

# Alzheimer Disease

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Updated: Aug 27, 2009

## Introduction

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### Background

Alzheimer disease (Alzheimer's disease, AD), the most common cause of dementia<sup>1</sup>, is an acquired cognitive and behavioral impairment of sufficient severity that markedly interferes with social and occupational functioning. Alzheimer disease is a major public health problem from the economic perspective. In the United States, the cost of caring for patients with dementia was \$84 billion per year in 2005, and the average yearly cost per patient was about \$24,500.<sup>2</sup>

Alzheimer disease affects approximately 5.2 million people in the United States. A larger number of individuals have decreased levels of cognitive function (eg, mild cognitive impairment) that frequently evolve into a full-blown dementia, thereby increasing the number of affected persons. By 2030, an estimated 7.7 million Americans aged 65 and older will have Alzheimer disease.<sup>3</sup> Statistical projections indicate that the number of persons affected by the disorder in the United States could range from 11-16 million by the year 2050.

### Pathophysiology

The anatomic pathology of Alzheimer disease includes neurofibrillary tangles (NFTs); senile plaques (SPs) at the microscopic level; and cerebrocortical atrophy, which predominantly involves the association regions and particularly the medial aspect of the temporal lobe. NFTs and SPs were described in by Alois Alzheimer in his original report on the disorder in 1907<sup>4</sup>; they are now universally accepted as a hallmark of the disease.

Although NFTs and SPs are characteristic of Alzheimer disease, they are not pathognomonic. NFTs are found in several other neurodegenerative disorders, including progressive supranuclear palsy and dementia pugilistica. SPs may occur in normal aging. Therefore, the mere presence of these lesions is not sufficient to diagnose Alzheimer disease. These lesions must be present in sufficient numbers and in a characteristic topographic distribution to fulfill the current histopathologic criteria for Alzheimer disease.

In addition to NFTs and SPs, many other lesions of Alzheimer disease have been recognized since Alzheimer's original papers were published. These include (1) the granulovacuolar degeneration of Shimkovicz; (2) the neuropil threads of Braak et al<sup>5</sup>; and (3) neuronal loss and synaptic degeneration, which are thought to ultimately mediate the cognitive and behavioral manifestations of the disorder.

Some authorities believed that NFTs, when present in low densities and essentially confined to the hippocampus, were part of normal aging. However, the histologic stages for Alzheimer disease that Braak et al formulated include an early stage in which a low density of NFTs is present in the entorhinal and perirhinal (ie, transentorhinal) cortices.<sup>5</sup> Therefore, even small numbers of NFTs in these areas of the medial temporal lobe may be abnormal.

In contrast, there is consensus that the presence of even low numbers of NFTs in the cerebral neocortex with concomitant SPs is characteristic of Alzheimer disease. Granulovacuolar degeneration occurs almost exclusively in the hippocampus. Neuropil threads, which are an array of dystrophic neurites diffusely distributed in the cortical neuropil, more or less independently of plaques and tangles. This lesion suggests neuropil alterations beyond those merely due to NFTs and SPs and indicates an even more widespread insult to the cortical circuitry than that visualized by studying only plaques and tangles.

NFTs are initially and most densely distributed in the medial aspect and in the pole of the temporal lobe; they affect the entorhinal cortex and the hippocampus most severely. As Alzheimer disease progresses, NFTs accumulate in many other cortical regions, beginning in high-order association regions and less frequently in the primary motor and sensory regions. SPs also accumulate primarily in association cortices and in the hippocampus. Plaques and tangles have relatively discrete and stereotypical patterns of laminar distribution in the cerebral cortex, which indicate predominant involvement of corticocortical connections.

## Frequency

### United States

The lifetime risk of Alzheimer disease is estimated to be 1:4-1:2. More than 14% of individuals older than 65 years have AD, and the prevalence increases to at least 40% in individuals older than 80 years.

### International

Prevalences of Alzheimer disease similar to those in the United States have been reported in industrialized nations. Countries experiencing rapid increases in the elderly segments of their population have rates approaching those in the United States.

## Mortality/Morbidity

- In the United States, Alzheimer disease is frequently considered a leading cause of death (sometimes ranked third after cardiovascular disease and cancer).
- The primary cause of death is intercurrent illness, such as pneumonia, in a patient who has become severely demented from Alzheimer disease. Patients lose the ability to walk and swallow. Difficulty swallowing may lead to aspiration pneumonia.

