Diagnosis and treatment of Alzheimer's disease

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Abstract—Alzheimer's disease (AD) is a chronic neurodegenerative disorder and the most common cause of dementia. It is one of the principal causes of disability and decreased quality of life among older adults. Progress in our clinical knowledge of AD has led to more reliable diagnostic criteria and accuracy, and research efforts are expanding to uncover the earliest manifestations and even the presymptomatic phases of the disease. The diagnosis of AD is primarily one of inclusion and usually can be made using standardized clinical criteria. There is currently no cure for AD. Current treatment focuses on establishing an early accurate clinical diagnosis, early institution of cholinesterase inhibitors and/or *N*-methyl-D-aspartate (NMDA) receptor–targeted therapy. Treating medical comorbidities and dementia-related complications, ensuring that appropriate services are provided, addressing the long-term well-being of caregivers, and treating behavioral and psychological symptoms with appropriate nonpharmacologic and pharmacologic interventions also are important. The initiating and propagating pathologic processes and the anatomic location of the earliest changes will become new targets of research and therapeutic development. A possible precursor of AD, mild cognitive impairment (MCI), is under investigation as a possible therapeutic starting point for disease-modifying interventions. This article provides a research update of current understanding in the diagnosis and treatment of AD and in emerging areas of interest such as MCI, detection of AD in the predementia phase, and neuroimaging in AD.

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Alzheimer's disease (AD) is a chronic neurodegenerative disorder with a devastating impact on public health. AD is the most common cause of dementia among people 65 years or older. AD involves loss of memory and other cognitive functions, a decline in ability to perform activities of daily living (ADL), changes in personality and behavior, increases in resource utilization, and eventual death. In the United States, AD is the fourth leading cause of death due to disease for people 65 years and older.[1] In 2000, there were 4.5 million people in the US with AD. Barring a cure, by 2050 this number will increase by almost threefold, to 13.2 million.[2] The prevalence of AD rises exponentially with age, from 5% in people aged 65 to 74 years to almost 50% in people aged >85 years. Despite the consensus on both clinical and neuropathologic definitions of AD, there is only limited information about its etiology and pathogenesis. It is caused by several mechanisms that have both genetic and environmental influences.

AD unassociated with any other pathology ("pure AD") is found in between 50% and 60% of most unbiased autopsy samples. The incidence rises to 80% if AD occurs in conjunction with other pathologic lesions.[3] Vascular dementia (VaD), dementia with Lewy bodies (DLB), frontotemporal dementias (FTDs), and other (unknown) causes account for the rest. Cerebrovascular disease (CVD) is the second most common cause of acquired cognitive impairment and dementia and contributes to cognitive decline in the neurodegenerative dementias.[4] Overlap is common among AD, VaD, and DLB.[5]

AD reduces life expectancy by half.[6] Features significantly associated with reduced survival at diagnosis are increased severity of cognitive impairment, decreased functional level, history of falls, physical examination findings of frontal release signs, and abnormal gait. The prognosis of AD is that of inexorable decline and eventual death. Key risk factors and protective factors for AD are listed in table 1.[7–14]

The annual treatment cost of AD in the US is approximately $100 billion: approximately $18,408/patient per year for mild AD, $30,096/patient per year for moderate AD, and $36,132/patient per year for severe AD.[15,16] This economic impact of AD is expected to worsen with the demographic, epidemiologic, technological, and economic transitions worldwide. The potential savings in illness costs attainable from treatment are small for mildly and very severely demented patients with AD. However, prevention of even a small decline [e.g., a 2-point decline in the Mini-Mental State Exam {MMSE) score[17]] in cognition for patients with moderate AD would save about $3,700 per patient annually, and relatively small improvements in cognition (e.g., a 2-point improvement in the MMSE score) in this patient subgroup would save about $7,000 per patient annually.[18]

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Table 1 *Key risk factors and protective factors for AD*

Primary risk factors: age; family history; genetic markers such as *APOE* ε4; trisomy 21; mutations in presenilin 1 and 2; female gender after 80 years of age; cardiovascular risk factors such as hypertension, diabetes, obesity, and hypercholesterolemia
Possible risk factors: head injury; depression; progression of Parkinson-like signs in older adults; lower thyroid-stimulating hormone (TSH) within the normal range; hyperhomocysteinemia; folate deficiency; hyperinsulinemia; low educational attainments
Possible protective factors: *APOE* ε2; regular fish consumption; regular consumption of omega-3 fatty acids; high educational level; regular exercise; NSAID therapy; moderate alcohol intake; vitamins C, E, B_6, and B_{12} and folate intake

