

# Advances in Diagnosis and Treatment of Alzheimer's Disease

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**A**lzheimer's disease (AD) is common in elderly patients. With the aging of the population, the prevalence of AD in the United States has been increasing at an alarming rate. AD was first described by Alois Alzheimer in 1907 in a published case report of a 52-year-old woman who had severe jealousy of her husband followed by amnesia, agnosia, apraxia, and aphasia.<sup>1</sup> On postmortem examination, her brain was found to have neurofibrillary tangles and senile plaques. This was the first documented case of AD. The prevalence of AD was not recognized until the 1970s,<sup>2</sup> and although the neuropathology was known at that time, the mechanisms of disease progression still remain unclear.

This article presents an overview of AD, including its epidemiology and pathophysiology, the differential diagnosis of dementia in the elderly patient, and recent advances in diagnosis and treatment.

## EPIDEMIOLOGY

AD currently affects 3 to 4 million persons in the United States.<sup>3</sup> AD is the most common form of dementia, accounting for 50% to 70% of cases. Its prevalence increases from approximately 1% of people at age 65 years to 45% of people at age 85 years and older.<sup>4,5</sup> Known risk factors for AD include age, female gender, positive family history, and Down syndrome.<sup>5,6</sup> AD most often appears in people older than 65 years, but the early-onset type has occurred in patients as young as 8 years. Women with AD outnumber men by a ratio of 2.8 to 1. The apolipoprotein E type 4 genotype (APOE  $\epsilon$ 4) appears to be a genetic risk factor for late-onset AD. History of head trauma and low education level have been implicated as risk factors but not proven.<sup>7</sup>

The socioeconomic impact of AD on the patient and their families is substantial. Patients with AD typically live 8 to 12 years following diagnosis. Although the majority of AD patients are cared for at home, a large portion of nursing home residents have AD, aver-

aging 50%.<sup>5,8</sup> The mean lifetime cost of AD per individual was estimated at greater than \$170,000.<sup>5</sup> Once a patient is placed in a nursing home, the costs increase to roughly \$42,000 to \$70,000 per year.<sup>5,8</sup>

## PATHOPHYSIOLOGY

AD is characterized by an increase in  $\beta$ -amyloid production, forming neuritic plaques that lead to cell death. The development of neurofibrillary tangles further contributes to neuronal loss. Cell loss in the nucleus basales of Meynert results in a deficit in the production of choline acetyltransferase, leading to subsequent inability to synthesize acetylcholine at the synaptic endings.<sup>7,9</sup>

Neurofibrillary tangles are composed primarily of tau proteins, which are poorly phosphorylated fibrillary proteins found in the neuronal cytoplasm.<sup>5,7</sup> When the tangles are present, the neuron can no longer properly maintain its cytoskeleton, which is needed for the branching of synaptic ends. This ultimately leads to cell death. A small number of neurofibrillary tangles are seen in normal aging, but an increased number of the tangles is pathognomonic for AD.<sup>10</sup>

The other major histopathologic finding in AD is senile plaques. These are complex plaques consisting of extracellular deposits of  $\beta$ -amyloid. They are associated with swollen, distorted neurons called *dystrophic neurites*.<sup>10,11</sup>  $\beta$ -amyloid is derived from a precursor called *amyloid precursor protein* (APP), which is encoded on chromosome 21.<sup>12,13</sup> These plaques are found predominantly

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in the hippocampus and temporal lobe cortex but also in the cerebral cortex and meninges.<sup>11</sup>

## ETIOLOGY

To date, AD is known to be a progressive degenerative disease with cognitive and behavioral manifestations.<sup>14</sup> Although its etiology is incompletely understood, AD is believed to develop in response to a combination of genetic and nongenetic factors, which may be different in different individuals.

### Genetic Factors in AD

Many patients and their families have reported that AD runs in the family, and this has been corroborated in many studies. One of the largest studies, the MIRAGE study, found that first-degree relatives of 1600 patients with AD had a 39% higher lifetime risk of developing AD. It was also estimated that if both parents had AD, the lifetime risk for acquiring AD increased to 54% by the age of 80 years.<sup>15,16</sup> The exact role heredity plays remains unclear, however.

