Early Diagnosis of Alzheimer's Disease: Clinical and Economic Benefits

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An estimated four million individuals in the United States have Alzheimer's disease (AD). This number is expected to more than triple by mid-century. Primary care physicians have a key role in evaluating older patients for early signs of dementia and in initiating treatment that can significantly retard its progression over the maximum period of time. That role and its challenges will inevitably grow along with the expected increase in the population aged 65 and older. The tendency for physicians to dismiss memory complaints as normal aging must be replaced by awareness of the need to assess and possibly intervene. Early intervention is the optimal strategy, not only because the patient's level of function will be preserved for a longer period, but also because community-dwelling patients with AD incur less societal cost than those who require long-term institutional placement. Institutionalization contributes heavily to the annual cost of care for AD in the United States, which is estimated to be $100 billion annually. **J Am Geriatr Soc 51:S281–S288, 2003.**

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The prevalence, human toll, and economic costs of Alzheimer's disease (AD) are mounting in step with the increasing number of elders in the population. Although dementia has long been assumed to be an inevitable accompaniment of advanced age, AD is beginning to yield to new insights into its molecular basis and to new pharmacological approaches that retard its progression. The subtle onset of AD may challenge diagnostic skills, but even early diagnosis is possible when clinicians ask the right questions, listen to input from family members, and use sensitive office-based screening tools. Early diagnosis benefits the patient, the family, the community, and the public health system.

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PREVALENCE OF AD

A number of factors, many of them related to differential diagnosis and lack of consensus regarding the pathophysiologic correlates of AD, make determining the prevalence of AD difficult. Although AD is the most prevalent cause of progressive cognitive impairment in the elderly, there are other potential causes of demented behavior that can be mistaken for AD in the clinic. These include, but are not limited to, vascular dementia, Lewy body dementia, Parkinson's disease, Creutzfeldt-Jakob disease, frontal lobe dementia, and progressive supranuclear palsy.[1] In addition, delirium and depression can produce symptoms and signs resembling those of AD.[2]

Although β-amyloid-rich plaques and tau protein–rich neurofibrillary tangles are accepted as the neuropathologic hallmark, there are several factors that confound the development of valid and comprehensive neuropathologic criteria to exclusively define AD.[3] For example, histological changes such as dystrophic neurites and synaptic and neuronal loss may correlate better with dementia.[4] The fact that widespread plaques and tangles can exist in the absence of disease symptoms and that disease can be present with relatively limited plaques and tangles further contributes to the lack of consensus.[5]

These caveats about diagnosis and pathophysiology notwithstanding, AD is considered the most common form of dementia worldwide, accounting for approximately two-thirds of cases in epidemiological studies. This is true in North America, where the prevalence of dementia in those aged 65 and older is estimated to be 6% to 10%. Japan appears to be the exception; historically, vascular dementia has been more common than AD in that population.[6] Prevalence rates double if milder cases of dementia are included.[7] The association between dementia and age is consistent across nearly all studies. The prevalence rate for AD doubles approximately every 5 years, from 1% to 2% in the 65- to 74-year age range to 25% and over in those aged 85 and older.[3] The Alzheimer's Association estimates that four million Americans currently have the disease (www.alz.org).[8]

Based on 1980 census projections, it is estimated that the number of AD cases in 2050 will reach 7.5 to 14.3 mil-

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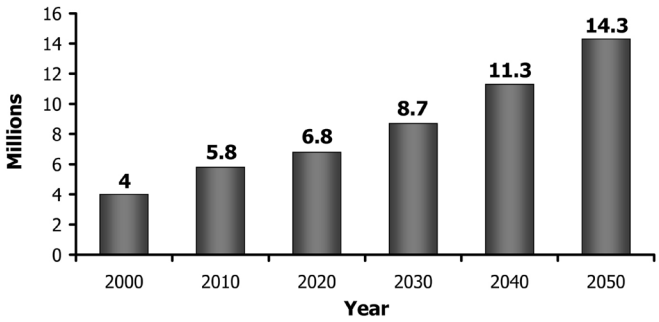

