Advances in Alzheimer's Disease

A Review for the Family Physician

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Alzheimer's disease accounts for approximately two thirds of all cases of dementia in the United States and $90 billion in health care costs annually. Clinical and laboratory diagnostic tools have been refined so that clinicians now can diagnose Alzheimer's disease with up to 90% accuracy. Criteria for clinical diagnosis have been outlined by a work group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. Key diagnostic tools include a complete patient history, mental status testing, and a thorough diagnostic workup to exclude the possibility of a reversible disease mimicking the symptoms of Alzheimer's disease. Currently, management of Alzheimer's disease involves a two-pronged approach: behavioral-supportive care and pharmacologic control of disruptive behavioral symptoms. In the future, drug therapy may be available to maintain memory and cognitive function. Cholinesterase inhibitors, which block the decrease in choline acetyltransferase activity associated with Alzheimer's disease, appear promising. The realistic goal of health care providers at the present time, however, should be symptom control rather than disease reversal.

Key words. Alzheimer's disease; dementia; patient care planning; cholinesterase inhibitors. (*J Fam Pract 1993; 37:593-607*)

Alzheimer's disease is one of the most ironic and tragic consequences of modern medicine's success in prolonging survival until the 7th, 8th, and even 9th decade of life. Family physicians can expect to encounter this relentless and debilitating disorder in an estimated 1 of 1000 patients aged 60 to 65 years of age, in 4 of 100 patients over 65 years of age, and in as many as half of patients over 85 years of age.[1]

In personal terms, Alzheimer's disease spells devastation for patient and family. Its course is characterized by worsening memory loss and personality changes (sometimes including psychotic behavior), progressing to global confusion, and ultimately, to complete cognitive disintegration. The death rate among patients with Alzheimer's disease is two to four times greater than that among unaffected subjects of the same age, and it has been suggested that the disease has become the third or fourth ranking cause of death (usually resulting from pneumonia)[2] among people between the ages of 75 and 85 years.[3]

Alzheimer's disease has now emerged as the leading cause of dementia before and after age 65 years, accounting for two thirds of all cases of dementia. As such, its public health impact is enormous. Alzheimer's disease affects approximately 4 million people and is the most common reason for admitting someone to a nursing home in the United States.[3–5] According to one widely cited analysis performed in 1987, the annual costs for a family to care for a patient with Alzheimer's disease amount to over $18,000[6]; the annual bill for the nation as a whole has now reached $90 billion.[4] As the US population ages, the financial and human toll of Alzheimer's disease will continue to increase.

Many clinicians regard the diagnosis and management of dementia with frustration, if not fatalism. Such an attitude, however, is unwarranted. First, dementia

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may stem from any of a number of medically or surgically correctable conditions unrelated to Alzheimer's disease. Since the cognitive impairment associated with these conditions is only reversible if identified and treated early,[7] a thorough diagnostic workup is always required in patients with suspected Alzheimer's disease. Second, although there is still no pharmacologic "quick fix" for Alzheimer's disease, recent research has sparked the development of promising new drugs that may help reverse or slow memory loss and cognitive impairment. Alzheimer's disease is one of several currently irreversible dementias and requires precise diagnosis. As with many other chronic disorders of older patients, reasonable therapeutic goals are improvement, control, or slowing of progression, rather than cure. Newly available therapies, including behavioral, environmental, and pharmacologic approaches, may permit a more active and optimistic approach to the management of Alzheimer's disease. New therapies may even alter the clinical course of Alzheimer's disease if the disorder can be diagnosed and treated early.

This review provides a summary of the most current research regarding the causes, diagnosis, and management of the disease, and potential therapies that may be used to treat Alzheimer's disease.

What Causes Alzheimer's Disease?

Histopathologic Features

It was 85 years ago that Alois Alzheimer first published his classic description of cerebral cortical changes in a middle-aged woman who had died with progressive dementia. Alzheimer's findings are still the defining pathologic features of the disease that now bears his name.