Intensive research has revealed 3 gene mutations, with autosomal dominant inheritance, that are associated with early-onset AD in some patients.<sup>7,17,18</sup> All three mutations are found on the gene locale for APP and alter the processing of this protein. A mutation of the *APP* gene on chromosome 21 has been identified in some patients with early-onset AD. A significant portion of Down syndrome patients older than 50 years have neuropathologic symptoms of AD, probably related to overexpression of the *APP* gene in these patients.<sup>5,12,13</sup> The other two mutations associated with early-onset AD are of the presenilin 1 (*PS1*) and presenilin 2 (*PS2*) genes, found on chromosomes 14 and 1, respectively. *PS1* and *PS2* have active roles in the process of cleaving  $\beta$ -amyloid. Without *PS1* or *PS2*,  $\beta$ -amyloid is not broken down and degraded but, instead, continues to build.

Apolipoprotein E (ApoE) has a role in lipid metabolism and tissue repair. The primary site for the synthesis of ApoE is in the liver and the secondary site is in the brain.<sup>16,18</sup> The role of the *APOE* gene in the development of AD has garnered substantial research interest in the past decade. The polymorphisms of *APOE* that have been studied the most are *APOE*  $\epsilon$ 2, *APOE*  $\epsilon$ 3, and *APOE*  $\epsilon$ 4. Inheritance of the *APOE*  $\epsilon$ 4 allele has been associated with sporadic late-onset AD. It is still unclear how the *APOE* gene and AD are linked, but it is certain that those who carry the *APOE*  $\epsilon$ 4 allele have an increased risk of AD.<sup>16</sup> Having one *APOE*  $\epsilon$ 4 allele increases the risk of AD by 29%, but two *APOE*  $\epsilon$ 4 alleles carry the highest risk for AD.<sup>5,19,20</sup> However, *APOE* geno-

type testing is neither sensitive nor specific for the development of AD and is not recommended for screening purposes.

## DIAGNOSIS

AD should no longer solely be considered a diagnosis of exclusion, although clearly other diseases must be ruled out. AD signs and symptoms follow a predictable clinical progression in most patients, which follows the progression of neuropathic changes in the brain over time.

The early signs of AD may be very subtle. The Agency for Health Care Policy and Research (AHCPR) suggests triggers to alert a clinician to evaluate for the presence of AD. Triggers include difficulties in the following areas: learning and retaining information, handling complex tasks, reasoning ability, spatial ability and orientation, language, and behavior.<sup>21</sup>

In 2001, the American Academy of Neurology published guidelines for the diagnosis and treatment of AD (**Table 1**). These guidelines support the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke in conjunction with the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for the diagnoses of definite, probable, and possible AD based on clinical, laboratory, and imaging evaluation techniques.<sup>22,23,25</sup>

The key elements of diagnosis of probable AD include the loss of memory and cognitive ability severe enough to interfere with past level of function. Although cognitive and functional loss is progressive, the patient with AD retains a clear state of consciousness. In addition to memory impairment, cognitive loss is present in at least 1 of the following domains: language, praxis, and visual and spatial processing. It is important in the diagnosis of AD to rule out systemic disorders or other brain diseases that could account for progressive deficits in memory and cognition.

A diagnosis of probable AD based on clinical history is supported by the above-mentioned cognitive deficits plus impaired activities of daily living and altered patterns of behavior. A family history of similar disorders, particularly if neuropathologically confirmed, supports a diagnosis of AD. Other clinical features include a plateau in the course of the illness; depression; insomnia; incontinence; delusions; illusions; hallucinations; catastrophic verbal, emotional, or physical outbursts; and weight loss. Neurologic abnormalities seen in some patients, especially those with advanced disease, include motor signs such as increased muscle tone, myoclonus, gait disorder, or seizures.

**Table 1.** Summary of American Academy of Neurology Guidelines for the Diagnosis and Treatment of Alzheimer's Disease

**Diagnosis**

Patients with mild cognitive impairment should be monitored for cognitive and functional decline because of their increased risk for dementia.

General cognitive screening instruments should be used for the detection of dementia (ie, Mini-Mental State Examination [good evidence], 7-Minute Screen [weaker evidence], Kokmen Short Test of Mental Status [weaker evidence]).

Neuropsychological batteries are considered useful in identifying patients with dementia.

The *DSM-III-R* definition of dementia (identical to the *DSM-IV* definition) is reliable.

The NINCDS-ADRDA criteria for the diagnosis of probable AD or the *DSM-III-R* criteria for dementia of the Alzheimer type should be used routinely.