Neuropathologic changes characteristic of AD. The neuropathologic hallmarks of AD include amyloid-rich senile plaques, neurofibrillary tangles of phosphorylated tau protein, neuron degeneration, and synaptic loss. Synaptic loss is the best pathologic correlate of cognitive decline, and synaptic dysfunction is evident long before synapses and neurons are lost.[19] Once synaptic function fails, even in the setting of surviving neurons, there may be little chance of effectively interfering with the disease process. Missense mutations in three genes are known to cause autosomal dominant forms of early-onset AD. These include the amyloid precursor protein gene located on chromosome 21 and the genes for presenilin 1 and presenilin 2 located on chromosomes 14 and 1, respectively.[20] Studies of these mutations have provided strong support for the "amyloid cascade hypothesis" of AD. The amyloid precursor protein mutations code for amino acids at or near points at which the precursor is cleaved enzymatically and result in secretion of the toxic form of amyloid (Aβ42). These aggregate readily into highly insoluble amyloid fibrils, which form the major component of senile plaques. Similar changes in β-amyloid production are observed with the mutations linked to AD in presenilin 1 and 2. Presenilin mutations also have amyloid-independent effects on the lysosomal system.[21]

The neuronal lysosomal system is a major degradative pathway, induced by cell stress and closely linked to AD. The *APOE* genotype is associated with AD risk. The *APOE* ϵ2 allele (*APOE* ϵ2) may be protective and the *APOE* ϵ4 allele (*APOE* ϵ4) is associated with increased risk.[7] The precise role of *APOE* ϵ4 in the pathogenesis of AD is unclear. *APOE* is found in Aβ plaques and neurofibrillary tangles and may affect protein–protein interactions. Although the amyloid cascade hypothesis is currently considered by many researchers as a key contributor to the pathogenesis of AD, some researchers have challenged this assertion. Lee et al.[22] have proposed that Aβ occurs secondary to neuron stress and functions as a protective adaptation to the disease rather than causing cell death.

Neurotransmitter changes associated with AD pathology. AD is characterized by disruptions in multiple major neurotransmitters, of which cholinergic abnormalities are the most prominent. There are reduced numbers of cholinergic neurons in late AD (particularly in the basal forebrain) and there is selective loss of nicotinic receptor subtypes in the hippocampus and cortex.[23] Acetylcholine (ACh) is an important neurotransmitter in areas of the brain involved in memory formation, and loss of ACh activity correlates with the severity of AD. Presynaptic nicotinic receptors control the release of neurotransmitters important for memory and mood such as ACh, glutamate, serotonin, and norepinephrine. It has been shown that the reduction in the number of ACh receptors precedes other pathologic changes.[24] Anticholinergic drugs induce amnesia, which can be reversed by withdrawal of the medication. Inhibition of the downregulation of ACh is therefore a strategy for the treatment of AD because it might augment ACh levels within synaptic clefts. In this context, cholinesterase inhibitors (ChEIs), which improve cognitive functions, are currently approved for the treatment of AD. Stimulation of ACh receptors is another strategy, and some drugs for this use are under investigation. In addition, nicotinic stimulation may exert a neuroprotective effect and may reduce the amyloid burden.[24] ChEIs may therefore have some disease-modifying effects. There is circumstantial evidence for increased excitotoxicity due to increased glutamatergic stimulation of *N*-methyl-D-aspartate (NMDA) receptors in AD.[23] Pathologic stimulation of glutamatergic receptors results in abnormally high levels of intracellular calcium and, in vitro, may ultimately lead to cell death. This may explain the beneficial effects of the moderate- to low-affinity NMDA receptor antagonist memantine on cognitive and functional measures, compared with placebo, in trials of moderate to severe AD.

Diagnosis of AD. Although a definitive diagnosis of AD can currently be made only by histopathologic examination of brain tissue after the patient's death, the classification of dementia disorders by neuropathology is not straightforward.[11] Only 50% to 60% of individuals fulfilling the neuropathologic diagnosis of AD have dementia or significant cognitive decline during life. Moreover, no neuroimaging or laboratory markers now exist for reliable presymptomatic diagnosis of AD.[25] Therefore, we are forced to wait until individuals become symptomatic.

