

Early Diagnosis and Management of Alzheimer's Disease

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It is only recently that Alzheimer's disease has become recognized as a major public health concern. Not only those diagnosed with Alzheimer's disease are impacted by the disease; the emotional toll exacted on caregivers is enormous, and the financial costs incurred by the United States are staggering. Early diagnosis of Alzheimer's disease can prevent costly and inappropriate treatment and permits earlier treatment of symptoms. There have been several recent pharmacologic advances in the treatment of Alzheimer's disease, including the development of acetylcholinesterase inhibitors. For any intervention to prove successful, however, early and accurate diagnosis and effective disease management are crucial. *(J Clin Psychiatry 1998;59[suppl 9]:15-21)*

Alzheimer's disease has been recognized only in fairly recent years as a major public health problem. Alzheimer's disease develops after the age of 65 years in most cases. Rarer forms of Alzheimer's disease occur from the fourth decade of life until age 65. Currently, Alzheimer's disease is the fourth leading cause of death among adults in the United States.¹ It is estimated that by the year 2020, 53 million Americans will be aged 65 years and older as compared with 33 million in 1994. The population of those aged 85 years and older is expected to increase from 3 million in 1990 to 7 million in 2020.² Based on these projections, it is estimated that by the year 2030, the number of Americans afflicted with Alzheimer's disease will double from the current 4.5 million to 9 million.³

In addition to those diagnosed with Alzheimer's disease, it is imperative to consider and provide educational, supportive interventions for the millions of Alzheimer's disease caregivers. These include spouses, children, relatives, friends, volunteers, and paid medical and nursing staff. Numerous studies have suggested that interventions designed for caregivers could prevent or postpone nursing home placement, particularly in the early-to-middle stages of the disease.⁴⁻⁹

The emotional toll exacted on caregivers is enormous, and they are at high risk for developing psychiatric disor-

ders. Major depression has been cited as occurring in 14% to 47% of adult caregivers in various samples, and anxiety disorders are reported in 10% of caregivers.¹⁰ Feelings of guilt, anger, and resentment are common and often increase through the course of disease.

The effects of Alzheimer's disease are also a financial burden on the U.S. health care system. Alzheimer's disease is currently the third most expensive disease to treat in the United States, following only cancer and heart disease, with annual treatment costs as high as \$100 billion.¹¹ It is estimated that over the course of the illness, patients and their families will pay more than \$200,000 for care-related expenses.¹

The characteristic neuropathologic changes were first discussed by Alois Alzheimer in 1907. In his historic paper describing a 51-year-old female patient, Alzheimer wrote of early pathologic jealousy, progressive memory impairments, paranoia, disorientation, gestures indicative of complete helplessness, agitation with prolonged screaming, apparent auditory hallucinations, delirium, perceptual disorders, and praxis. The patient died after 4.5 years, during which time she displayed progressive "mental regression" until she became completely apathetic. At the time of autopsy, using a newly developed staining technique, Alzheimer observed the plaques now known as the hallmark of the disease. He wrote: "Scattered through the entire cortex, especially in the upper layers, one found miliary foci that were caused by the deposition of a peculiar substance in the cerebral cortex."¹²

Although there is currently no cure for this tragic disease, advances in pharmacotherapy have been made with the acetylcholinesterase inhibitors, which may slow the progression of Alzheimer's disease symptoms. Two acetylcholinesterase inhibitors, tacrine and donepezil, are currently available; new agents that enhance cholinergic neu-

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rotransmission, such as metrifonate, rivastigmine, and physostigmine, may soon be available. Early diagnosis and treatment of cognitive decline may also detect potentially reversible illnesses and enhance the management of progressive dementing diseases. This allows patients and their caregivers the opportunity for proactive education, psychosocial support, and financial and legal planning, with the hope of an enhanced quality of life. However, to reap the maximum benefit from these interventions, it is necessary for health care providers to make an accurate diagnosis as early as possible.

Primary care clinicians are in a key position to identify those at risk for dementing illnesses, thus providing the opportunity for early diagnosis and intervention. Unfortunately, it has been shown that clinicians fail to diagnose dementia in 24% to 72% of cases and that symptoms, especially the mild cognitive deficits seen early in the disease process, are often dismissed as normal aging.¹³ Primary care clinicians were shown in one study to take up to 4 years before referring demented patients to a geriatric clinic.¹⁴ A greater appreciation for the prevalence of Alzheimer's disease may prompt primary care clinicians to include routine screening for cognitive decline in their aged patients.