## Race

Some claim that Alzheimer disease affects certain ethnic and racial groups more severely than others, but more study is needed before reliable statements about racial predilections can be made. In African-Americans, for example, Alzheimer disease and dementia are more prevalent than in Caucasians; however, several studies have shown that the quality of education and socioeconomic factors that affect a person's access to education are important factors to explain the discrepancy.<sup>1,6,7,8,9</sup>

## Sex

Alzheimer disease affects both men and women. Many studies indicate that the risk of Alzheimer disease is significantly higher in women than in men. Some authorities have postulated that this difference is due to the loss of the neurotrophic effect of estrogen in postmenopausal women. Other factors may also influence this relative difference.

## Age

The prevalence of Alzheimer disease increases with age.

- Alzheimer disease is most prevalent in individuals older than 60 years. Some forms of familial early-onset Alzheimer disease can appear as early as the third decade, but this represents a subgroup of the less than 10% of all familial cases of Alzheimer disease.
- More than 90% of cases of Alzheimer disease are sporadic and occur in individuals older than 60 years.
- Of interest, results of some studies of nonagenarians and centenarians suggest that the risk may decrease in individuals older than 90 years. If so, age is not an unqualified risk factor for the disease, but further study of this matter is needed.
- Savva et al found that the association between the pathological features of Alzheimer disease and dementia (eg, neuritic plaques, diffuse plaques, tangles) is stronger in younger old persons (ie, age 75 years) than in older old persons (ie, 95 years). These results were achieved by assessing 456 brains donated to the population-based Medical Research Council Cognitive Function and Ageing Study from persons 69-103 years of age at death. These results demonstrate that the relationship between cerebral atrophy and dementia persist into the oldest ages, but the strength of association between pathological features of Alzheimer disease and clinical dementia diminished. It is important to take age into account when assessing the likely effect of interventions against dementia on the population.<sup>10</sup>

# Clinical

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## History

Patients with Alzheimer disease most commonly present with insidiously progressive memory loss, to which other spheres of cognitive impairment are added over several years. After memory loss occurs, patients may also have language disorders (eg, anomia) and impairment in their visuospatial skills and executive functions.

The National Institutes of Health-Alzheimer's Disease and Related Disorders Association (NIH-ADRDA), the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision, Text Revision (DSM-IV-TR)*, and the Consortium to Establish a Registry in Alzheimer's Disease (CERAD) have formulated several clinical guidelines for the diagnosis of AD. The NIH-ADRDA criteria for the diagnosis of AD require the finding of a slowly progressive memory loss of insidious onset in a fully conscious patient. AD cannot be diagnosed in patients with clouded consciousness or delirium. Toxic metabolic conditions and brain neoplasms must also be excluded as potential causes of the patient's dementia.

The main focus of these diagnostic guidelines consists of verifying the initial finding of mild, slowly progressive memory loss, that additional spheres of cognition are also compromised, and that other possible causes for dementia (eg, cerebrovascular disease, cobalamin deficiency, syphilis, thyroid disease) are ruled out with a combination of clinical examination and ancillary radiologic and laboratory tests. These guidelines are widely believed to be 90-95% accurate (as histopathologically verified) when followed carefully, and they are important not only for routine management but also for selecting and enrolling patients in therapeutic trials.

Substantially less common, but biopsy or autopsy-proven, presentations include right parietal lobe syndrome, progressive aphasia, spastic paraparesis, and impaired visuospatial skills, which is subsumed under the visual variant of Alzheimer disease.

## Physical

The earliest evidence of Alzheimer disease is the onset of chronic, insidious memory loss that is slowly progressive over several years. This loss may be associated with slowly progressive behavioral changes. Patients with mild Alzheimer disease usually have somewhat less obvious executive, language, and/or visuospatial dysfunction. In atypical presentations, dysfunction in cognitive domains other than memory may be most apparent. In later stages, many patients develop extrapyramidal dysfunction.

Initial mental status testing should include evaluation of attention and concentration, recent and remote memory, language, praxis, executive function, and visuospatial function. Brief standardized examinations such as the Mini-Mental Status Examination are less sensitive and specific than longer batteries specifically tailored to individual patients. Nonetheless, screening exams have a role, particularly as a baseline.

