Alzheimer Disease

Report of the Council on Scientific Affairs

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Alzheimer disease (AD) takes a heavy economic, social, physical, and psychological toll on patients, families, and society. Because of the increasing life expectancy in the United States, AD is expected to afflict approximately 14 million people within the next few decades. There is currently no cure, only interventions that can temporarily ameliorate the profound cognitive losses and behavioral manifestations of the disorder. Community services are fragmented and underutilized. Physicians, in their traditional role as gatekeepers, can encourage more families to use supportive services. This article reviews the guidelines on the diagnosis and treatment of AD of the Agency for Health Care Policy and Research, the American Academy of Neurology, the Veterans Health Administration, and the American Psychiatric Association. Although these guidelines contain valuable information, they do not adequately address the role of the family physician and the need for continuity of care. Recommendations regarding AD from the Council on Scientific Affairs, which were adopted as American Medical Association policy in December 1997, are included in this article. *Arch Fam Med. 1999;8:347-353*

During the past few years, several documents containing guidelines and practice parameters on Alzheimer disease (AD) and related dementias have been published. In 1996, the Agency for Health Care Policy and Research published a clinical practice guideline for the early recognition and identification of AD and related disorders[1]; in 1994, the Quality Standards Subcommittee of the American Academy of Neurology produced practice parameters for the diagnosis and evaluation of dementia[2]; and in 1997, the Dementia Technical Advisory Group, convened by the Veterans Health Administration, developed guidelines for the identification and assessment of dementia.[3] Lastly, in May 1997, the American Psychiatric Association published its guidelines for the treatment of dementias of late life.[4] Each of these documents was developed after extensive literature review and with input from experts in the field who served on advisory boards and task forces or as reviewers. The American Medical Directors Association is currently developing guidelines for management of dementia in nursing homes. Organized medicine has taken an active role in these processes and has contributed to both the knowledge base and policy determinations related to AD.

This article reviews and synthesizes information from the existing guidelines, reviews the most recent findings in the literature relative to AD, and makes policy recommendations based on identification of gaps with respect to patient and caregiver education, financing of care, and research needs.

From the Council on Scientific Affairs, American Medical Association, Chicago, Ill. A list of the members of the Council on Scientific Affairs can be found on page 353.

BACKGROUND

Alzheimer disease is a chronic, degenerative, dementing illness, the cause of which is unknown and for which there is no cure. Dementia involves a progressive, multifaceted loss of cognitive and intellectual abilities such as memory, judgment, abstract thinking, and higher cortical functions; disorientation with regard to time, place, and person; and difficulty in word-finding and communication. The loss of intellectual abilities is severe enough to interfere with social and occupational functioning. In

many cases, there are personality and behavioral changes. These include anxiety, irritability, agitation, withdrawal, petulance, paranoid ideation that can result in hostility and violence, and nocturnal and diurnal wandering.[5,6] Although disease progression is highly variable, ranging from 2 to 10 or more years, persons with AD undergo progressive general debilitation, become unable to care for themselves, and eventually die.[7] While it is important to understand that the disease does not affect everyone in the same way, the following stages represent the general pattern that the illness follows.[8]

Stage 1: Decrease in energy and spontaneity, minor memory loss and mood swings, slowed reaction and learning, avoidance of new situations.

Stage 2: Slowing of speech and comprehension, loss of train of thought in midsentence, forgetting to pay bills, and getting lost while traveling. Awareness of loss of control may lead to depression, irritability, and restlessness.

Stage 3: Short-term memory loss, disorientation to time, place, and possibly person, paraphasic speech.

Stage 4: Behavioral disturbances, increasing need for care, incontinence.

Stage 5: Loss of ability to chew and swallow; vulnerability to pneumonia and other illnesses. Frailty precedes coma and death.