DEFINITION AND CRITERIA

Alzheimer's disease is a progressive, degenerative, brain disease characterized by increasing loss of cognitive functions, including memory, language, praxis, judgment, and orientation; psychiatric and behavioral disturbances; and an impaired ability to perform activities of daily living. Tissue pathology with the identification of the characteristic neuritic or amyloid plaques and neurofibrillary tangles is currently the only method to confirm the diagnosis.

Standard diagnostic criteria for Alzheimer's disease are described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*¹⁵ (Table 1). These criteria require that the diagnosis of Alzheimer's disease be considered only if the memory loss is progressive and there is evidence of a decline in at least 1 other cognitive function that compromises social or occupational functioning. Further, the patient must be alert, and the deficits cannot be due to a medical or neurologic disorder.¹⁵

Alzheimer's disease is an acquired disorder; therefore, new onset cognitive decline must be differentiated from a lifelong history of cognitive impairment. It is additionally imperative to differentiate between benign, age-related cognitive changes and Alzheimer's disease. In normal aging, information processing is slowed; however, the decline is not progressive, and it does not affect functional ability.

Although other diagnostic criteria for Alzheimer's disease have been developed, i.e., International Classification

Table 1. DSM-IV Diagnostic Criteria for Dementia of the Alzheimer's Type*

- A. The development of multiple cognitive deficits manifested by both
 1. memory impairment (impaired ability to learn new information or to recall previously learned information)
 2. one (or more) of the following cognitive disturbances:
 - (a) aphasia (language disturbance)
 - (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) agnosia (failure to recognize or identify objects despite intact sensory function)
 - (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
- B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. The course is characterized by gradual onset and continuing cognitive decline.
- D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
 1. other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
 2. systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B₁₂ or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, human immunodeficiency virus infection)
 3. substance-induced conditions
- E. The deficits do not occur exclusively during the course of a delirium.
- F. The disturbance is not better accounted for by another Axis I disorder (e.g., major depressive disorder, schizophrenia).

*From reference 15, with permission.

of Diseases-10th Revision¹⁶ and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association,¹⁷ the criteria described in the DSM-IV most succinctly capture the clinical presentation and do not require further classification by severity or into possible, probable, and definite categories.

Diagnosis of mild Alzheimer's disease is made more difficult because DSM-IV criteria stipulate that there must be at least 1 cognitive disturbance in addition to impaired memory. However, mild cognitive impairment has been identified as a predictor of Alzheimer's disease within the Framingham cohort, and this impairment occurs as early as 7 years before the Alzheimer's disease diagnosis.¹⁸ Flicker et al.¹⁹ found that 72% of elderly subjects with mild cognitive deficits on clinical examination and psychometric testing deteriorated significantly over a 2-year period. Other studies reveal that mild cognitive impairment will progress to dementia in 63% to 80% of patients. These findings suggest a preclinical phase for Alzheimer's disease.

"Mild cognitive impairment" refers to a condition characterized by memory impairment that is beyond normal limits in an alert person. Typically, a 4-point decline in scores on the Mini-Mental State Examination (MMSE)²⁰ in patients with Alzheimer's disease is expected per year.²¹

The MMSE is a 30-item test composed of structured questions and tasks to assess mental functioning in the areas of immediate memory, short-term recall, aphasia, apraxia, agnosia, constructional ability, concentration, spatial ability, and orientation.

False positives may occur with the MMSE in patients who do not speak the language or in those without much formal education. False negatives may occur in highly educated individuals with mild impairment.

DIAGNOSIS AND ASSESSMENT

Studies indicate approximately 90% accuracy of diagnosis based on a comprehensive general medical and psychiatric evaluation.²² In fact, the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society concluded in their consensus statement on the diagnosis and treatment of Alzheimer's disease and related disorders that "the most important diagnostic tools are the informant interview and office-based clinical assessment."^{23(p1365)}

The clinician must be alert for subjective complaints of difficulty with short-term memory and/or reports of forgetfulness by those close to the patient. These should serve as "red flags" or "triggers" to initiate screening for Alzheimer's disease. Initially, it is recent memory or newly learned material that cannot be retrieved. Over-learned tasks and long-term memory are preserved in the early stages of the disease. Additional triggers are difficulty handling complex tasks, i.e., balancing a checkbook or planning a meal; impaired ability to reason, i.e., diminished capacity to formulate plans, impaired decision making, or uncharacteristic disregard for rules of convention; impaired spatial ability and orientation, i.e., difficulty driving or navigating familiar territory; impairment in language skills, i.e., word-finding difficulty or diminished capacity to follow conversations; changes in behavior, i.e., passivity or social withdrawal, new onset paranoia or suspiciousness, irritability, or misinterpretation of visual or auditory stimuli.

