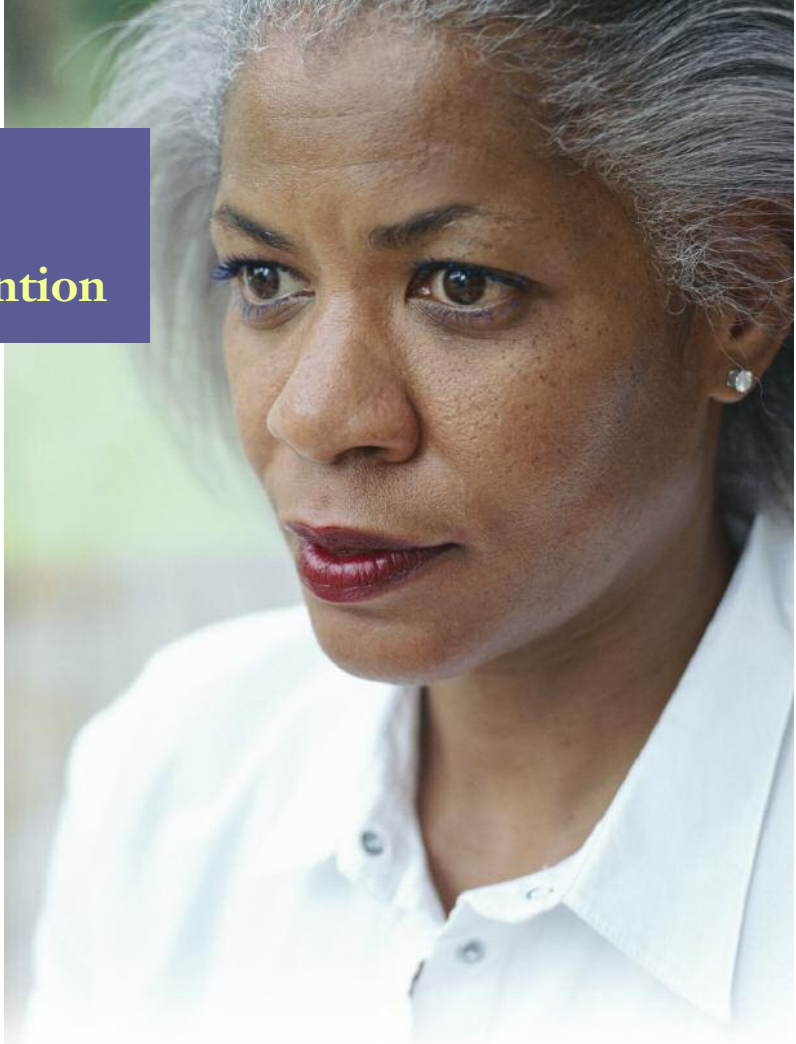


Modern Care for Patients With Alzheimer Disease: Rationale for Early Intervention

Katherine E. Galluzzi, DO
Denah M. Appelt, PhD
Brian J. Balin, PhD

More than 5 million people in the United States are afflicted with Alzheimer disease, a condition that is the seventh leading cause of death in the nation. Lacking definitive disease-modifying treatments, modern care for individuals with Alzheimer disease is necessarily multimodal, combining the use of approved pharmaceutical agents (ie, acetylcholinesterase inhibitors, N-methyl-D-aspartate receptor antagonists, antipsychotics), lifestyle and behavioral interventions, and components of palliative care. Some promising experimental treatments are undergoing clinical trials, including immunotherapy to prevent the deposition of β -amyloid, a protein implicated as an etiologic factor in the disease. The authors briefly examine the rationale and methods for screening patients for early indications of the onset of Alzheimer disease. They also describe current and potential treatments for patients with this disease.

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The Alzheimer's Association reports that there are 5.3 million Americans with Alzheimer disease, 200,000 of whom are younger than 65 years.¹ Alzheimer disease results in cognitive deficits that cause substantial decline in social and occupational functioning,² and it is the seventh leading cause of death in the United States.¹ We are about to enter the second decade of the millennium, and

we are still without a cure for patients with this devastating, progressive neurodegenerative disorder.