Figure 1. Projected prevalence of Alzheimer's disease.[9]

lion, depending on the model used (Figure 1).[9] Whatever the methodological differences, AD is an impending public health crisis.[10]

DIAGNOSTIC CRITERIA FOR AD

The diagnostic criteria for AD are delineated in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (Table 1).[11] The diagnosis rests on the development of multiple cognitive deficits. Memory impairment is a prerequisite, accompanied by at least one additional cognitive impairment, such as disturbed executive function, characterized by difficulties with planning, organizing, sequencing, and abstracting.[11] Manifestations typically take the form of deficits in judgment and problem solving.[10] Adults with late-life depression have also been found to have significant deficits in executive function compared with age-matched normal counterparts.[12] Therefore, it is important to differentiate AD from clinical depression in the elderly. At the same time, the clinician should be aware that depression and AD can, and often do, coexist. It is also important to realize that, in some cases, depression may be a prodromal state, signaling the onset of AD.[13]

NATURAL HISTORY OF AD

Although it has a subtle and insidious onset, AD can be readily detected, even in its early stages, by using available office-based screening tools and by being alert to patient and family complaints about memory. Increasing difficulties with language (aphasia), naming, and word finding follow impaired memory in early stages, evolving into loss of expressive ability in later stages. Performing everyday tasks becomes difficult, and visuospatial disability can lead to disorientation in familiar environments.[10,14] The complex, profoundly human capabilities of analysis and synthesis are lost. Typically, later in the disease course, purposeful movement becomes affected (apraxia) along with the ability to translate and interpret sensory input (agnosia). Behavioral changes such as irritability, agitation, aggression, and loss of inhibition set in as the disease progresses. Delusions and hallucinations may also be part of the syndrome.[14]

These changes take place gradually, over years, and are frequently grouped into stages for descriptive purposes.[14] Personality may be largely intact, and social skills are usually retained in the first stage, even with slightly impaired memory.[14] Aphasia and apraxia appear in the second stage, as memory continues to deteriorate and restlessness or agitation becomes apparent. Deteriorated cognition, verbal unresponsiveness, limb rigidity and immobility, and incontinence characterize the third, final, stage.[14] The rate of progression varies considerably between individuals. Duration of AD averages 10 years, with a range of 3 to 20 years.

Prodromal Phase

Logic would imply that, because AD is a neurodegenerative disease, there would be a prodromal period in which neuropathology develops before the onset of overt symptoms. Although there is a significant body of evidence to support the relationship between early neuropathology and later development of dementia, there is also evidence showing that this prodromal phase may not be clinically significant in many individuals.[5,14] For example, one group of researchers recently performed autopsies to ascertain the presence or absence of neuropathologically defined AD in 118 patients who had previously been clinically diagnosed with dementia and in 62 patients with no diagno-

Table 1. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Diagnostic Criteria for Alzheimer's Disease

Development of multiple cognitive defects manifested by
1. Memory impairment
2. One or more of the following
   a. Aphasia
   b. Apraxia
   c. Agnosia
   d. Disturbance in executive functioning

Cognitive defects cause significant impairment in social or occupational functioning and represent a significant decline from the previous level of functioning.

Gradual onset and continuing cognitive decline characterize the course.

Cognitive deficits are not due to
1. Other central nervous system conditions that cause progressive deficits in memory or cognition
2. Systemic conditions known to cause dementia
3. Substance-induced conditions

Deficits do not occur specifically during the course of delirium.

Disturbances are not better accounted for by another Axis I disorder (e.g., major depressive disorder or schizophrenia).