A complete neurologic exam is performed to look for signs of other diseases that could cause dementia such as Parkinson disease or multiple strokes.

## Causes

The cause of Alzheimer disease is unknown. Several investigators now believe that converging risk factors, which include advancing age, lipoprotein E epsilon 4 genotype, obesity, insulin resistance, dyslipidemia, hypertension, and inflammatory markers<sup>11,12</sup> trigger a pathophysiologic cascade that, over decades, leads to Alzheimer pathology and dementia.

Familial forms of Alzheimer disease account for less than 7% of all cases of Alzheimer disease, with most cases being sporadic (ie, not inherited). Mutations in genes coding for 3 proteins unequivocally cause Alzheimer disease. These genes (for amyloid precursor protein [APP, on chromosome 21], for presenilin I [on chromosome 14], and for presenilin II [on chromosome 1]) all lead to a relative excess in the production of the stickier 42-amino acid form of the beta-amyloid peptide over the less sticky 40-amino acid form.

This beta-pleated peptide is postulated to have neurotoxic properties and to lead to an incompletely understood cascade of events resulting in neuronal death, synapse loss, and the formation of neurofibrillary tangles (NFTs) and senile plaques (SPs) among other lesions. Nonetheless, mutations accounting for less than half of all cases of early-onset Alzheimer

disease have been found. Other than the ApoE epsilon 4 genotype, no polymorphisms in other genes have been consistently found to be associated with late-onset Alzheimer disease.

Considerable attention has been devoted to elucidating the composition of NFTs and SPs to find clues about the molecular pathogenesis and biochemistry of Alzheimer disease. Since the time of Alois Alzheimer, SPs have been known to include a starchlike (or amyloid) substance, usually in the center of these lesions, which is surrounded by a halo or layer of degenerating (dystrophic) neurites and reactive glia (both astrocytes and microglia).

One of the most important advances in recent decades has been the chemical characterization of this amyloid protein, the sequencing of its amino acid chain, and the cloning of the gene encoding its precursor protein (on chromosome 21). These advances have provided a wealth of information about the mechanisms underlying amyloid deposition in the brain, including information about the familial forms of Alzheimer's disease. Although the amyloid cascade hypothesis has gathered the most research dollars, other interesting hypotheses have been proposed.<sup>13,14,15</sup>

Attention has also been devoted to the mechanisms leading to the development of NFTs, the main constituent of which is the microtubule-associated protein tau that is hyperphosphorylated and that accumulates in the perikarya of large and medium pyramidal neurons. Somewhat surprisingly, mutations of the tau gene result not in Alzheimer disease but in some familial cases of frontotemporal dementia.

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## Differential Diagnoses

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Aphasia  
Cortical Basal Ganglionic Degeneration  
Dementia in Motor Neuron Disease  
Dementia With Lewy Bodies  
Frontal and Temporal Lobe Dementia  
Lyme Disease

Neurosyphilis  
Parkinson Disease  
Parkinson-Plus Syndromes  
Prion-Related Diseases  
Thyroid Disease  
Wilson Disease

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## Workup

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### Laboratory Studies

- Laboratory workup can be performed to rule out other conditions that may cause cognitive impairment.
- Current recommendations from the American Academy of Neurology include measurement of the cobalamin (vitamin B-12) level and a thyroid function screening test. Additional investigations are left to the physician, to be tailored to the particular needs of each patient.
- Laboratory tests may include the following:
  - Evaluation of the complete blood cell count and cobalamin (vitamin B-12) levels: Abnormalities in these measurements require further workup to rule out hematologic disease.
  - Screening of liver enzyme levels: Abnormalities in these measurements require further workup to rule out hepatic disease.
  - Analysis of thyroid stimulating hormone (TSH) levels: Abnormalities in this measurement require further workup to rule out thyroid disease.
  - Rapid plasma reagent (RPR) test: Abnormalities require further workup to rule out syphilis.