Clinical diagnosis of Alzheimer disease requires that cognitive deficits do not occur exclusively during delirium and that other causes are not responsible for the observed declines. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*³ criteria require a diagnosis to include, in addition to problems with memory, one or more of the following conditions: agnosia, aphasia, apraxia, or problems with executive functioning. Cognitive deficits progress to affect not only intellect, but also mood, behavior, personality, and the ability to carry out activities of daily living. Confirmatory diagnosis of Alzheimer disease continues to rely on

postmortem assessment of pathologic evidence, though diagnosis of most cases of Alzheimer disease is based on the presentation and clinical evaluation of the affected individual.

Alzheimer disease exacts a heavy toll on caregivers and loved ones, but the cost to the patient is the inexorable loss of mental and physical function and, ultimately, the loss of self. In the present article, we review the rationale and methods for screening patients for early indications of the onset of Alzheimer disease. We also describe current and potential treatments for patients with this condition.

Alzheimer Disease

Alzheimer disease is a disease of aging, though not all patients with Alzheimer disease are elderly. The commonly held

Katherine E. Galluzzi, DO, is a professor in the Department of Geriatrics at the Philadelphia College of Osteopathic Medicine (PCOM) in Pennsylvania. Denah M. Appelt, PhD, is a professor in the Department of Neuroscience, Pharmacology, and Physiology at PCOM. Brian J. Balin, PhD, is a professor in the Department of Pathology, Microbiology, Immunology, and Forensic Medicine at PCOM.

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Address correspondence to Katherine E. Galluzzi, DO, Department of Geriatrics, Philadelphia College of Osteopathic Medicine, 4190 City Ave, Rowland Hall, Suite 315, Philadelphia, PA 19131-1633.

E-mail: katherineg@pcom.edu

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misconception that advanced age itself causes cognitive decline leads to delay in evaluation of affected individuals, whose family members may see the initial memory lapses as an expected aspect of aging. Gifford and Cummings⁴ observed that nearly 75% of patients with moderate to severe dementia are unrecognized by primary care physicians as having cognitive impairment. In 2008, the British House of Commons Committee of Public Accounts reported that more than half of all individuals with dementia in the United Kingdom never receive a diagnosis of their condition from a physician.

The challenge for physicians and other clinicians who care for older persons is to identify those in whom initial changes of Alzheimer disease are present and to initiate appropriate interventions early in the course of the disease, when patients are most likely to benefit from treatment. Early identification of patients with Alzheimer disease also allows anticipatory guidance for patients and their families, allowing them to attempt to mitigate the effects of the disease and to begin to formulate a plan of care for patients during the disease's later stages.

Mild Cognitive Impairment

Several decades have elapsed since Reisberg et al⁵ observed a prodromal period in which individuals who will later have dementia first manifest milder cognitive deficits. The original criteria for this pre-dementia state required that a patient have memory complaints (preferably qualified by an informant) and memory impairment relative to the patient's age and education—but preserved general cognitive function and intact activities of daily living.⁵ Known as mild cognitive impairment (MCI), this period has been further described as a transitional state between the cognitive changes of normal aging and the fully developed features of dementia.²

Although the majority of cases of dementia are attributable to Alzheimer disease, it is important to recognize that MCI does not predict the onset of Alzheimer disease alone. Rather, MCI is the precursor to several types of dementia, including neurodegenerative

dementia (eg, Alzheimer disease, Parkinson disease, frontotemporal dementia, dementia with Lewy bodies); vascular dementia (eg, vascular cognitive impairment); and dementia caused by neoplasms, normal pressure hydrocephalus, metabolic factors, and psychiatric factors.⁶

Mild cognitive impairment is not a benign diagnosis. Individuals with MCI have an increased risk for Alzheimer disease and a faster rate of cognitive decline, compared to individuals without evidence of MCI. A recent study using data from the Chicago Health and Aging Project⁷ evaluated cognitive decline in incident Alzheimer disease within a community population. This longitudinal cohort study of older white and African American individuals residing in a geographically defined community measured cognition at 3-year intervals. Compared to the group with no cognitive impairment, the annual rate of cognitive decline was increased more than 2-fold in the group with MCI (mean estimate of decline = 0.086 unit per year; SE = 0.011; $P < .001$) and more than 4-fold in the group with Alzheimer disease (mean estimate of decline = 0.173 unit per year; SE = 0.020; $P < .001$).⁷ Results did not reliably vary by race, sex, or age.