Clues apparent to the clinician might include changes in behavior such as a formerly punctual patient arriving at the wrong time for an appointment, inability to discuss current events or former interests, word-finding difficulties, or changes in hygiene or weight that may indicate personal neglect. The above described signs are similar to those suggested by Costa et al.²¹ and the Alzheimer's Association.²⁴

With the appearance of any of these symptoms of possible dementia, and as clinical judgment indicates, an initial assessment should be pursued. This assessment should include (1) a history from the patient corroborated by an informed source, (2) an assessment of cognition, (3) a physical and neurologic examination, and (4) laboratory testing.

History

A detailed history is critical in the assessment of dementia. The history must be corroborated and supplemented by an informed source. This is necessary not only because of the patient's memory loss, but also because the patient may have impaired insight regarding the severity of cognitive decline. Informants may also be able to provide information regarding the patient's function in other cognitive domains. Often, it is the information from others that is most valuable in assessing symptoms of decline in those with higher levels of education when MMSE scores might be normal or in the earliest stages of the disease when declines are evident only to those closest to the patient. The clinician must be aware, however, that informants may have other motives for either minimizing or exaggerating the patient's symptoms. It is therefore desirable to have information from multiple sources to provide the most accurate and comprehensive history.

The history should focus on eliciting information about the duration of symptoms, onset (sudden vs. gradual), and progression (gradual vs. stepwise deterioration). This information will guide the clinician in the formulation of differential diagnoses, appropriate laboratory workup, and consideration of referrals.

Assessment of Cognition

Universal, routine screening for dementia is impractical and inaccurate due to multiple confounding variables. In lieu of this, the clinician must be aware of changes from baseline in cognition and/or functional ability in their elderly patient population that can serve as triggers, as previously discussed. The clinician may consider assessing cognition as part of an annual examination in their patients aged 65 years and older.

Multiple tests currently exist that provide valid, quantifiable measures of cognition. Ideally, the test should assess all areas of functioning affected by Alzheimer's disease; be easy to administer, score, and interpret; and be brief enough to be practical in the office setting. Of the available tests, the MMSE meets all of these criteria.

There are other tests, including the 26-item Blessed Information Memory and Concentration test,^{25,26} that are essentially equal in validity, reliability, and ability to differentiate between cognitively impaired and nonimpaired persons. One of these tests should be used to establish a baseline and assess subsequent declines or improvements on repeated administration. They are particularly useful in reassessment after treatment of reversible conditions such as depression and delirium. Serial tests revealing a trend of progressively lower scores may be of some assistance when utilized in confronting the denial or limited insight of the patient or significant others affected by the disease.

As there is no clearly superior test, it is recommended that the clinician become expert in the administration, scoring, and interpretation of 1 or 2 of these measures and

use them consistently in baseline and subsequent testing of their patients.

Unfortunately, in the very mildly impaired or in those with high levels of education, the MMSE or other tests may not be sensitive enough to detect early cognitive impairment.²⁷ More extensive neuropsychological testing is a consideration when uncertainty regarding the diagnosis persists. Neuropsychological testing may also be necessary for individuals with uncorrectable deficits in vision, speech, hearing, or other physical disability. This type of testing is also indicated when there is a discrepancy between cognition as assessed with standard cognitive testing and functional status.

It is crucial to recognize that despite the tests used for assessment, none can be viewed as diagnostic. All instruments must be interpreted in conjunction with the complete assessment and the use of clinical judgment. Information from multiple data sources increases the validity of the assessment.

Activities of Daily Living Status Assessment

Assessment of functional status should be undertaken as part of an initial screening for Alzheimer's disease. As with assessment of cognition, it is recommended that the clinician become familiar with the use of 1 or 2 standardized assessment tools and use them consistently to assess changes during follow-up examinations of the patient. Two examples of assessment instruments are the Activities of Daily Living²⁸ and the Functional Activities Questionnaire.²⁹

COMPREHENSIVE PHYSICAL AND NEUROLOGIC EXAMINATION

Medical conditions and medications can cause or contribute to cognitive impairment in suspected Alzheimer's disease. The focus of the examination should be on any illness, physical condition, or medication that may affect mental and functional abilities and to identify reversible illness or deficiencies. Consideration must be given to the discontinuation of any medication that may be contributing to cognitive and/or functional decline. The patient and informant should be queried regarding any exposure to heavy metals and toxins. An essential component of this examination is an alcohol and other substance abuse assessment.