EPIDEMIOLOGY

Alzheimer disease is the fourth leading cause of mortality among elderly persons in the United States, accounting for more than 100 000 deaths annually. Between 5% to 10% of the adult population is estimated to be affected by a dementing disorder, and the incidence doubles every 5 years among people aged 65 years and older.[1,9] Alzheimer disease is the most prevalent form of the irreversible dementias, which affect an estimated 3 to 4 million patients, accounting for 60% or more of cases.[10,11] Community epidemiological studies have estimated that as many as 40% of persons aged 85 years and older have symptoms of AD. It is projected that, with the increase in life expectancy in the United States, as many as 14 million individuals could develop AD within the next few decades.[12] Cognitive impairment is a strong predictor of institutionalization; approximately 50% of nursing home residents have a dementing disorder.[13-15] The incidence of AD is higher in women than in men; this is most likely because women live longer than men and therefore have a greater opportunity for disease expression.

Vascular or multi-infarct dementia is the second most prevalent form of irreversible dementia and accounts for 10% to 25% of cases.[16] Snowdon et al[17] suggest that because both cerebrovascular disease and AD can result in dementia, and the prevalence of both increases with age, a sizable number of older persons might develop dementia as a result of both disease processes. A group of disorders called frontal lobe or frontotemporal dementia, which includes Pick disease, accounts for about 9% of cases. A recently described condition, dementia of the Lewy body type, may account for 5% of cases. Other dementing disorders account for much smaller proportions. These include dementia associated with Parkinson disease, Huntington disease, and Creutzfeldt-Jakob disease. Variation in prevalence estimates among studies is due to the difficulty inherent in evaluation and differential diagnosis, differing criteria used in epidemiological studies, and the infrequency of autopsy.

Anti-inflammatory drugs such as ibuprofen, antioxidants, and estrogen replacement therapy have been associated with delayed onset of and decreased risk for AD in both animal and human studies. However, results are conflicting and further research is needed to support or refute these findings.

Potentially treatable causes of dementia include drug toxicity, alcohol abuse, depression, tumors, metabolic disorders, infections, vision or hearing problems, trauma, normal-pressure hydrocephalus, and nutrient deficiencies. Estimates of the incidence of these dementias range from 2% to 20% of cases.[18-20] Variation in these findings could be explained by the setting in which cases were evaluated (primary or tertiary care settings).

Because AD is the most prevalent form of dementing illness it is used as the prototype for dementia in this article.

ETIOLOGY AND NEUROPATHOLOGY OF AD

Numerous investigations using various approaches have provided evidence for a genetic basis for AD. These include family and pedigree studies,[21] life-table methods, and monozygotic and dizygotic twin studies.[22-25] Four loci that play a role in genetic susceptibility to AD have been identified thus far and others are likely to be found. Mutated genes on chromosomes 1,[26] 14, and 21 have been linked to the familial form of the disease, which has early onset (before age 60 years).[27,28] Apolipoprotein E-4, which has been found on chromosome 19, is implicated in the risk for late- and early-onset familial AD, as well as nonfamilial AD.[29-31] Although the presence of apolipoprotein E-4 combined with dementia increases the likelihood of an AD diagnosis, the absence of the allele does not confirm that an individual does not have AD. An association between apolipoprotein E-4 and vascular dementia has not been fully determined.[32,33] Closed-head injuries and Down syndrome increase the risk of developing AD in later life. Cerebral infarcts and atherosclerosis also may play a role in the expression and severity of AD. Thus, the cause of AD is not a unitary factor, but a combination of factors that interact differently in different people.[34,35]

Definitive diagnosis of AD is made only at autopsy by pathologic examination of brain tissue, in conjunction with a clinical history of dementia.[36] The hallmarks of AD include neurofibrillary tangles, neuritic plaques,[37-39] and neuronal thread protein.[40] While these are manifest in the brains of normal elderly persons, they are overexpressed in the brains of demented persons. Plaques are external to the neuron and have as a core component β-amyloid, a protein that is present in abnormal quantities in brains of patients with AD.[41] It is not known whether β-amyloid is a neurotoxin that causes destruction of neurons or if it is a result of neuronal damage caused by some other process. Neurofibrillary tangles, which are intra-

cellular, have as a core component abnormally phosphorylated proteins, especially τ. Cognitive impairment is more highly correlated with the density of neurofibrillary tangles than with the number of plaques. Recent data suggest that persons with AD have a decreased ability to remove excess phosphate from τ protein.[42] Plaques and tangles are not detectable with presently available neuroimaging techniques.