Adapted from Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; 2000.[11]

sis of dementia. All patients were aged 85 and older. Although a correlation was observed between clinical and neuropathologic AD, 55% of the individuals with neuropathologic AD fell into clinical non-AD groups (i.e., no dementia group or vascular dementia or other group). In addition, 35% of subjects with clinically diagnosed AD failed to meet the neuropathologic criteria for AD.[15]

Nevertheless, the fact that some individuals may not exhibit symptoms in the presence of pathology does not preclude the existence of a prodromal state, which may or may not become clinically significant depending on other factors such as aging. Therefore, persons with sporadic AD (those with no obvious inheritance pattern) may potentially be segregated into two groups, those with some measured deficits on testing who are said to have mild cognitive impairment (MCI) and those who are pre-MCI in whom disease may be present but not recognizable on testing.[14]

Patients with MCI, typically defined as those with impaired memory function in the absence of other symptoms that would lead to a diagnosis of AD (Table 2),[16] have been observed in numerous studies to convert to AD in later years.[17] Although results vary widely with the case definition employed, approximately 10% to 15% of persons with MCI convert to AD per year, resulting in a conversion rate of 50% to 70% over 5 years.[18–20] When working with the concept of MCI, it is important to note that current MCI criteria perform suboptimally when applied to a representative population sample, being nonspecific and unstable over time.[21]

In explaining the variability in the relationship between brain pathology and AD, researchers have performed a significant number of postmortem studies in normal individuals and in those with MCI/AD.[22] They posit that a limited, symmetrical loss of nerve cells in both hemispheres is more likely to impair cognition than a numerically similar but random destruction of cells. Consonant with the view that brain pathology signals preclinical disease, they have concluded from their studies that, "Whether or not the destructive process underlying AD manifests itself clinically depends solely on whether the length of an affected individual's lifespan allows its expression."[22]

Predictors of AD Progression

Patient- or disease-related factors associated with the rate of progression of AD have been difficult to identify. Published studies have used various indices at different stages of disease in patients unmatched for disease severity. Thus, studies have variously found no association between age and progression, an association of rapid progression with younger age of onset, and an association with older age of onset.[23]

One study examined 65 community-dwelling patients with probable AD, all of whom were mildly to moderately impaired at entry. They were followed for 4 years, during which cognitive and functional performance were assessed at biannual intervals. Cognitive and functional progression rates were significantly correlated, but considerable unshared variance suggested that their rates might reflect distinctive, albeit parallel, disease processes.[23]

In addition, clinical predictors differed for cognitive versus functional decline. Initial impairment in verbal cognition was significantly related to more-rapid cognitive degeneration, but it did not predict the rate of functional decline. Functional decline was related to extrapyramidal motor symptoms and nonverbal cognitive tests at entry. The investigators suggested that asymmetry in cerebral dysfunction, which has been observed in neuropsychological test performances, may be characteristic of AD. A disease process that preferentially affects the right hemisphere, for example, would be likely to produce a rapid decline in everyday functioning, which depends heavily on visuospatial abilities.[23] In contrast to these speculations, another investigator regarded functional dependence as a good predictor of rapid cognitive decline as well as shorter survival.[24]

In an earlier mentioned study,[23] psychotic symptoms (paranoid behavior, hallucinations, and delusions) that occurred early in the disease course predicted more-rapid progression. The occurrence of hallucinations was strongly related to rapid functional decline but not to severity of cognitive deficits. Delusions were related to disease severity as determined by cognitive measures. Although other prognostic indicators failed to provide a reliable basis for prediction, the presence of these behavioral problems early in the disease course may suggest that decline will be more rapid than gradual.[23]

Table 2. Diagnostic Criteria for Alzheimer's Disease

Mild Cognitive Impairment
Normal general cognitive function
Normal activities of daily living
Memory impairment in relation to age and education
Memory complaint corroborated by an informant
Signs of dementia absent

ACCURATE CLINICAL DIAGNOSIS: DON'T WAIT FOR THE AUTOPSY

General Principles of Diagnosis

A consensus statement issued by the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society set forth their guidelines for diagnosing AD. Foremost among them was the statement that the most important diagnostic tools are the informant interview and office-based clinical assessment. The consensus group also emphasized that the diagnosis of AD is one of inclusion rather than exclusion.[25]

Using standard cognitive tests and listening to family informants, the primary care physician can make an accurate and reliable clinical diagnosis more than 90% of the time.[25–27] Familiarity with AD risk factors (Table 3)[10,29] and other forms of dementia (Table 4)[1,10] will assist in the diagnosis. Complaints about short-term memory, especially if corroborated by a close informant, can point to the need for further evaluation and are critical for diagnosing early-stage disease. Inquiring about difficulties with routine daily tasks, changes in behavior, and seemingly minor impairments will bring the diagnosis closer.[28,29]