### Imaging Studies

- Brain MRI or CT: In assessing Alzheimer disease, brain MRIs or CT scans are not diagnostic of Alzheimer disease, but can show diffuse cortical and/or cerebral atrophy. In clinical research studies, atrophy of the hippocampi as demonstrated on coronal MRI (structures important in mediating memory processes) is considered a valid biomarker of Alzheimer disease neuropathology. Nonetheless, measurement of hippocampal volume is not used in routine clinical care in the diagnosis of Alzheimer disease. American Academy of Neurology recommendations indicate that structural neuroimaging with MRI or CT is appropriate to detect lesions that may result in cognitive impairment (stroke, small vessel disease, tumor, etc).

- SPECT or PET scans: Under most circumstances, SPECT or PET scan is not recommended for the routine workup of patients with typical presentations of Alzheimer disease. These modalities may be useful in atypical cases or when some form of frontotemporal dementia is a more likely diagnosis.

## Other Tests

- EEG (see EEG in Dementia and Encephalopathy): EEG is valuable when Creutzfeldt-Jakob disease or other prior-related disease is a likely diagnosis. Periodic high amplitude sharp waves can eventually be detected in most cases of Creutzfeldt-Jakob disease. EEG is also useful if pseudodementia is a realistic consideration when a normal EEG in a patient who appears profoundly demented would support that diagnosis. Multiple unwitnessed seizures rarely can present as dementia and an EEG would be valuable for evaluating that possibility.
- Lumbar puncture for measurement of CSF tau and amyloid: Tau and phosphorylated tau are often elevated in Alzheimer disease and amyloid is usually low (the reason is not known but perhaps because the amyloid is deposited in the brain rather than the CSF). By measuring both proteins, sensitivity and specificity of at least 80% and more often 90% can be achieved. When effective therapies that slow the rate of progression of Alzheimer disease are developed, lumbar puncture for tau and amyloid may become part of the diagnostic work-up, particularly if the therapies are specific for Alzheimer disease and carry significant morbidity. Until then, routine measurement of CSF tau and amyloid is not recommended, except in research settings.
- Genotyping for apolipoprotein E alleles: This test is a research tool that is helpful in determining the risk of Alzheimer disease in populations, but it is of little, if any, value in making a clinical diagnosis and developing a management plan in individual patients.
- Genetic testing for APP and presenilin mutations. After appropriate counseling, such testing is appropriate in early onset cases.
- In a prospective, randomized, controlled trial, Green et al examined the effect of disclosing apolipoprotein E (APOE) genotyping results to 162 asymptomatic adults who had a parent with Alzheimer disease. Follow-up testing performed 6 weeks, 6 months, and 1 year after disclosure or nondisclosure showed no significant differences between the 2 groups in changes in time-averaged measures of anxiety (4.5 in the disclosure group and 4.4 in the nondisclosure group,  $P=0.84$ ), depression (8.8 and 8.7, respectively;  $P=0.98$ ), or test-related distress (6.9 and 7.5, respectively;  $P=0.61$ ). Test-related distress was reduced among those who learned that they were APOE epsilon4-negative. Persons who had high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure.<sup>16</sup>

## Procedures

Perform lumbar puncture in select cases to rule out conditions such as normal-pressure hydrocephalus, neurosyphilis, neuroborreliosis, and cryptococcosis.

## Treatment

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### Medical Care

Therapeutic approaches to Alzheimer disease will someday include both symptomatic therapy and disease-modifying therapies. To date, only symptomatic therapies are available. All approved drugs for the treatment of Alzheimer disease modulate neurotransmitters - either acetylcholine or glutamate. Disease-modifying therapies would delay the onset of disease and/or slow the rate of progression. Although phase III trials for several potential disease-modifying therapies have been completed, as of August 2008, none have been clearly shown to be efficacious and hence none have been approved in the United States by the FDA.

The standard medical treatment for Alzheimer disease includes cholinesterase inhibitors (ChEIs) and partial *N*-methyl-D-aspartate (NMDA) antagonists.

Psychotropic medications are often used to treat secondary symptoms of Alzheimer disease such as depression, agitation, and sleep disorders. These include antidepressants, anti-epileptic drugs used for their effects on behavior, and neuroleptics. Several studies have examined the efficacy of psychotropic drugs; most have demonstrated no or limited efficacy, but many issues make interpretation of data from these studies difficult.