Neuronal thread proteins are expressed in brain cell lines and accumulate in abnormal amounts in the brains of patients with AD. Neuronal thread proteins are detectable in cerebrospinal fluid early in the course of the disease, and levels in cerebral tissue and cerebrospinal fluid increase as the dementia progresses. It is speculated that the increase in neuronal thread protein expression is associated with chronic neuronal atrophy and synaptic disconnection. Despite recent research advances, the precise process by which cerebral neurodegeneration occurs remains undetermined.

CAREGIVER ISSUES

Caregiving in the context of dementing illness is a demanding and distressing job for which most caregivers are untrained. Caregiving involves tremendous financial costs and burdens, including lost wages due to decreased work hours or the need to stop working to provide full-time care.[43] Frequently, families become socially isolated or social contacts are diminished because of the demands of caring for the patient with AD. A sizable proportion of family caregivers experience profound burden, characterized by emotions such as anxiety, guilt, and anger.

The effect of caregiving on physical and psychological health may result in blood pressure changes, altered immune response, depression, fatigue, and depersonalization. Preexisting health problems may become exacerbated, and caregivers are also at increased risk for back strain, loss of sleep, gastrointestinal tract problems, and headaches.[44] The burden of care has been described as a "36-hour day" and an "ongoing funeral."[45-47] Despite their best efforts at caring for a demented relative, the only outcome is deterioration and loss. In effect, AD is an "ecologically devastating" disorder, not only for the victim, but also for the entire family.

Within the formal health care system, there exists an array of support services, such as adult day care, respite care, and supportive counseling, which could be beneficial to families of patients with AD. However, the system is fragmented and varies from state to state. Services can be very costly; however, even subsidized services are often underutilized.[48] Nursing home placement is usually considered as a last resort and occurs when the family can no longer cope with the patient at home.

THE ECONOMIC BURDEN OF AD

The economic burden of dementia to society and families is substantial. It includes the direct costs of medical care and social services, as well as the indirect costs of disease-associated morbidity and mortality and lost productivity on the part of both patients and family caregivers.[49] Estimated costs of AD range from $80 to $120 billion annually.[50] While Medicaid pays for nursing home care after the patient's resources have been consumed, family out-of-pocket costs are estimated to average $450 per month for supplies, medicines, and services. Given the potential duration of the disease and the propensity for families to keep their relatives at home for as long as possible, these expenses often lead to financial impoverishment of the family.[9,16]

STATUS OF CURRENT PHARMACOLOGICAL TREATMENTS

Despite many research endeavors, there is currently no clinically proven treatment available that either reverses or halts the neurological damage of AD. In the absence of a curative treatment, the goals of therapies for AD have been 3-fold: (1) to slow the progression of the disease; (2) to prevent further deterioration once the process has started; and (3) to reduce symptoms.

Two major pharmacological agents are available for treatment of cognitive deficits. These are the cholinesterase inhibitors tacrine hydrochloride and donepezil hydrochoride. In 50% to 80% of patients, cholinergic agents may improve or help maintain cognitive function equivalent to the deterioration observed during a span of 6 to 12 months. However, tacrine may adversely affect the liver, and liver function monitoring is necessary. Donepezil does not cause liver toxicity and may cause less nausea and vomiting.[51] Both tacrine and donepezil have been approved for use with patients in early to moderate stages of the disease.

Psychoactive drugs commonly used to treat the behavioral symptoms of AD are the same classes of drugs used in the general population, including antidepressants, antipsychotics, and antianxiety medication.[9] Because patients with AD tend to be very sensitive to the central nervous system effects of these drugs, they must be used especially carefully.