Table 3. Risk Factors for Alzheimer's Disease

Increasing age
Female sex
Family history of dementia
Fewer years of education
Lower income
Lower occupational status
Depression, other emotional illnesses
Head injury
Low serum levels of folate, vitamin B_{12}
Elevated plasma homocysteine levels
Presence of apolipoprotein E ε4 allele
Postoperative delirium
Alcohol abuse

At least one informant should supplement the history, if possible. Usually a spouse or adult child, an informant provides a more objective and reliable cognitive assessment than the patient's self-report.[1] Determining the onset and duration of symptoms and whether they have been gradual, as in AD, or abrupt, as in vascular dementia, will limit diagnostic possibilities. The physical examination, including a neurological examination, should be directed to an illness or physical condition that could affect functioning and cognition. Prescription and over-the-counter medications, exposure to toxins and heavy metals, and substance abuse should be queried.[28]

Differential Diagnosis

Despite increased understanding of the pathogenesis of AD, no clinically useful diagnostic assay or pathognomonic sign has yet emerged. Differential diagnosis is clinically based, and diagnostic accuracy can be high even lacking a biological marker for AD.[1]

Table 4. Other Primary Dementias

Diffuse Lewy body dementia
Vascular dementia
Frontotemporal atrophy/dementia (Pick's disease)
Postcortical or postthalamic stroke
Postanoxic encephalopathy
Progressive supranuclear palsy
Parkinson's disease
Amyotrophic lateral sclerosis with dementia
Genetic disorders (e.g., Huntington's disease, Wilson's disease)
Hydrocephalus
Neoplastic disease
Infectious disorders (e.g., meningitis, Creutzfeldt-Jakob disease)
Drug related (e.g., polypharmacy)
Affective disorders (depression)
Delirium
Toxins (drugs, alcohol, heavy metals, industrial pollutants)
Human immunodeficiency virus/acquired immune deficiency syndrome–associated dementia

Cognitive Deficits of Normal Aging Versus AD

A majority of the population experiences some cognitive decline in the seventh and eighth decades and beyond. Most typically, mental, physical, and physiological functions decline as comorbidities (e.g., cardiovascular disease) take their toll.[7] Although deficits associated with normal aging share some aspects of the mildest cognitive deficits of AD, differences can be identified. In one longitudinal series, for example, information from family informants suggested that subtle memory complaints interfered with usual activities in patients with dementia, whereas the everyday activities of controls were not affected, despite minor memory complaints.[1]

AD Versus Vascular Dementia

After AD, vascular dementia is the most common form of dementia, accounting for up to 15% of pathologically diagnosed cases. Unlike AD, vascular dementia often has an abrupt onset, and cognition may deteriorate in a stepwise progression rather than the gradual steady decline seen in patients with AD. Individuals with vascular dementia are likely to have focal neurological symptoms and signs and a history of stroke or hypertension, the major risk factor for vascular dementia. When dementia occurs as a result of cerebral ischemia, a large volume of brain tissue is likely to have been destroyed.[1,30]

AD Versus Lewy Body Dementia

Lewy bodies are spherical inclusions within the cytoplasm of cortical neurons. Dementias associated with Lewy bodies constitute part of the spectrum of disorders that includes Parkinson's disease. Estimates of dementia with Lewy bodies range from 15% to 25% of dementia cases.[1,30]

Onset of memory deficit and other symptoms is gradual, as in AD, but unlike AD, cognitive deficits generally fluctuate. Parkinsonian motor symptoms are early features, but extrapyramidal dysfunction is often mild and may not respond to levodopa. Psychotic features (e.g., visual hallucinations) may accompany Lewy body dementia. These patients are more inclined to react adversely to neuroleptics, which can exacerbate psychotic symptoms and lead to excess disability.[1,30] The dementia syndrome of Parkinson's disease may coexist with AD, and many cases of Lewy body-type dementia meet histological criteria for AD.[1]

AD Versus Parkinson's Disease

About 25% of patients with Parkinson's disease develop dementia. Advanced age and severe extrapyramidal dysfunction increase the risk of Parkinson's dementia. Although the gradual onset and progression of dementia associated with Parkinson's disease resembles that of AD, mood disturbances are more frequent in Parkinson's disease.