- Cholinesterase inhibitors
  - Numerous lines of evidence suggest that cholinergic systems that modulate information processing in the hippocampus and neocortex are impaired early in the course of Alzheimer disease.
  - These observations have suggested that some of the clinical manifestations of Alzheimer disease are due to loss of cholinergic innervation to the cerebral cortex. Centrally-acting acetylcholinesterase inhibitors (ChEIs) prevent the breakdown of acetylcholine.
  - Patients on ChEIs decline more slowly on cognitive and functional measures than patients on placebo. Nonetheless, as the treatment is symptomatic, it cannot be concluded that the underlying rate of progression of Alzheimer disease is affected.
  - Centrally acting anticholinergic medications should be avoided. Patients not uncommonly receive both ChEIs and anticholinergic agents, which counteract each other. Medications with anticholinergic effects such as diphenhydramine (Benadryl) and tricyclic antidepressants (such as amitriptyline or nortriptyline) can cause cognitive dysfunction. Therefore, a careful listing of the patient's medications is important to reduce the doses of, or ideally eliminate, all centrally acting anticholinergic agents.
  - See also the Medication section.
- *N*-methyl-D-aspartate antagonists: The partial NMDA antagonist memantine (Namenda) is believed to work by improving the signal-to-noise ratio of glutamatergic transmission at the NMDA receptor. This agent is approved by the FDA for treating moderate and severe Alzheimer disease. Several studies have demonstrated that memantine can be safely used in combination with ChEIs.
- Antidepressants: Antidepressants have an important role in the treatment of mood disorders in patients with Alzheimer disease. Depression is observed in more than 30% of patients with Alzheimer disease, and it frequently begins before Alzheimer disease is clinically diagnosed. Therefore, palliation of this frequent comorbid condition may improve cognitive and noncognitive performance. Other mood modulators, such as valproic acid, can be helpful for the treatment of disruptive behaviors and outbursts of anger, which patients with moderately advanced or advanced stages of Alzheimer disease may have.
- Psychotropic medications and behavioral interventions
  - A variety of behavioral and pharmacologic interventions can temporarily alleviate clinical manifestations of Alzheimer disease, such as anxiety, agitation, depression, and psychotic behavior. The effectiveness of such interventions is often modest and temporary, and they do not prevent the eventual deterioration of the patient's condition.
  - Behavioral interventions range from patient-centered approaches to caregiver training to help manage cognitive and behavioral manifestations of Alzheimer disease. These interventions are often combined with the more widely used pharmacologic interventions, such as anxiolytics for anxiety and agitation, neuroleptics for aberrant and/or socially disruptive behavior, and antidepressants or mood stabilizers for mood disorders and specific manifestations (eg, episodes of anger or rage).
  - No specific agent or dose of individual agents is unanimously accepted for the wide array of clinical manifestations. At present, the US Food and Drug Administration (FDA) has not approved any psychotropic agent for the treatment of Alzheimer disease. In 2005, the FDA decided to add a "black box warning" on the use of atypical neuroleptics in the treatment of secondary symptoms of Alzheimer disease such as agitation. Analyses suggested that patients on atypical neuroleptics had increased risk of death or stroke compared with patients on placebo. As of August 2008, the FDA has not added a black box warning for older neuroleptics such as haloperidol; yet few clinicians believe these older drugs are more efficacious and safer than the atypical neuroleptics because randomized clinical trials are lacking or are difficult to apply to specific clinical settings. Medications that many practitioners prefer are risperidone, olanzapine, and quetiapine. Physicians using these drugs are advised to tell patients (when appropriate) and caregivers of potential risks, but indicate that these drugs may still be the best choice in their individual case.
- The general recommendation is to use such agents as infrequently as possible and at the lowest doses possible to minimize adverse effects, particularly in frail, elderly patients.
- Particular concern has been raised about the potential for dopamine-depleting agents to aggravate the motor manifestations of dementia with Lewy bodies (DLB), because patients with DLB may be extremely sensitive to these agents.
- Results of several studies indicate that anticonvulsants (eg, gabapentin, valproic acid) may have a role in the treatment of behavioral problems in patients with Alzheimer disease.
- Many studies have suggested that intense inflammation occurs in the brains of patients with Alzheimer disease. Epidemiologic studies suggest that some patients on chronic anti-inflammatory therapy have a

decreased risk of developing Alzheimer disease. Nonetheless, no randomized clinical trial of greater than 6-months duration has demonstrated efficacy of anti-inflammatory drugs in slowing the rate of progression of Alzheimer disease.