Clinical criteria for Creutzfeldt-Jakob disease should be used in rapidly progressive dementia syndromes.

Structural neuroimaging by computed tomography or magnetic resonance imaging is appropriate in the initial evaluation of patients with dementia.

RPR screening (for syphilis) is *not* recommended unless the patient has specific risk factors.

SPECT scanning is *not* recommended in the initial or differential diagnosis.

PET scans are *not* recommended for routine use.

Evaluation of genetic markers is *not* recommended for the diagnosis of dementia (including *APOE* genotyping, markers for dementia with Lewy bodies or Creutzfeldt-Jakob disease, CSF 14-3-3 protein, tau mutations).

**Pharmacologic therapy**

Cholinesterase inhibitors should be considered in patients with mild to moderate dementia.

Vitamin E (1000 IU twice daily) should be considered in an attempt to slow disease progression.

Estrogen should *not* be prescribed to treat AD.

Antipsychotic agents should be used to treat agitation or psychosis in patients with dementia when environmental manipulation fails.

Selected tricyclic antidepressants, MAO-B inhibitors, and SSRIs should be considered for the treatment of depression in patients with dementia.

**Educational interventions**

Short-term programs directed toward educating families and caregivers about AD should be offered.

Long-term education and support services should be offered to caregivers to delay time to nursing home placement.

The staff of long-term care facilities should be educated about AD to reduce the use of unnecessary antipsychotic agents.

**Functional performance modifications**

Behavioral modification, scheduled toileting, and prompted voiding should be used to reduce urinary incontinence.

Graded assistance, practice, and positive reinforcement should be used to increase functional independence.

Persons with AD may experience decreased behavioral problems with the following: music during meals and bathing, walking or light-weight exercises.

**Interventions for caregivers**

Comprehensive psychoeducational caregiver training may be beneficial.

Support groups for caregivers may be beneficial.

AD = Alzheimer's disease; *DSM-III-R* = *Diagnostic and Statistical Manual*, 3rd edition, revised; *DSM-IV* = *Diagnostic and Statistical Manual*, 4th edition; MAO = monoamine oxidase; NINCDS-ADRDA = National Institute of Neurologic, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; PET = positron emission tomography; RPR = rapid plasma reagin; SPECT = single-photon emission computed tomography; SSRI = selective serotonin reuptake inhibitor.

Adapted from Petersen et al,<sup>22</sup> Knopman et al,<sup>23</sup> and Doody et al.<sup>24</sup>

When the clinical elements of probable AD are present, the likelihood of a corresponding pathologic diagnosis of AD has been found to be 80% to 90%.<sup>26</sup> The gold standard for the diagnosis of AD, however, is findings of amyloid production, neuritic plaques, and neurofibrillary tangles on pathologic examination of brain tissue.

AD may be classified into 3 stages: early, middle, and late.<sup>27</sup> The early stage of AD is seen in the first 2 to 3 years of illness and is marked by mild cognitive im-

pairment. Folstein Mini-Mental State Examination (MMSE) scores generally range from 20 to 30 points (out of a maximum of 30 points). The middle stage of AD occurs after 3 to 4 years of illness. The patient often has a MMSE score ranging between 10 and 19 points, and may present with aphasia, apraxia, and agnosia. In late stage AD, the patient's MMSE score ranges between 0 and 9 points. Gait disturbance as well as bowel and bladder incontinence are often present.

**Table 2.** Differential Diagnosis of Dementia

**Nonreversible causes**

- Alzheimer's disease
- Dementia with Lewy bodies
- Amyotrophic lateral sclerosis
- Dementia pugilistica
- Pick's disease
- Hippocampal sclerosis
- HIV infection
- Vascular disease
- Parkinson's disease
- Progressive supranuclear palsy
- Creutzfeldt-Jakob disease

**Reversible causes**

- Encephalopathies
- Subdural hematomas
- Vitamin B<sub>12</sub> deficiency
- Thyroid disease
- Tumors
- Normal pressure hydrocephalus
- Korsakoff's psychosis
- Wernicke's encephalopathy
- Neurosyphilis

**DIFFERENTIAL DIAGNOSIS**

**Differential Diagnosis of Dementia**

The differential diagnosis of dementia encompasses a broad range of diseases and must be considered carefully. Dementia may result from both reversible and nonreversible disease entities (Table 2). Approximately 10% of dementias are reversible, but only if investigated. Some of the disorders listed in Table 2 can be easily assessed by performing blood tests or brain imaging or by discontinuing certain medications.