AD Versus Depression

Depression must also be considered a possible source of dementia symptoms when performing the differential diagnosis. Certain clues may be helpful in making this discrimination. In cases of depression, it is the patient who typically reports cognitive difficulties, whereas the family is more likely to deliver the patient to the clinic in response to problems with memory in their loved one. Depression is generally of shorter duration and has a more discrete onset

than AD. In cases where depression cannot be excluded, it may be advisable to see if improvement results from antidepressive therapy.[2]

In a recently reported analysis of the relationship between AD and late- versus early-onset depression, the authors noted that, although the cognitive impairment that seems to accompany depression in the elderly has been referred to as a relatively benign and reversible pseudodementia, more-recent data suggest this might often not be the case,[31] because several studies have shown that cognitive impairment persists in many patients after depressive symptoms have been ameliorated.[13,32] One study reviewed the literature of late-life depression, searching for differences between early- and late-onset depression, cognitive impairment and neuropsychiatric findings, and structural imaging studies and studies evaluating the role of the apolipoprotein (ApoE) gene. They found that depression occurring for the first time in later life was associated with an increased likelihood of a poorer prognosis and response to treatment than were cases of earlier onset depression. The authors note that these findings support, although not conclusively, the proposition that late-onset depression may be a prodromal illness to dementia.[31] Although the pathophysiological mechanisms underlying this putative relationship are unknown, they may be related to the depletion of neurotransmitters known to be involved in both depression and dementia (e.g., serotonin, dopamine, and norepinephrine).[31]

Depression might also play a prodromal role in cases of vascular (poststroke) dementia, because it appears to occur more often in patients with vascular dementia than in patients with AD,[33,34] but more research is needed to further refine an understanding of depression in the context of AD, that is, its role as a prodrome of AD and vascular dementia, its manifestation as a possible early reaction to perceived cognitive decline, and its effect on the threshold for manifesting symptoms need further study.[35]

AD Is Significantly Underdiagnosed

Despite their ideal position for identifying risk for dementing illnesses, primary care physicians fail to diagnose dementia in 24% to 72% of cases. This is due, in large part, to the fact that the mild cognitive deficits seen early in the disease process are often dismissed as being related to normal aging.[36] Family members in denial may compound obstacles to early diagnosis by delaying a physician consultation by 1 to 2 years after symptom onset. Typically, the lag between symptom onset and diagnosis is up to 4 years.[37]

A survey of households that included a patient with diagnosed AD found that only 38% of 1,480 patients received the diagnosis from the first physician they consulted. A neurologist was most likely to make the diagnosis; a primary care physician was least likely. "Normal aging" was a common diagnostic label.[38]

Research into primary care practices suggests that primary care clinicians do not use mental status examinations or use examinations that lack sensitivity for AD. The advent of managed care and its emphasis on time-limited clinic visits may negatively influence the use of mental status examinations, even when cognitive deficits are suspected.[39]

Rationale and Feasibility of Early AD Diagnosis

Why diagnose a disease in its earliest stages if it cannot be cured? AD is not the first disease entity to be subject to this question, but important benefits do accrue to early AD diagnosis. Patients who are diagnosed in the prodromal or MCI stages of AD will be better able to actively participate in future planning of their affairs. Additionally, patients have the moral right to know their diagnosis. On a practical level, potential hazards can be minimized or eliminated (e.g., driving, use of a stove), and education of caregivers regarding the disease and its implications will allow them to adjust and adapt over a longer period of time.[40] Finally, therapy with acetylcholinesterase inhibitors (AChEIs) may prove to have the greatest benefit in prolonging function if they are instituted at an early stage of the disease, potentially resulting in improved patient quality of life, reduced caregiver stress, and lower healthcare expenditures. Further studies regarding the potential benefits of early intervention with AChEIs are currently underway.