REVIEW OF PUBLISHED GUIDELINES

Agency for Health Care Policy and Research

Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias[1] was developed principally for primary care physicians to help them recognize and assess the early stages of AD and related dementias. Recognition of early-stage dementia is emphasized because of the benefits that accrue to patients and families. These include avoidance of inappropriate treatments due to misdiagnosis and the opportunity to perform legal, financial, and medical care planning. The following areas are addressed:

- Triggers that should prompt an assessment for early-stage dementia, as distinct from ascribing signs of decline to the aging process.
- The components of an initial assessment, including history and physical examination, mental status tests, and tests of functional performance.
- A flowchart for early recognition and initial assessment, including assessment for depression and delirium (**Figure 1**).
- Guidelines for the interpretation of test results and appropriate inter-

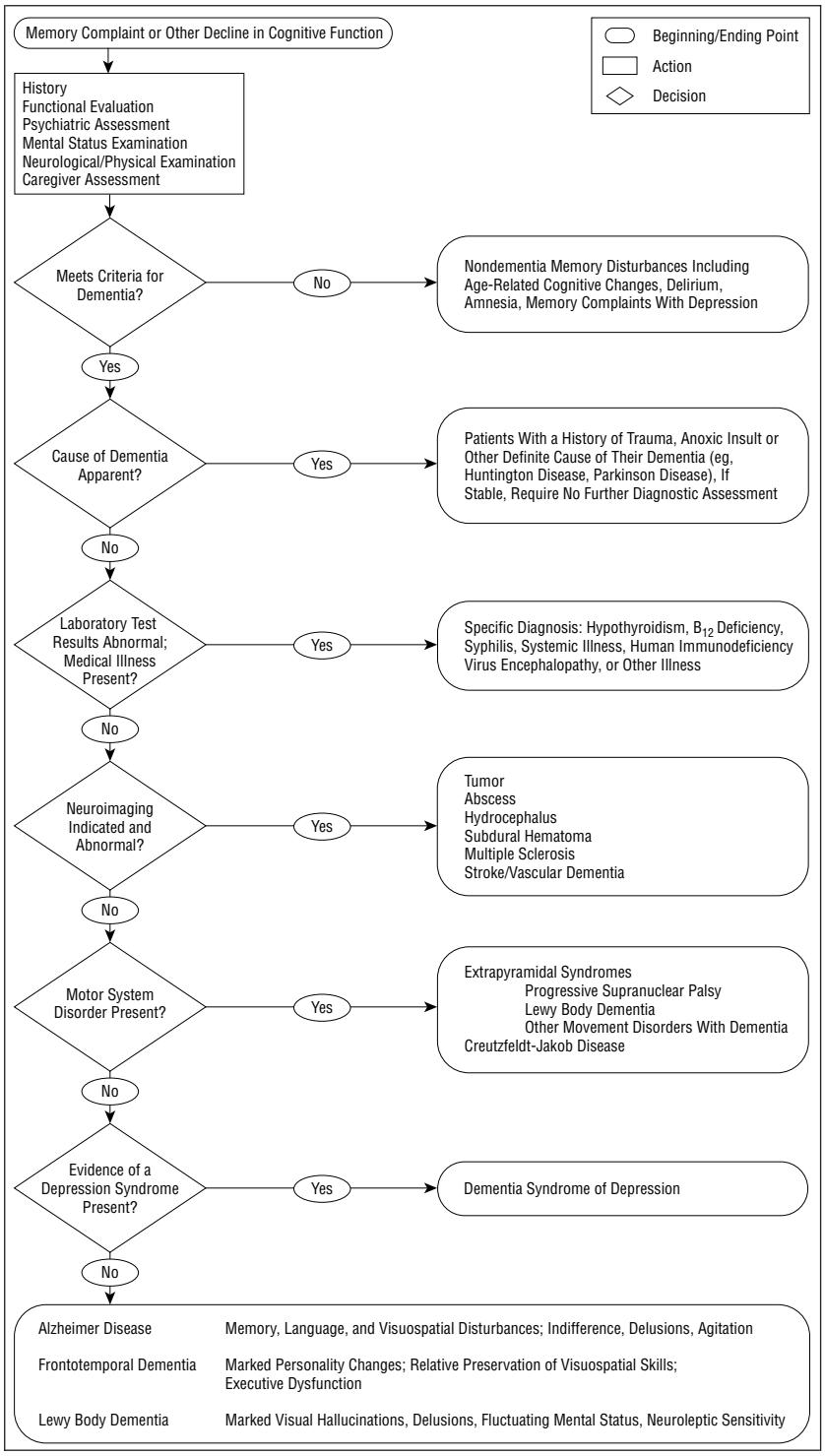

Figure 1. *Algorithm guiding the differential diagnosis of dementia. Adapted from* Dementia Identification and Assessment.[3] *Copyright 1997, Veterans Health Administration.*

ventions. Clinicians should take into account and assess factors such as physical disability, sensory impairment, and other variables such as age, level of education, and cultural influences when selecting and interpreting test results.