- No data exist showing that women with Alzheimer disease who are then placed on estrogen therapy (ET) have fewer symptoms or progress more slowly than women treated with a placebo. Furthermore, a randomized clinical trial of estrogen in cognitively normal women aged 65 and older with a first-degree relative with Alzheimer disease showed that ET might actually increase the risk of stroke and dementia. Whether ET might decrease risk if started well before the age of 65 is not known.
- Excess levels of free radicals in the brain are neurotoxic. Nonetheless, no study has demonstrated efficacy of free-radical scavengers in the treatment of the cognitive symptoms of Alzheimer disease.
- In the past 10 years, numerous studies have been conducted, and many are still ongoing, that test therapies designed to decrease toxic amyloid fragments in the brain. A wide variety of approaches have been tried. These include vaccination with amyloid species, administration of monoclonal anti-amyloid antibodies, administration of intravenous immune globulin that may contain amyloid-binding antibodies, selective amyloid-lowering agents, chelating agents to prevent amyloid polymerization, brain shunting to improve removal of amyloid, and beta-secretase inhibitors to prevent generation of the A-beta amyloid fragment, among others. To date, no phase III study with these approaches has shown an acceptable combination of efficacy and acceptable side effects.
- Studies are also ongoing with agents that may prevent or reverse excess tau phosphorylation and thereby diminish formation of neurofibrillary tangles.
- Brain changes associated with Alzheimer disease probably start decades before clinical dementia is apparent. Many investigators believe that disease-modifying therapies are much more likely to be effective if they are started in a presymptomatic stage. Studies are identifying patients at increased risk with neuropsychological, neuroimaging, and genetic methods. Some of the disease-modifying therapies discussed above may possibly be effective if started in presymptomatic patients.

## **Surgical Care**

No accepted surgical treatments exist for Alzheimer disease. Potential surgical treatments in the future may include the use of devices to infuse neurotrophic factors, such as growth factors, to palliate Alzheimer disease.

## **Diet**

No special dietary considerations exist for Alzheimer disease.

## **Activity**

Both physical and mental activities are recommended for patients with Alzheimer disease.

- Mental activity
  - Many patients with normal cognition or those with mild impairment are concerned that they may develop Alzheimer disease. Many experts believe that mentally challenging activities, such as doing crossword puzzles and brainteasers, may reduce the risk in such patients.
  - Whether working on crossword puzzles or similar games for patients who already have Alzheimer disease might slow the rate of progression is not known. Clinical trials are underway to determine the effect these cognitive activities have on Alzheimer disease progression.
  - The mental activities should be kept within a reasonable level of difficulty for the patient. They should preferably be interactive, and they should be designed to allow the patient to recognize and correct mistakes.
  - Most important, these activities should be administered in a manner that does not cause excessive frustration and that ideally motivates the patient to engage in them frequently.
  - Unfortunately, little standardization and rigorous testing has been done to validate this treatment modality.
  - Some investigators have attempted various forms of cognitive retraining, also known as cognitive rehabilitation. The results of this approach remain controversial, and a substantial experimental study must still be performed to determine if it is useful in Alzheimer disease.
- Physical activity: Routine physical activity and exercise may have an impact on Alzheimer disease progression. Exercise training has been associated with some improvement in cognitive function in patients with

dementia<sup>17</sup> and physical activity in mid-life is associated with a reduced risk of developing Alzheimer disease in late-life.<sup>18</sup>

## Medication

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The mainstay of therapy for patients with Alzheimer disease is the use of centrally acting cholinesterase inhibitors to attempt to compensate for the depletion of ACh in the cerebral cortex and hippocampus. Four ChEIs have been approved by the FDA in the United States for the treatment of AD—tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne, formerly Reminyl). Tacrine has potential liver toxicity, requires frequent blood monitoring, and has been rarely prescribed since the other agents have become available. All 4 drugs inhibit acetylcholinesterase at the synapse (specific cholinesterase). The drugs tacrine and rivastigmine also inhibit butyrylcholinesterase. Although butyrylcholinesterase levels may be increased in AD, it is not clear that rivastigmine or tacrine have greater clinical efficacy than donepezil and galantamine.