Diagnostic Screens and Tests

The possible evaluations for AD range from asking the subject to draw a clock, to an hours-long battery of neuropsychological tests, to the latest techniques in neuroimaging, but, more often than not, an early diagnosis is made via astute questioning of patient and family members combined with the results of rapid, office-based tests, a sampling of which is provided below.

The Folstein Mini-Mental State Examination (MMSE) is the most commonly used test to assess serial cognitive changes in AD. On average, MMSE scores change at a rate of about 4 points per year in patients with AD.[41] Although the MMSE is a useful tool for detecting mild to severe AD, it has been criticized for lack of sensitivity in detecting mild dementia in the absence of reports from a family informant. Even a perfect MMSE score does not exclude MCI or mild AD.[1] Age and education affect performance on the MMSE.[28] Age- and education-adjusted norms have recently been published.[42,43]

The Clock Drawing Test is a rapid test for office-based practice. Although some contest its utility as a screen for very mild dementia, it does offer some degree of validity across different cultural backgrounds.[44,45] Scores are based on the ability to draw the face of a clock with the hands pointing to the appropriate numbers of a designated time.[46]

The Blessed Information Memory Concentration Test is also useful and widely used, but it has been criticized for failing to sample a number of cognitive functions (e.g., language and visuospatial abilities).[39]

The 7-Minute Screen was developed for use at a memory disorders clinic. A technician can administer it rapidly, and it requires little training and no clinical judgment. It is scored objectively. The screen can distinguish between AD and cognitive changes associated with normal aging by evaluating cognitive areas typically compromised in AD (e.g., verbal fluency and time orientation.)[39]

Neuropsychological Testing

Neuropsychological evaluation assesses abilities in several areas of cognitive functioning, identifies behaviors and behavioral changes, and measures performance in compari-

son with other persons of the same age. If the patient's performance is two to three standard deviations below the expected level, performance is considered impaired.[45]

Laboratory Tests

Once a state of dementia has been diagnosed, the degenerative and irreversible types of dementia must be differentiated from reversible (treatable) forms. For example, thyroid function tests may reveal hypothyroidism, which can be associated with depression, irritability, and slowing of mental processes. Vitamin B_{12} deficiency may produce psychiatric symptoms and myelopathy, with or without neuropathy, and may occur in the absence of hematopoietic abnormalities. Tests for sexually transmitted disease or human immunodeficiency virus, which can also produce psychiatric symptoms along with dementia, should be included only for patients who appear to be at specific risk for this etiology.[2,28]

Neuroimaging Techniques

Once dementia becomes clinically apparent and can be assessed using other methods, neuroimaging does not generally increase the diagnostic yield. In general, these tests are more likely to assist in excluding other causes of dementia than in pointing definitively to AD.[40] The American Academy of Neurology's practice parameter for diagnosis of dementia recommends the use of structural imaging (generally computed tomography) to exclude clinically significant structural lesions such as subdural hematoma and hydrocephalus.[47]

Positron emission tomography (PET) has aroused recent interest as a more-specific positive marker for AD.[40] PET is a relatively noninvasive procedure that measures cerebral glucose metabolic rates. Patients with AD have shown reduced use of cerebral glucose that begins in the parietal and temporal regions and later involves the prefrontal cortices. Other regions of the brain are largely spared. These patterns, which have been consistent in patients with AD, have been observed years before clinical diagnosis. PET scans have been able to distinguish between AD and certain other dementias with a fairly high level of accuracy.[48,49]

Genetic Markers

AD is genetically heterogeneous.[1] The majority of cases of AD have no obvious inheritance pattern. Early-onset AD, which may affect persons as young as 30, accounts for 5% to 10% of cases and is associated with genetic abnormalities.[1] Almost half of the early-onset cases are linked to mutations in three genes: β-amyloid precursor protein, presenilin-1, and presenilin-2. The presenilin mutations cause particularly aggressive forms of AD.[1]