In a review of the literature by Clarfield in 1988, 13.2% of 2889 subjects with dementia were judged to have potentially reversible causes of dementia. In a subset of studies that included follow-up, 3% of dementias showed complete reversal and 8% showed partial reversal. The presumed causes of these reversible cases of dementia were metabolic disorders (16%), depression (26%), and drugs (28%).<sup>28</sup> Treatment of many of the reversible conditions may improve cognition.<sup>27</sup>

The following mnemonic can be helpful for remembering possible reversible causes of dementia<sup>5</sup>:

**D** = Drugs

**E** = Emotional disorders

**M** = Metabolic and endocrine disorders

**E** = Eye and ear disorders

**N** = Nutritional disorders, normal-pressure hydrocephalus

**T** = Tumor, trauma

**I** = Infection

**A** = Atherosclerosis, alcohol

**Distinguishing Dementia from Delirium or Depression**

Clinical judgment is crucial in diagnosing such disorders as depression and delirium. Both may be mistaken for dementia and can coexist with dementia, making accurate diagnosis difficult.<sup>29-31</sup> Delirium is characterized by sudden onset of disturbances of consciousness, cognition (including memory loss, language difficulty, attention deficit, and disorientation), and/or perception (eg, auditory or visual hallucinations). A simple bedside assessment can be performed by observing how well a patient can interact and follow a conversation. One can also ask the patient to recite the days of the week or months of the year, tasks that a patient with delirium usually cannot complete.<sup>29</sup>

Depression is extremely common in the elderly and is sometimes mistakenly diagnosed as dementia. In addition, depression may be an unrecognized comorbid condition in some patients with dementia. Some symptoms of depression, including sleep disturbance, anorexia, irritable behavior, apathy, and social withdrawal, can also be seen in patients with AD. No definitive test exists for distinguishing depression from AD. If a physician suspects depression in a patient with signs of dementia, a trial of antidepressants is warranted. This can result in a significant improvement in mood and cognition.<sup>32</sup>

**EVALUATION OF PATIENTS WITH DEMENTIA**

The general work-up of any patient for dementia includes a thorough history and physical examination, with attention focused on the hearing, visual, and neurologic portions of the examination. Appropriate diagnostic tests at this time would include measurement of serum electrolyte and vitamin B<sub>12</sub> levels, a complete blood count, thyroid function tests, and an HIV test (if indicated). Brain imaging (computed tomography and/or magnetic resonance imaging) remains controversial but can be

helpful for ruling out vascular insults or mass lesions. Cognitive testing also should be performed.

The MMSE is one of the most widely used cognitive tests. This simple questionnaire is administered by the physician in the office and take only a few minutes to complete. The MMSE assesses cognitive function in the domains of short-term memory, concentration, and spatial orientation, and scoring ranges from 0 to 30 points.<sup>29,32,33</sup> It is important to keep in mind that lower levels of education and the presence of language barriers or speech impairment reduce the validity of the MMSE. Likewise, a higher level of education has been associated with higher scores despite obvious decline. The MMSE should be administered on initial evaluation, before and after beginning therapy, and then at 3-month intervals to assess deterioration or response to medication.<sup>34</sup>

The Functional Activities Questionnaire (FAQ) evaluates the patient's abilities to complete activities that are essential to independent living. Tasks evaluated for include writing checks, paying bills, shopping for clothes and household necessities, preparing a balanced meal, remembering appointments, traveling out of the neighborhood by car or bus, and watching and understanding a TV show with the ability to discuss it. Tasks are scored as follows:

- 3 = Inability to complete a task
- 2 = Requires assistance to complete a task
- 1 = Able to complete a task with difficulty
- 0 = Performance of task is normal

The questionnaire consists of 10 questions, and thus scores may range from 0 to 30 points. A total score of 9 or more suggests functional impairment.<sup>29</sup>

Most experts agree that a clinical diagnosis of AD can usually be made based upon results of the general work-up and cognitive testing. Additional testing should proceed only in those patients with an atypical presentation or for research purposes. These additional tests may include lumbar puncture, an electroencephalogram, *APOE* genotyping, single-photon emission computed tomography (SPECT) scan, or neuropsychological examination.