Galantamine has a different second mechanism of action; it is also a presynaptic nicotinic modulator. No data exist that this second mechanism is of clinical importance.

In a multicenter, randomized, placebo-controlled trial, donepezil (5 mg/d for 6 wk, then 10 mg/d for 42 wk) was compared with placebo to measure change from baseline in the modified Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-Cog) and Clinical Dementia Rating Scale-sum of boxes (CDR-SB) in patients with mild cognitive impairment. A small, but significant, improvement on the primary measure of cognition was observed. No change was observed on the primary measure of global function. Most other measures of global impairment, cognition, and function were not improved, possibly because these measures are insensitive to change in mild cognitive impairment (MCI). Responses on subjective measures suggest subjects perceived benefits with donepezil treatment. More donepezil-treated subjects (18.4%) discontinued treatment due to adverse events than placebo-treated subjects (8.3%).<sup>19</sup>

All ChEIs have shown modest benefit compared with placebo on measures of cognitive function and activities of daily living. The ChEIs may also alleviate the noncognitive manifestations of AD such as agitation, wandering, and socially inappropriate behavior.

In general, the benefits are temporary because ChEIs do not address the underlying cause of the degeneration of cholinergic neurons, which continues during the disease. Although the ChEIs were originally expected to be efficacious in only the early and intermediate stages of AD (because the cholinergic deficit becomes more severe later in disease and fewer intact cholinergic synapses are present), they are also helpful in advanced disease. Furthermore, ChEIs are helpful in patients with AD with concomitant infarcts and in patients with dementia with Lewy bodies. (Frequently, AD and dementia with Lewy bodies occur in the same patient; sometimes this is called the Lewy body variant of AD).

The ChEIs share a common profile of adverse effects, the most frequent of which are nausea, vomiting, diarrhea, and dizziness. These are typically dose related and can be mitigated with slow up-titration to the desired maintenance dose. As antimuscarinic drugs are used for the treatment of incontinence, logically, ChEIs might exacerbate incontinence. One brief report has supported this hypothesis.<sup>20</sup>

ChEIs prescribed to treat dementia can provoke symptomatic bradycardia and syncope and precipitate fall-related injuries, including hip fracture. A population-based cohort study that identified community-dwelling older adults with dementia who were taking cholinesterase inhibitors (n=19,803) and controls who were not (n=61,499) found hospital visits for syncope were more frequent in people receiving ChEIs than in controls (31.5 vs 18.6 events per 1000 person-years; adjusted hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.57-1.98). Other syncope-related events, including hospital visits for bradycardia, permanent pacemaker insertion, and hip fracture, were also more common among people receiving cholinesterase inhibitors compared with controls. ChEI use in older adults with dementia is associated with increased risk of syncope-related events; these risks must be weighed against the benefits of taking ChEIs.<sup>21</sup>

Anecdotal reports exist of acute cognitive and behavioral decline associated with the abrupt termination of ChEIs. In several of these cases, restarting the ChEI was not associated with substantial improvement. These reports have implications concerning the best practice when switching a patient from one ChEI to another in this class. Reasons for switching might include undesirable side effects or seeming lack of efficacy. Nonetheless, no published data help clinicians know when switching to another ChEI would be helpful. The common practice of tapering a patient off one

CNS-active medication before starting a new one should not be followed when changing ChEIs. For example, a patient who had been taking 10 mg of donepezil should be started the next day on galantamine, at least 8 mg/d and possibly 16 mg/d.

No current evidence supports the use of more than 1 ChEI at a time.

A report by Sano et al in 1997 suggested that high dose vitamin E (2000 units per day of alpha-tocopherol) might decrease the risk of death or the rate of conversion to severe dementia. This benefit presumably resulted from the antioxidant effects of vitamin E. Nonetheless, later studies suggest that vitamin E supplementation may actually increase risk of adverse cardiovascular outcomes. Therefore, use of these agents is not currently recommended, and most practitioners have abandoned their use.

## **NMDA antagonists**

The newest class of agents indicated for the treatment of AD. As of July 2008, the only approved drug in this class is memantine. These agents may be used alone or combined with AChE inhibitors. Studies suggest memantine use with donepezil has an effect on cognition in moderate to severe AD<sup>22</sup> but not with mild to moderate AD.<sup>23</sup>

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### **Memantine (Namenda, Axura)**

NMDA antagonist indicated for all stages of AD. NMDA-receptor overstimulation in CNS by glutamate (excitatory amino acid) may contribute to symptoms; no evidence confirms glutamatergic deficit in AD.