The common form of AD has also been associated with a specific gene, the ApoE ε4 allele on chromosome 19.[48] ApoE is a serum lipoprotein involved in cholesterol transport that has three common isoforms. Inheriting the ApoE ε4 allele is the most-potent risk factor for late-onset AD, but developing the disease does not invariably follow. The lifetime risk of AD for a carrier of at least one copy of the ε4 allele is 29%, compared with 9% for a noncarrier.[3]

Population-based studies of AD suggest that the APOE ε4 mutation may account for 10% to 20% of all cases. Case-control estimates are higher, at 30% to 40%. Women who are gene carriers appear to have a higher risk for developing the disease than men who are carriers, and African-American gene carriers may have a lower risk than white carriers.[4] Routine genetic testing is not recommended for diagnosis of AD at this time, but combining genetic risk with brain imaging has been suggested as a promising strategy for early diagnosis.[48]

CURRENT THERAPIES FOR AD

Pharmacological Therapies

The first and only drugs approved by the Food and Drug Administration for treatment of cognitive defects in AD are AChEIs, which increase the availability of acetylcholine in central synapses.[50] Treating AD with cholinergic agents is a biologically plausible strategy because loss of presynaptic cholinergic function in the cerebral cortex has been linked to memory and cognitive deficits in AD.[51] Data on the efficacy of AChEIs are now sufficient to support their use as a standard of care in mild and moderate AD.[52,53] The clinical use of AChEIs is discussed in greater detail in the paper by Geldmacher in this supplement.

Non-AChEI Therapies

Vitamin E

The production of neurotoxic free radicals during oxidative metabolism has been implicated as a possible mechanism for destruction of neurons in AD. Vitamin E (α-tocopherol) has antioxidant properties, and it has reduced degeneration of neurons in the hippocampus of animal models.[30] Although modest reductions in risk and delayed onset of disease have been reported with vitamin E supplementation, no studies have reported improvement in cognition with this therapy.[54]

A 2-year study compared functional results of treatment with vitamin E (2,000 IU/d), selegiline (10 mg/d), or both with treatment with placebo in 341 patients with moderately severe AD. In analyses adjusted for baseline MMSE scores, treatment with the antioxidant agents selegiline, vitamin E, or both significantly delayed time to the primary outcome: a combination of death, institutionalization, inability to perform activities of daily living, or severe dementia. The median time to the outcome was longer for each treatment than for placebo, and time to institutionalization was significantly delayed in the vitamin E–treated patients. Combining the two drugs showed no increased benefit.[55] Vitamin E is low in cost and is relatively safe, and the results of clinical trials support its use as an addition to AChEI therapy in slowing progression of AD.[30]

Psychotropic Agents

Antipsychotics and antidepressants are frequently used to treat behavioral symptoms of AD. The atypical antipsychotics risperidone, olanzapine, and clozapine have been effective for treatment of psychosis and agitation in patients with AD. Avoiding antidepressants and other drugs with anticholinergic effects can be an important consideration in therapy, because anticholinergic agents can exacerbate underlying dementia or delirium. Tricyclic antidepressants are effective drugs, but several have anticholinergic

side effects. Monoamine oxidase inhibitors interact with several drug classes and some foods.[25]

Estrogen

There is some evidence to support the argument that estrogen replacement therapy (ERT) improves cognitive function and reduces the risk of subsequent AD in postmenopausal women,[56] but recent data from the National Heart, Lung, and Blood Institute's Women's Health Initiative indicate that the safety of ERT is highly questionable. This trial was stopped because of findings showing that administration of estrogen plus progestin in postmenopausal women can increase the likelihood of breast cancer, venous thromboembolism, coronary heart disease, stroke, and cholecystitis.[57,58] ERT therapy should therefore be used with extreme caution, if at all, for purposes of modifying the risk for later development of AD.