- Algorithm for reassessment and referral.
- The role of neuropsychological testing in cases of mixed test results.
- Collaborative continuity of care for patient and caregivers.
- Knowledge of the individual patient is stressed, with emphasis on changes in ability from a baseline observation and the value of having a reliable informant to aid in assessment and clinical judgment.

The guideline does not address differential diagnosis but does include a list of resources for follow-up evaluation once probable dementia has been identified. There is also an accompanying guide for patients and families and a quick reference guide for clinicians.

American Academy of Neurology

The practice parameter on the diagnosis and evaluation of dementia[2] was developed to inform neurologists about diagnostic procedures, treatment modalities, and related clinical disorders. The essential requirements for diagnosis are assessment of current level of cognitive functioning, documentation of a higher level of previous functioning, or confirmation of a decline in intellectual function over time. Cognitive deficits due to nondementia disorders, including psychiatric problems, must be excluded. Diagnosis of dementia requires further evaluation to determine etiology and to stage disease severity. Accurate diagnosis enables the physician to provide guidance to the patient and family and facilitates legal and financial planning and access to community resources.

The American Academy of Neurology document contains recommendations designated as "standards," "guidelines," and "options," based on the strength of supporting evidence. These recommendations are as follows:

- Indications for evaluation for dementia include memory loss or other cognitive complaints with or without functional impairment. The following cases should be evaluated: elderly persons for whom there is a question of competency, anxious or depressed patients with cognitive complaints, and persons with no complaints who are suspected to have cognitive impairment during the interview.
- Substantiation of cognitive and functional deficits by a reliable informant; inquiry into family history of AD or other dementia.
- Cognitive or mental status testing should include assessment of attention, level of arousal, orientation, recent and remote memory, language,

visuospatial function, calculations, and judgment. Techniques used to assess these domains are discretionary and may include tests and screening instruments combined with clinical impressions. Clinicians are advised to take into account educational and cultural factors when interpreting test results.
- Neurological history and examination with special attention to gait disorders, focal abnormalities, and extrapyramidal signs.
- Diagnostic tests recommended to rule out metabolic and structural causes depend on suspected diagnosis, and may include complete blood cell count, serum electrolyte level, glucose level, blood urea nitrogen/creatinine levels, liver and thyroid function tests, serum vitamin B_{12} and folate levels, and syphilis serology.
- Neuroimaging should be considered based on the clinical manifestation and to aid in the identification of potentially treatable conditions that otherwise might be missed.

The practice parameter lists the signs, symptoms, and other clinical criteria necessary to perform a differential diagnosis.

Veterans Health Administration

Dementia Identification and Assessment[3] provides specific recommendations for procedures at each step of the assessment process, complete with formulated questions, appropriate flowcharts, and listing of required laboratory tests. The document also contains instructions for the administration of subtests and scoring for the Mini-Mental State Examination, as well as a listing of other standardized screening tests. A list of drugs in current use, under study, and awaiting Food and Drug Administration approval is also provided. The Veterans Health Administration guidelines recommend referral for neuropsychological testing as an important aid in defining cognitive deficits, differential diagnosis, and treatment planning.

Suggested guidelines for referral to neuropsychological services include:
- Complaints of memory and other cognitive impairments without functional impairment.
- Report of functional change with normal performance on cognitive screening tasks.
- Established diagnosis and need for further information for future clinical decision making, treatment, and patient and family education and counseling.
- Lack of physician experience with cognitive screening tests and their interpretation, or when a second opinion is desired.
- Techniques regarding behavioral and environmental interventions and the need for caregiver information and education.

The Veterans Health Administration document also provides an algorithm to guide the differential diagnosis of dementia (**Figure 2**). It is accompanied by a pocket reference guide and a videotape. An extensive list of resources for caregivers is included.