The diagnosis of AD is primarily one of inclusion, not exclusion, and usually can be made using standardized clinical criteria.[26] Potentially reversible causes of dementia should be investigated (table 2).[27] AD can be accurately diagnosed even in very mildly impaired individuals.[28] Unfortunately, only 60% of patients with AD are correctly diagnosed and only approximately 50% of those people are treated.[29] This is consistent for all stages of AD. Using standardized and easy-to-use scales to assess cognition (such as the MMSE) and ADL [such as the Functional Activities Questionnaire (FAQ)[30]] in older

Table 2 *Potentially reversible causes of dementia*

Neurosurgical: normal pressure hydrocephalus; obstructive hydrocephalus; subdural hematoma; brain tumor
Nutritional: vitamin B_{12} deficiency; folate deficiency
Endocrine disorders: hypothyroidism
Metabolic: hyponatremia
Alcoholism
Drug toxicity (e.g., due to benzodiazepines or anticholinergics)
Vasculitis
Psychiatric: severe depression
Infection
Sleep disorders: obstructive sleep apnea syndrome, narcolepsy

adults experiencing cognitive deficits may help clinicians make early, accurate diagnoses.[31] Input from collateral sources is also recommended for early diagnosis because those are accurate in reporting the cognitive capabilities of individuals with AD, even in the very mild stage.[32]

In a typical case, onset of AD is slow. Some individuals with incipient AD are aware of their declining abilities, but most patients with evolving AD never acknowledge that they have memory dysfunction.[33] Eventually, recognition may occur because of an apparent sudden crisis, such as getting lost, an accidental fall, or discovery by neighbors or relatives of an unsafe, messy home environment, or acute confusion (delirium) during illness, after surgery or hospitalization, or environmental stress. Careful questioning will usually reveal that cognitive impairment and dysfunction have been present for several years before the acute crisis. A decline in calculation abilities is one of the hallmark cognitive features of AD.[34] Other clinical presentations of AD are psychosis, depression, and agitation/behavioral disturbances.

Neuroimaging in AD. AD starts at a molecular level, possibly decades earlier than could be detected by neuropsychological tests. Neuropathologic and neuroimaging data suggest that amyloid accumulation precedes the clinical onset of AD.[35] Disease-modifying agents would have to be used early to alter the course of AD. Therefore, preclinical diagnosis is necessary. Neuroimaging with MRI and PET can provide objective measures of preclinical disease and, when measured serially, the rate of change. Such information can be used in prevention trials. Because there is a high frequency of clinically unrecognized CVD among patients who present with AD, neuroimaging with CT or MRI should be part of the routine dementia assessment. Unrecognized CVD may be especially common at greater ages because the frequency of silent infarcts increases with age, and silent infarcts are related to an increased incidence of dementia.[11] The effectiveness of PET for distinguishing patients with dementia with Lewy bodies from AD may be higher than that of clinical evaluation.[36] Coverage for PET scans has recently been approved by the Center for Medicare and Medicaid Services (CMS) for diagnosis of AD in certain patients in whom a specific diagnosis of dementia remains uncertain, despite a thorough clinical/laboratory evaluation.

Nonroutine laboratory testing. Determination of the *APOE* ϵ4 genotype is not currently recommended for use in diagnosis because this genotype is found in many elderly people without dementia and is not found in many patients with AD.[37] Empirical data on the benefits and potential harm of genetic susceptibility testing with *APOE* ϵ4 are now being collected and studied. The most extensively evaluated biological markers of sporadic AD are Aβ-protein levels and levels of both total and phosphorylated microtubule-associated protein tau.[38] These markers assessed in CSF or plasma, alone and in combinations, are being studied to clarify their potential clinical applicability, including sensitivity in the diagnosis of AD and mild cognitive impairment (MCI), specificity in discriminating AD from other dementias, and correlations with the disease progression and *APOE* genotype. At present, CSF screening for these potential markers is not recommended.

MCI. MCI is a common precursor to AD. Criteria for MCI include memory test scores 1 standard deviation below that of age-adjusted normals, no significant objective loss of function, and no diagnostic criteria for dementia. Approximately 12% of cases of MCI convert to AD each year.[39] Neuroimaging, especially PET, may be valuable in predicting future development of AD in patients with MCI.[36] Treatments for MCI are now under investigation.

The best predictors of conversion from MCI to AD are functioning in everyday situations requiring judgment and problem-solving, presence of depression, and hippocampal atrophy.[25,40] Without exhaustive questioning, MCI is often difficult to detect clinically. The MMSE scores of patients with MCI are typically normal (24 to 30), but they often do poorly on the memory component of the test, which require the recollection of three words.[17,25] Referral to a neuropsychologist is needed to accurately differentiate MCI from the cognitive impairment associated with normal aging.