Recent work by Goldberg et al⁸ demonstrated that individuals who met diagnostic criteria for MCI but not for AD had statistically significant impairments in a performance-based measure of everyday function. The authors pointed out that although basic activities of daily living, such as bathing, dressing, and toileting, remain intact in individuals with MCI, more complicated tasks, characterized as *instrumental activities of daily living*, may be subtly affected. For example, executive function (ie, the ability to perform such complex tasks as planning or coordinating travel, financial, shopping, or work-related activities) is adversely affected much earlier in individuals with dementia than are the basic activities of daily living.

The finding that everyday function declines in patients with MCI underscores the need for both early recognition of cognitive decline and the alignment of early cognitive change with its functional consequences.⁸

Screening Tools for Alzheimer Disease

Screening must not be confused with diagnostic testing. Screening strives to identify individuals who have a specific condition that can be confirmed with a diagnostic test. As previously noted, no clinically available confirmatory diagnostic tests exist for Alzheimer disease (other than pathologic evaluation of brain tissue). Thus, the importance of screening tools for diagnostic findings as well as for evaluating disease progression and patient response to treatment cannot be overstated.

Formal neuropsychiatric testing, though extremely valuable in delineating the extent and nature of cognitive deficits, is not readily available in most primary care centers. There are numerous other screening tools for Alzheimer disease for use in multiple settings, including the primary care office, but many of these methods lack the sensitivity and specificity needed to identify individuals who exhibit cognitive deficits that may be indicative of MCI.

Although there is general agreement that elderly individuals should undergo routine baseline mental status evaluation by their primary care providers, several barriers to such evaluation exist, including time and reimbursement constraints and lack of knowledge and acceptance of appropriate screening tools by patients and physicians. A brief overview of commonly used cognitive screening evaluations for Alzheimer disease is presented in *Figure 1*.

The Alzheimer's Disease Assessment Scale-Cognitive Subset (ADAS-Cog) has been widely used in clinical research for Alzheimer disease.⁹ Although some researchers consider the ADAS-Cog to be the "gold standard" for Alzheimer disease screening, this test has not seen widespread use in the primary care setting because of lack of acceptance and knowledge of it and lack of reimbursement for it. The test consists of 11 tasks measuring attention, language, memory, praxis, and other cognitive abilities that are often referred to as core symptoms of Alzheimer disease.⁹ The ADAS-Cog shares elements of its tasks with many other screening tools.

The Mini-Mental State Examination

- Alzheimer's Disease Assessment Scale-Cognitive Subset (ADAS-Cog)
- Consortium to Establish a Registry for Alzheimer's Disease (CERAD)
- Mini-Mental State Examination (MMSE)
- Short Portable Mental Status Questionnaire (SPMSQ)
- St Louis University Mental Status (SLUMS)

Figure 1. Commonly used cognitive screening evaluations for Alzheimer disease and mild cognitive impairment.

(MMSE) has demonstrated clinical usefulness in primary care settings, including ambulatory, acute, and long-term care settings. Developed by Folstein et al¹⁰ in 1975, this 30-item test measures attention, calculation, immediate memory, orientation, and recall, as well as various aspects of language and visuospatial skills. The MMSE is well-validated and easily reproducible and scored. A cut-point score of less than 24 on the test is generally considered indicative of dementia.¹⁰ However, this score may be affected by advanced age, education, culture, and language.