American Psychiatric Association

The practice guideline for the treatment of patients with AD and other dementias of late life[4] is intended to aid psychiatrists in managing patients with dementia. It assumes a diagnosis of dementia, according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria; a prior evaluation for coexisting mental disorders, such as depression and delirium; and an evaluation for treatable factors that might cause or exacerbate the dementia. Most of the emphasis is on management of behavioral symptoms because almost all of the effective treatments available for dementia are in this domain. Additional treatment suggestions are aimed at cognitive and functional deficits, and stress is placed on providing support for caregivers.

The recommendations in the American Psychiatric Association guideline are classified into 3 categories, representing different levels of clinical confidence. The following are the essential components of the document:
- Psychiatric management, including: ongoing assessment, including symptom monitoring at 4- to 6-month intervals and prompt intervention, patient and family counseling with regard to driving, environmental management, types of supportive services, and legal and financial planning.
- Behavioral management, including pet and art therapies, environmental interventions, behavior modification, and reality orientation.
- Discussion of treatment with psychoactive and general medications relative to sensitivity and adverse effects.
- Treatment of cognitive symptoms with cholinesterase inhibitors, vitamin E, and seligilene.
- Treatment of depression and sleep disorders.

With the exception of the American Academy of Neurology document, all the guidelines discussed have extensive lists of resources to help physicians direct families to supportive services. Both documents intended for primary care physicians[1,3] have excellent graphics that can be easily used in the clinical setting. Only the American Psychiatric Association and the Veterans Health Administration documents list current pharmacological agents in use or under investigation. Neither the Veterans Health Administration nor the Agency for Health Care Policy and Research guides, both intended for primary care physicians, provide direction for continuity of care. For most AD cases, follow-up care is most likely to be provided by primary care practitioners. Because of the volume of research being conducted into AD, it is likely that any guideline or practice parameter will need frequent revision.

RESEARCH DIRECTIONS

Research on AD can be categorized in 3 broad overlapping areas: causes/risk factors, diagnosis, and treatment/caregiving. Two primary approaches are used to resolve the question of AD pathogenesis. The first are biochemical studies designed to explicate the molecular nature and formation of plaques and tangles; the second involves the use of molecular genetic techniques to study mutant genes that may cause AD in families with the autosomal dominant form of the disease. Re-