#### INITIAL MANAGEMENT CONSIDERATIONS

Once reversible causes of dementia have been ruled out and a diagnosis of probable AD has been made, the first step in management is to inform the patient and family. Usually, prior to the initial doctor's visit, the patient and/or family have recognized some type of cognitive decline, primarily short-term memory. By all

rights, they are anxious and scared, wanting to know what the future will bring and looking for a cure. It is of utmost importance that the physician is truthful, compassionate, and supportive at this time. Family members will generally want a definitive diagnosis, reassurance regarding genetic risk factors, and a treatment plan. It is often very difficult to explain to a family that a definitive diagnosis cannot be made without a biopsy, but an honest attempt at full disclosure should be made. It is important to state that there is currently no known cure for AD but that medications are available that can slow the disease progression and that research into other treatment options are underway.

This discussion is also the opportunity to present all of the available treatment options and develop an individualized plan for the patient. Management of behavioral issues on a daily basis is a vital issue. Behavioral disturbances are stressful not only for the caregivers but for the patient themselves, who may have varying degrees of insight. Providing the family with information regarding other resources, such as counseling, AD support centers, adult day care centers, and possible alternative living situations, is appropriate at this time.

#### PHARMACOLOGIC MANAGEMENT

Research for possible cures for AD and slowing of disease progression has been going on for decades. Unfortunately, a cure has not been found, but medications are available to slow the progression of AD. Recently the American Academy of Neurology published guidelines for both the diagnosis and the treatment of AD (Table 1).<sup>22-24</sup>

#### Cholinergic Agents

Currently, cholinergic agents are the mainstays of treatment aimed at slowing disease progression. The brain of a patient with AD shows damaged neurons with decreased amounts of the neurotransmitter acetylcholine (ACh); this neurotransmitter is thought to preserve cognitive function. Thus, maintaining higher levels of ACh by inhibiting acetylcholinesterase (AChE), which cleaves ACh, is thought to cause a decrease in AD progression. Cholinergic agents do not halt or reverse AD; they can slow its progression, however. If the medication is stopped, the patient's original disease progression returns. Cholinesterase inhibitors are the only drugs thus far that have been shown to delay the progression of AD.<sup>35</sup> As is true for other medications, individual responses vary; some patients do not respond to cholinesterase inhibitors.

The first cholinergic agent approved by the US Food and Drug Administration (FDA) for treatment of

AD was tacrine (Cognex) in 1986. Tacrine, a tetrahydroaminoacridine, has anticholinesterase ability and is also a monoamine oxidase B inhibitor that binds to muscarinic receptors and potassium and calcium channels. Dosing for tacrine is 4 times daily, which raises the possibility of poor patient compliance. Due to gastrointestinal (GI) side effects and severe hepatotoxicity, tacrine is no longer the initial drug of choice for AD and is rarely used.<sup>5,9</sup>

Donepezil (Aricept), a piperidine-based AChE inhibitor, was released on the market in 1996. Donepezil is generally well tolerated, with minimal GI side effects. A 24-week, double-blind trial of donepezil revealed a significant improvement on the AD Assessment Scale–Cognitive Subscale (ADAS-Cog) in those patients taking donepezil compared to placebo.<sup>36</sup> Donepezil is taken once daily. The usual dose is 5 mg once daily for the first 6 weeks, after which the dosage is increased to 10 mg daily.

Another more recent cholinergic agent on the market is rivastigmine (Exelon). Rivastigmine is generally well tolerated, but the dosing is twice daily. A recent trial of rivastigmine randomized 699 patients into 3 groups: low dose, high dose, and placebo. It was shown that at the high dose of rivastigmine, higher scores on the ADAS-Cog were maintained compared to low-dose rivastigmine and placebo.<sup>37</sup> The usual starting dose of rivastigmine is 1.5 mg twice daily, increasing gradually, as tolerated, to a maximum of 6 mg twice daily.