The patient should be counseled to bring in all medications to the evaluation appointment for review by the clinician. It should be stressed that over-the-counter medications be included, as patients frequently do not consider these to be "real" medications. In subsequent visits, all medications should be reviewed and assessed for the possibility of discontinuation, if possible, to decrease the risk of interactions in the polypharmacy so prevalent in this population.

Additionally, environmental and psychosocial stressors must be assessed, such as recent geographical moves, deaths of or illness in significant others, changes in social support systems, legal/financial issues, and life cycle adjustments such as retirement.

The clinician must be especially alert for symptoms of delirium and depression. The elderly population is at high risk for the development of both of these disorders. Moreover, clinicians frequently underdiagnose, misdiagnose, or fail to recognize these conditions. As delirium and depression are both associated with high rates of morbidity and mortality, it is imperative that the clinician entertain them in the differential diagnoses and, if present, treat them promptly.

The diagnosis of delirium and depression is complicated by the fact that these conditions can frequently occur with dementia. Depression, although it can occur at any stage of Alzheimer's disease, frequently presents prior to any significant cognitive decline. As such, it can be seen as a harbinger of Alzheimer's disease or as part of the prodromal symptomatology.³⁰ Moreover, treatment of depression with antidepressants that have anticholinergic effects may exacerbate an underlying dementia or cause delirium in this vulnerable population. Delirium is a medical emergency that must be treated promptly. Additionally, failure to recognize dementia by making a misdiagnosis has the potential to create undue distress for the patient and the caregivers, as well as further delaying available intervention.

The primary focus of the neurologic examination is to facilitate decision making for the differential diagnosis and to determine if there are abnormalities in the nervous system that contribute to altered mental status. Once again, the patient's presenting complaints and symptoms, history, and clinical judgment, in association with neurologic findings, combine to increase the validity of a diagnosis of Alzheimer's disease, uncover reversible causes of dementia, or diagnose and treat unrecognized neurologic disorders.

Specifically, the neurologic examination will focus on ruling out focal abnormalities, i.e., stroke, masses, trauma, and infection. Additionally, processes associated with dementing illnesses can be assessed, i.e., Parkinson's disease, Huntington's chorea, Pick's disease, and normal pressure hydrocephalus. Lewy body disease, a variant of Alzheimer's disease that has received increased attention and recognition, is characterized by progressive cognitive decline with social or occupational dysfunction, fluctuations in attention, detailed visual hallucinations, and the spontaneous motor features of parkinsonism. Significant memory loss may not be evident until the disease progresses.³¹ Findings on the neurologic examination will guide decisions regarding laboratory work-up.

Laboratory Testing

Uncovering reversible dementias is difficult; however, thorough laboratory testing of selected blood tests is vital

to rule out correctable causes. Standard blood testing in the assessment of dementia should include complete blood count, SMA 19, vitamin B₁₂ and folate levels, thyroid screening, tests for sexually transmitted disease, and, if indicated, screening for heavy metals. Findings on the physical examinations or history may warrant pursuing other laboratory testing. Chest x-ray and electrocardiogram may be ordered on the basis of the history and presenting symptoms.

Although computed tomography (CT) and magnetic resonance imaging scans are not diagnostic for Alzheimer's disease, many clinicians and experts recommend them. They may be considered optional unless the patient presents with focal neurologic signs or symptoms. In its consensus statement on practice parameters for the diagnosis and evaluation of dementia, the American Academy of Neurology (AAN) stated:

Neuroimaging should be considered in every patient with dementia based on the clinical presentation and may facilitate identification of potentially treatable conditions that can otherwise be missed, such as tumors, subdural hematomas, hydrocephalus, and strokes. However, these conditions are uncommon when not anticipated clinically, particularly when clinical evaluations are performed by experienced examiners. In particular, there is no consensus on the need for such studies in the evaluation of patients with the insidious onset of dementia after age 60 without focal signs or symptoms, seizures, or gait disturbances.³²

If used, non-contrast CT is generally adequate and can identify cerebral atrophy and diffuse white matter disease.