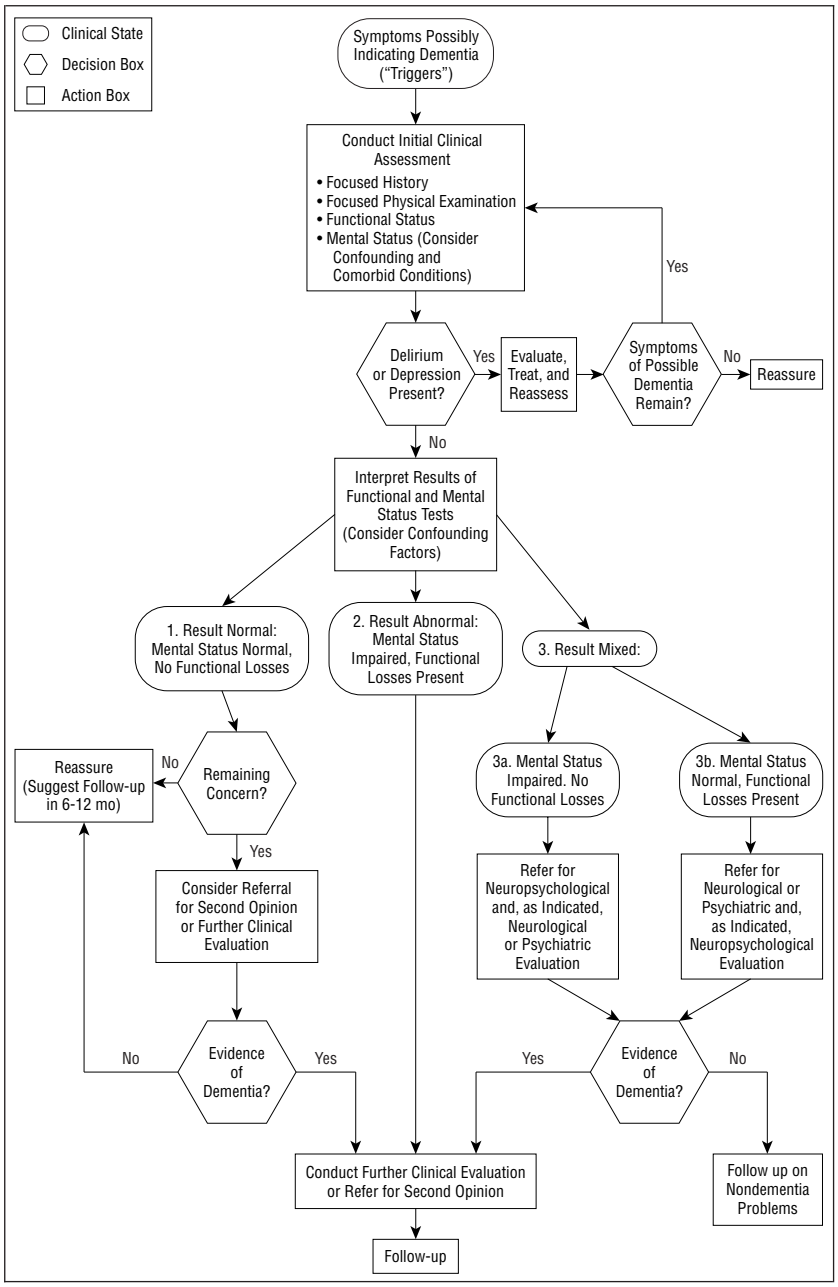

Figure 2. *Flowchart for recognition and initial assessment of Alzheimer diesase and related dementias. Adapted from* Recognition and Initial Assesment of Alzheimer's Disease and Related Dementias.[1] *Copyright 1996, Agency for Health Care Policy and Research.*

search into the basic neurobiology of aging is also vital to the understanding of neurodegenerative processes and in leading to the discovery of a cause, or causes, of AD.

Research also has sought predictors of which cognitively impaired, nondemented patients will ultimately meet criteria for AD.[52] Algorithms are being developed to predict the rate of progression of the disease to end stage and length of time to institutionalization.[53] These approaches may facilitate preparation and planning, but also pose ethical quandaries; eg, how does knowing the likelihood of developing AD affect the quality of life and well-being?

Research is continuing on improved methods for diagnosis and symptom management as well as strategies for supporting caregivers and improving care of patients with AD.

Among the ethical considerations to be addressed in research protocols are situations in which patient competence precludes informed consent to research or experimental treatments that might improve functioning or enhance quality of life but where there are no surrogate decision-makers. In cases where surrogates have been appointed by the courts, the process of informed consent has been prolonged. Some experts have argued that a substitute procedure should be put in place; for example, empowering appropriate medical professionals to make surrogate decisions on behalf of patients may be desirable.[54]

CONCLUSIONS

Alzheimer disease and related disorders are a common and costly public health problem. Owing to the increasing life expectancy in the United States, AD is expected to afflict approximately 14 million people within the next few decades. Irreversible dementia takes a heavy economic, social, physical, and psychological toll on patients and family members, who provide most of the care for affected individuals. The financial costs to society are enormous. There is currently no cure for AD, only interventions that ameliorate to some extent the profound cognitive losses and difficult behavioral manifestations of the disorder. While community services exist to provide relief for the burden of care, they are underutilized. As traditional gatekeepers for services, physicians can encourage more families to use supportive services. Several authoritative documents on the diagnosis and treatment of AD and related disorders are available. However, there is a need for increased and intensive medical education, seminars, and continuing medical education whereby the information contained in these documents can be widely disseminated.

RECOMMENDATIONS

The following statements, recommended by the Council on Scientific Affairs, were adopted as American Medical Association (AMA) policy in December 1997.

1. The AMA encourages physicians to make appropriate use of guidelines for clinical decision making in the diagnosis and treatment of AD and other dementias.

2. The AMA encourages physicians to make available information about community resources to facilitate appropriate and timely referral to supportive caregiver services.

3. The AMA encourages studies to determine the comparative cost-effectiveness/cost benefit of assisted in-home care vs nursing home care for patients with AD and related disorders.

4. The AMA encourages studies to determine how best to provide stable funding for the long-term care of patients with AD and other dementing disorders.

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