of cardiovascular risk factors such as hypertension and hyperlipidemia in mid-life and in older age may lower the rate of cognitive impairment in the elderly.⁸⁴⁻⁸⁶

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