In a study comparing the ADAS-Cog and MMSE scores for their association with Alzheimer disease severity, Sevigny et al⁹ noted that orientation was the most sensitive item for differentiating patients across levels of cognitive impairment. Several other items exhibited a ceiling effect for patients with relatively mild cases of Alzheimer disease. The study authors suggested that orientation may be most useful for assessing cognitive change in patients with mild to moderate Alzheimer disease.⁹ The research by Sevigny et al⁹ also demonstrated that across the range of baseline MMSE scores in the study cohort, a consistent association with disease severity was observed with only three items: orientation, word recall, and word recognition, with orientation being the most sensitive for dif-

ferentiating severity of cognitive impairment.

The Short Portable Mental Status Questionnaire (SPMSQ) has been used for several decades. The SPMSQ is a verbally based 10-item test of long-term memory, attention, and concentration.¹¹ The clock drawing test (CDT) has been touted as a quick and easy screen for cognitive deficits and, as such, it has gained popularity in primary care settings.¹⁰ The CDT has also been incorporated into other cognitive screening tools as a simple measure of executive functioning. Several authors have attested to a fair degree of sensitivity and specificity with the CDT, but a lack of clear scoring recommendations limits its usefulness for disease staging.¹²

Evaluation of Mild Cognitive Impairment

Evaluation of MCI is similar to that for Alzheimer disease. Both conditions require a detailed history of the patient, usually with corroboration from a close family member or friend. Jorm and Jacombe¹³ have suggested that rather than testing all older individuals, mental status testing should be targeted toward those for whom a family member or friend has reported a change in function. Patients with MCI will typically score in the 26 to 28 range on MMSE and are classified as having "normal cognition" for their age. A less than near-perfect score on mental status testing is of greatest concern for patients who have had higher education or high levels of social or occupational functioning—in which case further memory testing is warranted.²

A potentially useful additional test may be the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychologic battery of tests.¹⁴ The CERAD total score has demonstrated good test/retest reliability. The CERAD, which has been used to differentiate between normal controls and patients with Alzheimer disease, has produced similar results as the MMSE, though with fewer false negatives.¹⁴ A recent study demonstrated that the CERAD total score is effective in identifying annualized rates of cognitive change.¹⁵ The study authors proposed that establishment of cut-off scores for

mild, moderate, and severe cognitive change would allow for the use of CERAD as a sensitive screening tool.¹⁵

The St Louis University Mental Status (SLUMS) examination is a screening tool that combines questions similar to those in the MMSE with the CDT, tests of attention and recall, and a story followed by four comprehension/memory questions. A pilot study¹⁶ that compared the SLUMS to the MMSE suggested that the former may be more effective at identifying MCI.

Depression and Alzheimer Disease

In an analysis of data collected over a 17-year period from the 949 participants in the Framingham Heart Study,¹⁷ depressive symptoms were assessed at baseline (1990-1994) using the 60-point Center for Epidemiologic Studies Depression Scale (CES-D). Depression was found to be associated with an increased risk of dementia and Alzheimer disease in older men and women—even when the diagnosis of MCI was excluded.¹⁷

Antidepressants have long been used to treat patients for whom depression was believed to complicate or worsen symptoms of dementia. However, studies have not yet determined whether interventions aimed at managing depression cause a reduction in the risk for dementia. Mental status testing should include measures of mood, demeanor, deportment, and behavior to differentiate patients who may have dementia from those with depression.

Current Treatments and Therapies Under Investigation

As previously noted, no effective treatments are available for preventing or halting progression of Alzheimer disease or for curing patients with Alzheimer disease. Based on the cholinergic hypothesis of Alzheimer disease,¹⁸ therapeutic approaches have focused on modulating the cholinergic neurotransmitter deficits that have been shown to be affected early in disease onset. This hypothesis was formulated as a result of evidence for reduced synthesis of the neurotransmitter acetylcholine. In an attempt to effectively manage Alzheimer disease by maintaining adequate levels of acetylcholine,

inhibitors of acetylcholinesterase (an enzyme that breaks down acetylcholine) have been developed. There are currently four acetylcholinesterase inhibitors approved by the US Food and Drug Administration (FDA) to treat patients with cognitive deficits of Alzheimer disease. These medications are donepezil hydrochloride (Aricept; Eisai Inc, Woodcliff Lake, New Jersey); rivastigmine tartrate (Exelon; Novartis Pharmaceuticals Corp, Basel, Switzerland); galantamine hydrobromide (Razadyne; Janssen Pharmaceutica NV, Beerse, Belgium); and tacrine hydrochloride (Cognex; Shionogi Inc, Florham Park, New Jersey). A list of current treatments for patients with Alzheimer disease is presented in *Figure 2*.