The AAN additionally recommends in their practice parameters that lumbar puncture and electroencephalogram should not be considered as routine studies but should be pursued only in special instances such as dementia in a person under age 55 or for suspected Creutzfeldt-Jakob disease.³²

Apolipoprotein E (ApoE) testing for Alzheimer's disease has received considerable attention and created a great deal of controversy. Regarding this issue, the American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer's disease stated that

at the present time, it is not recommended for use in routine clinical diagnosis nor should it be used for predictive testing. Studies to date indicate that the ApoE genotype alone does not provide sufficient sensitivity or specificity to allow genotyping to be used as a diagnostic test.^{33(p1627)}

The advice given in the guidelines proposed by the National Institutes of Health regarding the differential diagnosis of dementia is as follows:

Dementia is a clinical state diagnosable only by clinical methods. . . . A laboratory test whether chemical, biological,

imaging or psychological, should never be used as a substitute for the physician's time, expertise and clinical judgment.^{34(p3416)}

In an attempt to further guide the clinician, a flowchart for the recognition and assessment of Alzheimer's disease and related dementias developed by the U.S. Department of Health and Human Services²⁰ (Figure 1) is provided.

Management Issues

During the evaluation phase, emphasis must be placed on establishing a positive relationship with the patient and significant others. A partnership between clinician and those affected by the disease can be instrumental in determining the way coping and adjustment will proceed. The clinician has the responsibility of serving as educator, advocate, mediator, and source of support and affirmation, as well as managing the psychiatric symptoms that occur in the course of the disease process. To this end, regularly scheduled visits every 3 to 6 months for health maintenance and routine patient assessment will assist in maximizing independence and functioning, and minimize behavioral disturbances associated with the progression of the disease.

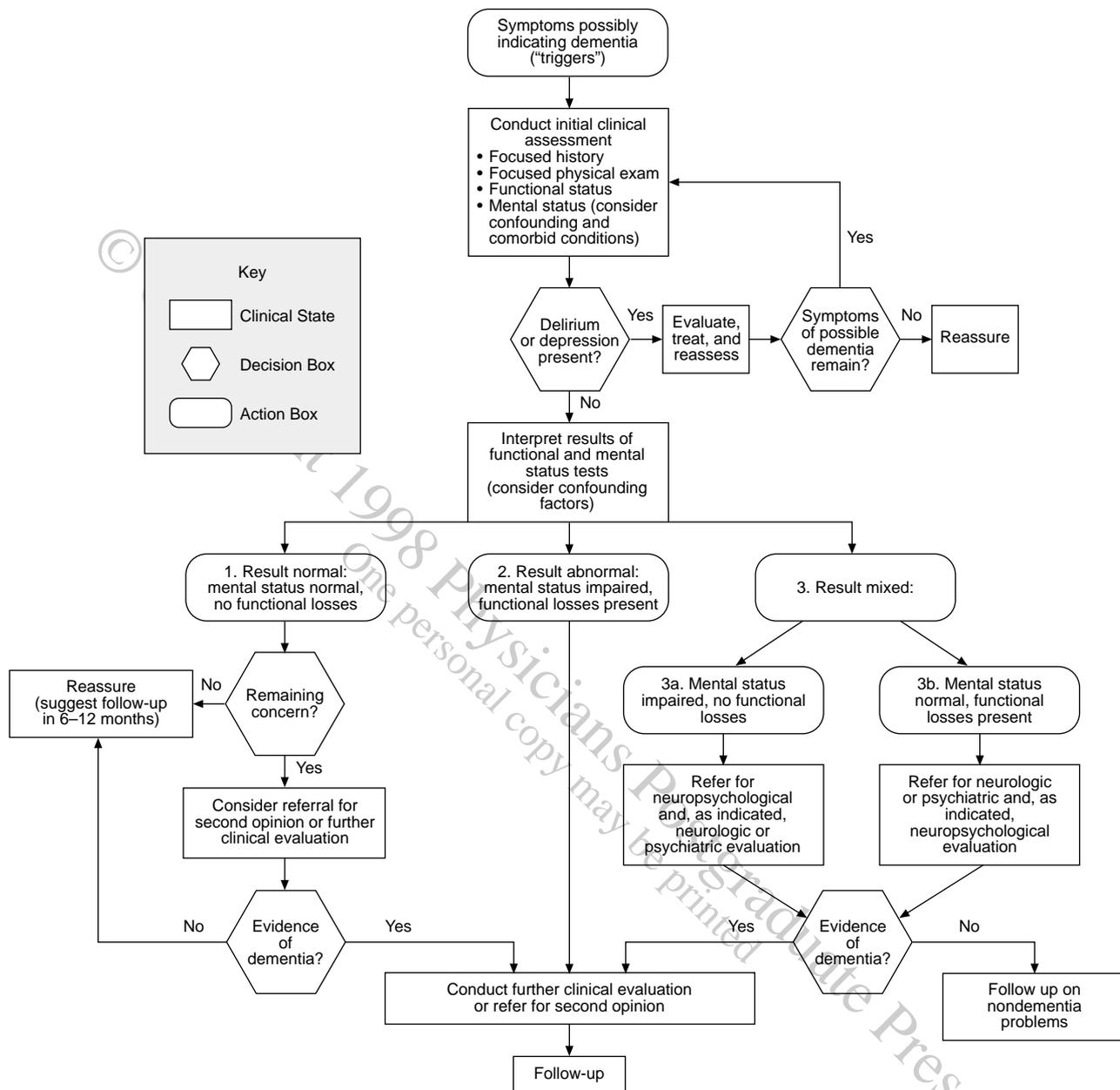
During the workup and in disclosing the diagnosis to the patient and the family, the clinician begins to educate about Alzheimer's disease. This discussion should include a frank, honest, balanced view of what is known about the disease process and available treatment options. Education regarding the recognition of current symptoms and the symptoms likely to occur with progression of the disease will assist in formulating plans for safety and health maintenance. Additional sources of education should be provided. These may include material written for the lay person such as *The 36-Hour Day*³⁵ and *Forget Me Not*.³⁶