Because MCI represents an alteration in normal functioning, patients with MCI should undergo the same laboratory studies as other patients with dementia. Patients suspected to have MCI should be counseled regarding AD risk reduction strategies, such as mental and physical exercise, continuing social engagement, stress reduction, proper nutrition, antioxidants (such as vitamins E and C), and aggressive treatment of cardiovascular risk factors.[41]

Detection of AD in the predementia phase. AD is characterized by a predementia phase during which cognitive deficits are seen.[42] Older adults with subjective memory complaints and objective cognitive impairment have a high risk for development of AD.[43] The more stringent the measures of both variables, the better the prediction of conversion. A

three-step procedure [self-report of memory complaints, test of global cognitive functioning (such as MMSE), and domain-specific cognitive tests (neuropsychological testing)] has been found to have a positive predictivity of 85% to 100% for AD at 3 years.[44] However, only 18% of future dementia cases were identified in the preclinical phase using this procedure. About half of the people in the preclinical phase of AD did not report problems with their memory in the 3 years before diagnosis.[44] Another study found that simple tests of cognitive ability can provide useful predictive information up to a decade before the onset of AD and that the addition of cognitive tests improved prediction of AD based on age, family history, and *APOE* genotype.[45] Although it is known that personality changes (such as apathy) and mood changes (such as depression) can antedate cognitive decline by many years, at present there is no reliable way to identify people who have these conditions and have preclinical AD.[46] A number of issues, such as improving consistency of the MCI definition and studies using large cohorts, must be addressed in greater depth before a predementia diagnosis of AD can be made in the routine evaluation of patients with isolated memory loss.[42]

Treatment options. There is currently no cure for AD. Treatment of AD focuses on establishing an early, accurate clinical diagnosis, early institution of ChEIs and/or NMDA receptor-targeted therapy, treating medical comorbidities and dementia-related complications, ensuring that appropriate services are provided, addressing long-term well-being of caregivers, and treating behavioral and psychological symptoms of AD with appropriate nonpharmacologic and pharmacologic interventions (table 3).[47] ChEI and memantine provide modest but clinically relevant symptomatic benefits in cognition, ADL, and behavior. Although they may have intrinsic disease-modifying activity, this remains to be proved.[48] Early institution of ChEI treatment may delay the onset of behavioral and psychological symptoms of AD by 1 year.[49] Emerging data support beneficial effects of ChEIs in moderate to severe AD and in long-term treatment.[50,51] ChEIs may be helpful in DLB and VaD, and memantine may be helpful in VaD. The combination of donepezil and memantine has been shown to have superior efficacy to donepezil alone in moderate to severe AD, potentially supporting a role for dual treatment in more advanced AD.[52]

There is evidence that decisions regarding palliative care for patients with AD are not being made optimally.[53] A disease management model for AD that incorporates a diagnostic protocol to identify and assess people with possible dementia and care management involving interventions in domains such as patient function, caregiver support, medical treatment, psychosocial, nutritional, and advance directives planning, and family caregiver information and support has been proposed.[54] To improve end-of-life care for people with AD, any treatment model should also incorporate patient-centered care and palliative care from the initial diagnosis of AD though its terminal stages.[55] In many patients with AD, treating comorbid conditions such as depression, hearing or vision impairment, congestive heart failure, symptomatic urinary tract infection, or hypothyroidism may produce a greater benefit than focusing treatment only on AD.[33] It is important to search for treatable cardiovascular risk factors and CVD in the evaluation of AD patients because these may influence the expression and clinical manifestations of the disease.[11] For a patient with AD, all of the following should be given consideration: decision-making capacity of the patient; altered benefits and burdens of therapeutic interventions; the patient's ability to adhere to a regimen and to report adverse effects; the availability of caregivers; and mechanisms to

Table 3 *AD treatment options*

Pharmacologic	
Approved by FDA	Cholinesterase inhibitors for mild to moderate AD (tacrine 80–160 mg/d; donepezil 5–10 mg/d; rivastigmine 6–12 mg/d; galantamine 16–24 mg/d) and *N*-methyl-D-aspartate receptor–targeted therapy for moderate to severe AD (memantine 10–20 mg/d)
Use supported by controlled clinical trial	Selegiline hydrochloride (5 mg BID), vitamin E (2,000 IU/d)
Compounds under investigation	Vaccine, anti-inflammatory drugs (including aminopyridazines), secretase inhibitors, glutamate antagonists, huperzine X (acetylcholinesterase inhibitor), xanomeline patch (m1/m4 muscarinic receptor agonist), AIT-082 (purine hypoxanthine derivative), multitransmitter compounds, beta-sheet blockers
Benefit not generally accepted	Chelation therapy (possible benefit of zinc chelation), lecithin, ergot mesylate, choline
Preventive effect supported by epidemiologic evidence but not confirmed by prospective trials	NSAIDs, statins, estrogen
Nonpharmacologic	Caregiver education (regarding safety, exercise, nutrition, recreation, communication, understanding the disease process and stages, advanced directives and end-of-life decisions, financial planning, and community resources), reminiscence therapy, music therapy, aromatherapy, environmental manipulation, reality orientation, pet therapy
Surgical intervention under investigation	Low-flow CSF drainage

compensate for communication and other deficits. Aggressive medical care for patients with terminal AD does not decrease progression of the disease, increase comfort, or extend survival.[56]