Unfortunately, these medications have limited effectiveness in delaying progression of Alzheimer disease, leading to the evaluation and use of another drug, memantine hydrochloride (Namenda; Forest Pharmaceuticals Inc, New York, New York) for treating patients with moderate to severe Alzheimer disease.¹⁹ This drug targets the glutamatergic system as an antagonist to the N-methyl-D-aspartate glutamate receptors that are involved in the regulation of intracellular calcium levels. Although memantine has produced beneficial effects in later stages of Alzheimer disease, progression of the disease remains problematic.

Other theories and hypotheses have led to therapeutic strategies that target inflammation, oxidative stress, and mitochondrial dysfunction. A number of these strategies involve evaluation of medications that are FDA-approved for other conditions, as well as nutraceuticals that have demonstrated numerous health benefits. Clinical trials of these drugs (eg, statins,²⁰ nonsteroidal anti-inflammatory drugs²¹) and nutraceuticals (eg, ginkgo biloba,²² vitamin E²³) have demonstrated limited efficacy for treatment of patients with Alzheimer disease. However, these drugs and nutraceuticals may provide benefit to individuals before the onset of the disease and at the earliest recognition of cognitive deficits, including MCI. Thus, evaluation of many of these compounds is ongoing as potential preventive agents for the onset of dementia.

- Donepezil hydrochloride (Aricept; Eisai Inc, Woodcliff Lake, New Jersey)
- Galantamine hydrobromide (Razadyne; Janssen Pharmaceutica NV, Beerse, Belgium)
- Rivastigmine tartrate (Exelon; Novartis Pharmaceuticals Corp, Basel, Switzerland)
- Tacrine hydrochloride (Cognex; Shionogi Inc, Florham Park, New Jersey)
- Memantine hydrochloride (Namenda; Forest Pharmaceuticals Inc, New York, NY)
- Cognitive training exercises

Figure 2. Currently approved treatments for patients with Alzheimer disease.

An additional therapeutic method for preserving and maintaining cognitive function is the use of cognitive training exercises.²⁴ Such approaches, which are safe, engaging, and nonpharmacologic, have potential for patients with MCI or mild Alzheimer disease. A number of cognitive training exercises are available on the Internet (eg, <http://www.happy-neuron.com>). Training exercises have been shown to be more efficacious than memory strategy training, and training using multiple cognitive domains is more beneficial than single-domain cognitive training.²⁴

Emerging Therapies

In light of data gathered over the past 2 decades, additional hypotheses have arisen for which emerging therapeutic approaches are being explored. One of the main postulates is the amyloid hypothesis.^{25,26} This hypothesis is based on the cleavage of amyloid precursor protein (APP), leading to excess accumulation of β -amyloid, which is thought to be toxic to neurons. The deposition of β -amyloid precedes symptomatic Alzheimer disease.^{25,26}

Experimental evidence from transgenic mouse models supports the involvement of β -amyloid in the development of Alzheimer disease. These mice

over-express the mutant form of β -amyloid, characterized by fibrillar amyloid plaques in the brain that cause cognitive deficits.^{27,28}

As a result of these findings, emerging therapeutic approaches target APP cleavage, β -amyloid degradation, and removal of β -amyloid from the brains of patients with Alzheimer disease. Strategies involving APP cleavage have focused on modulating secretase activity, which has been implicated in Alzheimer disease. Three secretase enzymes are associated with cleavage of APP into peptide fragments. Two of these secretases, β -secretase (β -site APP-cleaving enzyme [BACE1]) and γ -secretase, result in cleavage of APP into neurotoxic forms.²⁹ The other secretase, α -secretase (ie, tumor necrosis factor α converting enzyme [TACE]) results in the generation of non-neurotoxic peptides.