Reminyl (galantamine), a tertiary alkaloid AChE inhibitor, is the newest FDA-approved medication for AD. In addition to its anti-AChE activity, galantamine stimulates pre- and postsynaptic nicotinic receptors. It is suspected that this may improve impaired nicotinic transmission.<sup>38,39</sup> Recent studies have shown evidence of significant cognitive improvement as assessed by the ADAS-Cog test. As with all AChE inhibitors, GI upset is the most common adverse effect; this can usually be avoided by starting with a low dose and titrating upward. The optimal dosage is 24 mg daily given in 2 doses.<sup>38,39</sup>

### **Anti-Inflammatory Agents**

It has long been suspected that inflammation plays a role in AD; this suspicion has been supported by the observation of the unexpectedly low incidence of AD in patients taking nonsteroidal antiinflammatory drugs (NSAIDs).<sup>5,16,40</sup> It has been hypothesized that either a primary inflammation or an inflammatory reaction to deposition of abnormal proteins such as  $\beta$ -amyloid can produce neuronal damage. This has led to several studies investigating NSAIDs and corticosteroids and their effect on AD. A long-awaited study published in 2000

showed no association between prednisone use and decreased progression of AD.<sup>41</sup> The Cache County Study published in 2000 did find a reduced occurrence or a delayed onset of AD with the use of NSAIDs.<sup>42</sup> NSAIDs have not been approved to date for the treatment or prevention of AD, but additional studies are underway.

### **Antioxidants**

The production of neurotoxic free radicals during oxidative metabolism has been suggested as a mechanism of neurodegeneration in AD. This neurobiological consideration, coupled with the demonstration that the monoamine oxidase inhibitor selegiline positively affects the course of Parkinson's disease, has stimulated investigation of drugs with antioxidant activity as therapeutic agents in AD. Although it is not clear that the effects of selegiline in Parkinson's disease are mediated by reduction of oxidative metabolism and the subsequent reduction of free radicals, this hypothesis has led to studies of selegiline and other agents with antioxidant activity (eg, vitamin E) in the treatment of AD.

Findings from several small, placebo-controlled studies of selegiline in AD provided encouragement for therapeutic efficacy. These results prompted a larger study of selegiline and Vitamin E by the Alzheimer's Disease Cooperative Study group.<sup>43</sup> Patients with moderately severe AD were given either selegiline, vitamin E, both, or placebo for a 2-year period. The efficacy of the drugs was measured by indices of substantial functional decline (eg, nursing home placement, increase in disease severity, loss of the ability to perform major activities of daily living). Both selegiline and vitamin E were superior to placebo in delaying disease progression. Vitamin E delayed the progression of nursing home placement by approximately 7 months when compared to placebo.<sup>35,43</sup> Although the drugs were active in the delay of disease progression, they did not improve cognitive function. The dosage of vitamin E in these studies was 1000 IU taken twice daily. This is a high dose of vitamin E, and patients on this regimen who are also taking anticoagulants must be monitored carefully.

Estrogen has been closely scrutinized regarding its possible role as an antioxidant in the delay of AD. Epidemiologic studies suggest that postmenopausal estrogen replacement therapy reduces the risk for developing AD later in life. In several uncontrolled pilot studies, estrogen appeared to improve cognitive function in women with AD. Unfortunately, three recent studies of placebo-controlled trials of estrogen replacement therapy in women with AD showed no improvement or delay of decline.<sup>44-46</sup> This finding does not

exclude the possibility of estrogen having a potential effect on AD, but further investigations are needed.

### Ginkgo

Extract of the leaf of the *Ginkgo biloba* tree has been used in traditional Chinese medicine for thousands of years based on its believed benefits to the brain. Pre-clinical studies suggest that such extracts have both antioxidant and anti-inflammatory properties. In a recent study, ginkgo was evaluated in a 52-week, randomized, double-blind, placebo-controlled study in patients with multi-infarct dementia. The patients were randomly assigned with outcomes measured by the ADAS-Cog, Clinical Global Impression of Change (CGIC), and Geriatric Evaluation by Relative's Rating Instrument (GERRI).<sup>47</sup> A small but statistically significant difference was found between the ginkgo and the placebo groups on the ADAS-Cog and the GERRI. No difference was found in the CGIC ratings. A more recent study of ginkgo that took place in the Netherlands showed no improvement in memory in patients with dementia.<sup>48</sup> Ginkgo is an over-the-counter medication that is not regulated by FDA standards for quality or effectiveness. In addition, ginkgo carries an increased risk of bleeding in patients who are already taking vitamin E and warfarin.

### CONCLUSION

AD is devastating to patients and their families, and a rising number of cases are diagnosed yearly. An understanding of the etiology and natural disease progression of AD is of paramount importance to the goal of finding a cure. All of the currently approved medications available for the treatment of AD are AChE inhibitors. These agents, which work at the level of the synaptic endings, may delay the progression of AD but do not prevent or halt the disease. Additional drugs are under investigation, however, and these may alter the approach to AD in the future. **HP**

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