Ginkgo Biloba

A Chinese herbal medicine, ginkgo biloba, is believed to increase cognition and elevate mood. Theoretically, it acts as an antioxidant, an antiinflammatory, and an anticoagulant agent. A 52-week, randomized, placebo-controlled trial of ginkgo biloba demonstrated a modest gain on the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-COG) in the active-treatment group, but a high attrition rate and methodological flaws have called the results into question.[30] In a carefully executed 24-week, randomized, double-blind, placebo-controlled trial, the effect of ginkgo biloba was studied in 214 older patients from 39 homes for the elderly with mild to moderate AD, vascular dementia, or age-associated memory impairment. Participants were allocated to randomly receive high-dose (240 mg/d) or low-dose (160 mg/d) ginkgo biloba or placebo. Outcomes were assessed at 12 and 24 weeks using neuropsychological testing, digit memory span, and verbal learning tests. No benefit of a higher dose or a prolonged treatment (12 vs 24 weeks) with ginkgo biloba was found relative to placebo.[59] Available data do not support its use as a treatment for AD.[30]

THE HIGH COST OF AD

AD is the third-most-expensive disease to the U.S. economy after cardiovascular disease and cancer (Figure 2).[60] Estimated costs of treatment for AD range from $50 billion to $100 billion annually, depending on prevalence figures and method of calculation. Costs are generally considered as formal or direct (e.g., long-term care, physician visits) and informal or indirect (e.g., lost productivity of family caregivers).[61]

For community-dwelling AD patients, two major costs are incurred: the patient's direct medical costs and the indirect cost of caregivers' lost productivity. In 1998 dollars, the direct costs of treatment were estimated to be as high as $29.1 billion annually. Per-patient cost estimates for the lost productivity of unpaid caregivers ranged up to $47,000 annually.[62]

COST SAVINGS ASSOCIATED WITH TREATMENT

Recent research indicates that significant savings can be achieved through the use of AChEI therapy. For example, one study examined the effect of donepezil use on the healthcare costs in a large Medicare managed care plan.[63] Medical costs and utilization for patients with AD who received donepezil (n = 204) were compared with those of a random sample of AD patients who were not receiving donepezil (n = 204). Estimates were obtained from administrative data on enrollment, medical claims, pharmacy claims, and records of services received at the managed care clinic. After controlling for sex, age, comorbid conditions, pharmacy benefits, and dementia complications, the annual costs for prescription drugs and medical services were $3,891 lower for the study group than for the control group. The authors concluded that medical management benefits by improving cognition and daily functioning with AChEIs.[63]

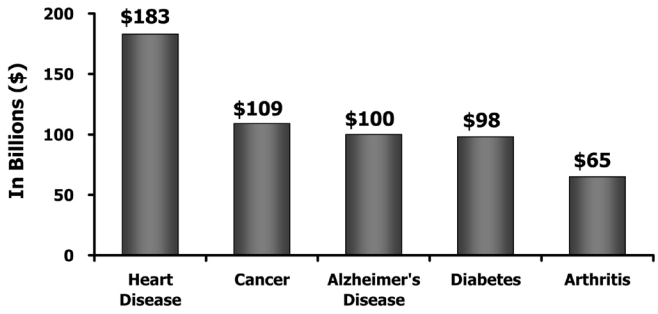

Figure 2. Alzheimer's disease is the third-most-costly disease after cardiovascular disease and cancer.

It is important to note that managed care organizations are expected to assume an increasing portion of overall healthcare costs as the number of AD patients continues to grow. Therefore, it will become increasingly important to institute programs targeted toward effective early management to curtail spiraling costs.[61]

CONCLUSION

The many benefits to the patient, caregiver, and society are the motivating factors for establishing a diagnosis of AD as early in the course of the disease as possible. This goal can be obtained by watching for prodromal AD or MCI, which may occur before clinical AD. Early diagnosis can be facilitated by using validated office-based tests and by paying close attention to reports from family members.

Once the diagnosis is made, it is critically important to educate patients and caregivers regarding the reality of the disease and the limitations of available treatments. Nothing will alter the ultimate outcome of AD, but it is nonetheless a treatable disorder in pharmacological and nonpharmacological realms. To reinforce this and other key messages, it is imperative to refer family caregivers to the Alzheimer's Association or other local caregiving advocacy groups. AChEIs prolong the retention of mental function, and probably quality of life, for patients and caregivers alike.

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