Agents to inhibit secretase activity are also being investigated in clinical trials. Posiphen³⁰ and CTS-21166³¹ are candidates for β -secretase inhibition, and semagacestat³² is a candidate for γ -secretase inhibition (though semagacestat clinical trials were recently halted³³). Alternatively, stimulation of α -secretase activity may accomplish the task of preventing β -amyloid from accumulating in the brain.

Immunotherapeutic approaches are being used in some clinical trials to target β -amyloid plaque formation as a treatment strategy for Alzheimer disease. The vaccine approach using AN1792 initially showed promise in stimulating the immune system to target β -amyloid. However, meningoencephalitis developed in 6% of the vaccinated patients, resulting in the termination of the AN1792 clinical trial.

Other immunomodulatory agents have been developed, such as bapineuzumab, a monoclonal antibody that targets the inflammatory and specific immune response to β -amyloid.³⁴ This drug, currently in phase 3 clinical trials, has demonstrated improvement in both cognitive and functional efficacy endpoints in the ADAS-Cog, the Neuropsychological Test Battery (NTB), and the Clinical Dementia Rating-Sum of Boxes (CDR-SB).³⁴ Additional emerging

immunotherapy approaches include intravenous immunoglobulin, which is speculated to target β -amyloid, and etanercept, which blocks tumor necrosis factor- α and interferon γ .³⁴

Some alternative approaches to treatment involve degradation of β -amyloid and modification of β -amyloid receptors to ameliorate symptoms in patients with Alzheimer disease. These treatments focus on the enzymes neprilysin and insulin degrading enzyme, which have been demonstrated to degrade β -amyloid.³⁵ These enzymes have also been shown to be down-regulated in the brains of aged individuals and of patients with Alzheimer disease.³⁵ Thus, reversing or enhancing the up-regulation of these enzymes could produce beneficial effects. Receptor modification has focused on the receptor for advanced glycation endproducts (RAGE), because this receptor is considered to be a primary mechanism for β -amyloid transport into the brain.³⁶ A RAGE-targeting substance known as PF-04494700 is being evaluated in a phase 2 clinical trial.³⁷

Another neuropathologic change that has received attention in Alzheimer disease research involves the microtubule associated protein tau. A number of research groups are studying how inhibition of aggregation of the tau protein into neurofibrillary tangles would alleviate symptoms of Alzheimer disease.³⁸ Methylthioninium chloride and the peptide NAPVSIPQ are being studied for their abilities to dissolve neurofibrillary tangles and block tau phosphorylation, respectively.^{26,38} These substances are in mid- to late-stage clinical trials.

Future Therapeutic Options

Future therapeutic approaches in Alzheimer disease research may incorporate other hypotheses, such as a proposal that infection is a trigger for the pathogenesis of the disease.³⁹ In this regard, infectious agents such as *Chlamydia pneumoniae*,³⁹ herpes simplex virus type 1,⁴⁰ and *Borrelia burgdorferi*⁴¹ are being investigated as viable candidates for the development of therapeutic strategies to combat Alzheimer disease. Such strategies may initially involve antimicrobial agents to attenuate pathogenic effects in this disease or to

stimulate the innate immune system to better control infection in at-risk individuals.

Alternatively, a cocktail approach using multiple therapeutic regimens may become necessary as the ever-evolving complexity of Alzheimer disease continues to unfold.

Conclusion

Despite decades of focused research, Alzheimer disease continues to require diagnosis by exclusion, and the disease still has no standardized, effective level of care. The need for identification of patients with early signs of cognitive impairment has resulted in the development of several useful screening methods. A public health goal should be an increase in primary care awareness and clinical use of screening tests for MCI and Alzheimer disease.

It may be feasible to delay or mitigate Alzheimer disease with appropriate early intervention, and several promising new therapeutic approaches are on the horizon. Our hope is that basic science coupled with enhanced clinical recognition of the onset of MCI and its progression to Alzheimer disease will bridge the gap toward effective therapeutic intervention for patients.

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