Referrals to local and national groups dedicated to the education and support of patients with Alzheimer's disease is strongly recommended. Information about agencies such as the Administration on Aging ([202]-619-1006), the Alzheimer's Association ([800]-272-3900), and the Alzheimer's Disease Education and Referral Center ([800]-438-4380) should be provided.

Proactive, early planning for the progressive decline of the patient should be encouraged. In the early stages of the illness, the patient and the family should be counseled to take care of "old business," such as resolving communication issues, prioritizing values, and enjoying interests that may have been deferred.

It is also necessary to begin discussion about options for supportive care. Options may include both formal and informal supports. Informal supports include family members and friends that may be willing to provide respite for the primary caregiver and support to the patient by assisting with transportation, shopping, and other activities. Formal options include the visiting nurse associations,

Figure 1. Flowchart for Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias*



*From reference 21.

home-health agencies, religious and civic organizations, and adult day-care centers. Families should also be advised to think about the possibility of long-term nursing home placement for the time that care needs exceed what the family is able to provide.

It is additionally imperative to address legal and financial issues. Open discussions regarding role and responsibility changes within the family system should be encouraged. Assignment of durable power of attorney and discussion of end-of-life issues, including living wills and the updating of wills, should be addressed while the pa-

tient is competent to make informed decisions regarding these concerns. The clinician is advised to investigate local resources to assist in providing appropriate referrals. An additional resource is the American Bar Association Commission on Legal Problems of the Elderly ([202]-662-8690).

To assist the clinician, patient, and caregivers, it is advisable to consider referrals to consultants that specialize in the care of those with Alzheimer's disease. These consultants may include geriatric psychiatrists and clinical nurse specialists who can provide invaluable assistance in

the management of behavioral symptoms that may develop as the disease progresses or in the management of comorbid psychiatric illness. Social workers may assist the family and bolster its ability to cope with this chronic illness through the introduction of community supports and resources. All of the above disciplines can provide psychotherapy or counseling to identify and support adaptive coping mechanisms and provide ongoing education and support for the patients and their caregivers.

Quality-of-life issues for all affected must also be approached. Patients and their caregivers will require support, affirmation, and recognition. All involved must be warned of the dangers of emotionally and physically depleting themselves, and regular assessments must be made to screen for psychiatric disorders in patients and their caregivers. Encouragement to properly care for oneself is crucial. The availability of the clinician throughout the disease course and the multiple losses and grieving that are inherent in this devastating illness can make a crucial difference in determining how long a patient and caregivers are able to remain at a level of functioning that permits community dwelling and supports quality of life.

Drug name: tacrine (Cognex).

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