Although antidepressants are effective for major depression in AD, data regarding treatment of minor depressive syndromes in AD are limited.[57] Recreational activities are effective for major and minor depression categories. Antipsychotics are also effective and remain the most studied medications for treating severe agitation, with or without psychotic symptoms, in patients with AD.[57] Exercise training combined with behavioral management techniques can improve physical health and depression in patients with AD.[58] Short-term intensive counseling, in conjunction with readily available support, can significantly reduce the long-term risk for depression among those who care for spouses or partners with AD.[59] One study found that the positive impact of these interventions continued for more than 3 years after the initial counseling sessions ended, and persisted even after those with AD died or were placed in nursing homes. Family intervention may delay long-term care placement of those with AD.[60]

The mutations in amyloid precursor protein, presenilin 1, and presenilin 2 allow genetic screening to be used in suspected cases of familial AD with early onset and for appropriate genetic counseling and support. Although preimplantation genetic diagnosis (PGD) of the embryos, prenatal diagnosis, preimplantation embryo selection, and presymptomatic testing have been offered to families of patients who have early-onset familial AD, complex legal and ethical issues surrounding these interventions must be addressed before these interventions can be routinely recommended.

Disease-modifying treatments. Current drugs approved for treatment of AD have modest symptomatic benefits but do not have profound disease-modifying effects.[61] Three main classes of disease-modification approaches can be defined: one that is broadly neurotrophic or neuroprotective; one that targets specific aspects of AD pathology; and one that is based on epidemiologic observation. Among these, antiamyloid treatment is now the most active area of investigation. Oxidative stress and cell cycle-related abnormalities are early events in AD, occurring before any cytopathology can be identified, and together may propagate disease pathogenesis.[62] Therefore, antioxidants are an AD prevention strategy appropriate for investigation. In addition, clinicopathologic and neuroradiologic studies show that inflammation via activation of microglia is a relatively early pathogenic event that precedes the process of neuron destruction in AD.[63] Nonsteroidal anti-inflammatory drug (NSAID) use has been associated with decreased risk for AD.[13] Therefore, despite the negative clinical trials with NSAIDs for the treatment of AD, these and other anti-inflammatory agents may still have a role in reducing the risk for AD. Modulation of cardiovascular risk factors may also reduce the risk for AD.[64] Although hormone replacement therapy with estrogen showed no benefit and even a potential deleterious effect in patients with AD, estrogen may still have a role in reducing the risk for AD if given early in menopause and when neurons are in a healthy state.[65] Other neurodegenerative processes, such as excitotoxicity and apoptosis, may also have a pathophysiologic role in AD and are now under study. New treatments under investigation are aimed at slowing the progression and treating the symptoms of AD (table 3).

Caring for the caregivers. The overwhelming majority of patients with AD live at home and are cared for by family and friends. Most caregivers are women (spouse or daughters) and are over 50 years of age. Caregivers spend from 40 to 100 hours per week with the person with AD. Ninety percent are affected emotionally (frustrated, drained) and 66% have significant depression. Factors that create a "breaking point" for caregivers include the amount of time spent caring for the patient with AD, loss of identity, patient misidentifications and clinical fluctuations, and the patient's nocturnal deterioration.[66] Throughout the process of caring for patients with AD, caregivers frequently experience social, emotional, physical, and financial losses, which become more significant as the disease progresses.[67] Minimizing these losses is a goal in the overall management of AD. Successful treatment of the patient has been shown to positively impact quality of life for the caregivers.

Conclusion. AD is a growing problem in an aging world. Early accurate diagnosis using standardized criteria can be made clinically through assessment, use of standardized easy-to-use scales for assessment of cognition and ADL, and collateral sources of information. Slowing of cognitive impairment, duration of disease, and behavioral disturbances and increasing self-sufficiency represent the best outcomes of available treatment options for AD. Early intervention is key to the successful management of AD. Current drugs improve symptoms but do not have profound disease-modifying effects. Although AD cannot be cured at this time, there is reason to be optimistic. Rapid progress toward understanding of the cellular and molecular alterations that are responsible for the neurons' demise may soon help in development of effective preventive and therapeutic strategies.

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