#### **Adult**

5 mg PO qd, gradually titrate to 20-mg/d target dose as follows (allow > 1 wk between increases): 5 mg PO bid, 5 mg PO q am, 10 mg PO q pm, 10 mg PO bid

#### **Pediatric**

Not indicated

## **Centrally acting AChE inhibitors**

These agents are used to palliate cholinergic deficiency.

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### **Donepezil (Aricept)**

Centrally acting AChE but not BuChE inhibitor

#### **Adult**

5 mg PO qd for 3-4 wk, then 10 mg PO qd

#### **Pediatric**

Not established

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### **Rivastigmine (Exelon)**

Centrally acting AChE and BuChE inhibitor.

#### **Adult**

1.5 mg PO bid for 1 mo, 3 mg PO bid for 1 mo, 4.5 mg PO for 1 mo, then 6 mg PO bid thereafter

#### **Pediatric**

Not established

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### **Rivastigmine transdermal patch (Exelon patch)**

Competitive and reversible acetylcholinesterase inhibitor. While mechanism of action unknown, may reversibly inhibit cholinesterase, which may, in turn, increase concentrations of acetylcholine available for synaptic transmission in CNS and thereby enhance cholinergic function. Effect may lessen as disease process advances and fewer cholinergic neurons remain functionally intact.

Available as 5-cm<sup>2</sup> patch containing 9 mg (releases 4.6 mg/24 h) and 10-cm<sup>2</sup> patch containing 18 mg (releases 9.5 mg/24 h). Indicated for dementia of Alzheimer disease and for dementia associated with Parkinson disease.

#### **Adult**

Apply patch to upper or lower back, upper arm, or chest

Initiating patch therapy (not switching from oral therapy): 4.6 mg/24 h patch (5 cm<sup>2</sup>) applied qd initially; if well tolerated and after minimum of 4 wk, increase to 9.5 mg/24 h patch (10 cm<sup>2</sup>) applied qd

Switching from oral administration to patch therapy:

Apply first patch on day following last oral dose

Total daily oral dose <6 mg/d: Switch to 4.6 mg/24 h patch

Total daily oral dose 6-12 mg/d: Switch to 9.5 mg/24 h patch

#### **Pediatric**

Not indicated

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### **Galantamine (Razadyne, Razadyne ER)**

Enhances central cholinergic function; likely to inhibit AChE.

#### **Adult**

IR: 16-24 mg/d PO divided bid

ER: 16-24 mg PO qd

#### **Pediatric**

Not established

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## **Follow-up**

### **Deterrence/Prevention**

Although previous reports reflect delayed onset of Alzheimer disease (AD) in individuals who used nonsteroidal anti-inflammatory drugs (NSAIDs), a study by Breitner et al showed NSAIDs do not protect against AD, at least in very old people. Relying on computerized pharmacy dispensing records and biennial dementia screening, investigators found Alzheimer disease incidence was increased in heavy NSAID users. These findings may represent deferral of Alzheimer disease symptoms from earlier to later old age.<sup>24</sup>

### **Patient Education**

For excellent patient education resources, visit eMedicine's Dementia Center. Also, see eMedicine's patient education articles Alzheimer Disease, Alzheimer Disease in Individuals With Down Syndrome, Dementia Overview, and Dementia Medication Overview.

## Miscellaneous

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### Medicolegal Pitfalls

- Patients with dementia, in general, and those with Alzheimer disease, in particular, usually have a progressive deterioration in their behavior, cognition, and ability to perform activities of daily living.
  - These changes may result in patients making inappropriate or adverse psychosocial decisions, such as the mismanagement of funds or serious lapses in their family, social, and occupational responsibilities.
  - Medical advice should include a warning about these possibilities, given to both the patient and to their caregivers (at least those most directly responsible for the patient's care) to minimize the risk of adverse legal effects on the patient or others.
- Particular attention should be given to the need to make a legal statement about the patient's competency to handle his or her affairs and about assigning power of attorney for the patient's estate and other matters. These delicate decisions must be individualized and coupled with an attorney's advice.

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