Changes found in all patients with Alzheimer's disease include neurofibrillary tangles (tangles of fibers); neuritic plaques (clusters of degenerating nerve endings); widespread, nonuniform atrophy of the brain; and loss of predominately large neurons and synapses.[5] Cell loss, plaques, and tangles regularly occur in the neocortex (especially the association areas) and the hippocampus. Loss of cholinergic neurons from the basal nucleus of Meynert is a common finding. A less common finding is the loss of serotonergic neurons from the dorsal segmental nuclei, and noradrenergic neurons from the locus serialize.[8] Conversely, the primary motor, somatosensory, and visual cornices tend to be spared.[1] In addition, the brains of patients with Alzheimer's disease weigh some 10% to 15% less than those of age-matched controls. There is some overlap, however, since with normal aging the brain atrophies and decreases in weight.[5] The more typical changes found in Alzheimer's-type dementia contrast with changes observed during the normal aging process (Table 1).

Table 1. Brain Changes in Alzheimer's-Type Dementia Compared With Normal Aging Process

Alzheimer's-Type Dementia	Normal Aging
• Senile plaques throughout the general cortex	• Senile plaques absent or scanty
• Large numbers of neurofibrillary tangles in medial temporal structures, including the hippocampus; also frequently present in the general cortex	• Neurofibrillary tangles absent or scanty; if present, usually confined to the hippocampus
• Granulovacuolar degeneration and Hirano bodies in hippocampus frequent	• Much less frequent
• Severe cholinergic deficit present	• Absent
• Marked reduction of brain weight: brains from patients with Alzheimer's-type dementia weigh ± 10%–15% less than those from age-matched nondemented persons	• 7%–10% reduction of brain weight by the 9th decade

NOTE: The important feature is that the brain changes in Alzheimer's-type dementia appear in combination and profusion.
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Neurochemical Alterations

A good correlation exists between the histopathological changes, neurochemical abnormalities, and some cognitive and memory deficits found in patients with Alzheimer's disease. For example, loss of neurons from the basal nucleus of Meynert has been associated with a concomitant decrease in cholinergic function, and this decrease in cholinergic function has been linked to memory dysfunction.

The above relationship, termed *the cholinergic hypothesis of memory dysfunction,* theorizes that changes in cholinergic activity occur in the brains of patients with dementia, and that these changes play an important role in contributing to the memory loss and cognitive problems seen in patients with Alzheimer's disease. Thus, it follows that improvement of cholinergic function by drugs that enhance cholinergic transmission should also improve some of the symptoms of dementia. The evidence in support of a cholinergic involvement in Alzheimer's disease follows.

Choline acetyltransferase (CAT) is the enzyme responsible for the formation of the neurotransmitter acetylcholine. Autopsy analysis of the brains of patients with Alzheimer's disease show a 40% to 90% reduction in

CAT activity in the cerebral cortex and hippocampus,[5] brain areas traditionally associated with learning. This decrease in CAT activity is considered one of the chief biochemical hallmarks of Alzheimer's disease and correlates well with the degeneration of neurons originating in the basal nucleus of Meynert and projecting into the hippocampus and cortex.[9] The loss of CAT, which begins as early as the first year of Alzheimer's disease,[5] is far more severe and consistent than the cholinergic deficit associated with decreased muscarinic receptor density in normal aging.[10] In addition, some studies have revealed the synthesis of acetylcholine in biopsy samples from patients with Alzheimer's disease to be less than that in those of age-matched controls.[10]

Evidence linking the cholinergic deficit with memory loss has been supported by experimentation in which deficits in learning were produced from the destruction or blockade of cholinergic neurons.[11] For example, animal studies have shown that the surgical or pharmacological destruction of cholinergic neurons results in memory impairment.[9] Injections of the anticholinergic agent scopolamine into healthy young subjects results in the development of confusion and memory loss, resembling the symptoms of early Alzheimer's disease.[5] Similar effects on memory have not been observed after adrenergic or dopaminergic receptor blockade.[10] Most important, the loss of CAT activity in patients with Alzheimer's disease correlates well with declining cognitive function as well as with the density of neuritic plaques and neurofibrillary tangles.[9] Similar cortical cholinergic deficits are found in a number of degenerative diseases that cause memory loss, including Parkinson's disease associated with dementia.[11]

The literature supports the theory that the cholinergic deficit in patients with Alzheimer's disease contributes to their symptoms. Therefore, enhancement of cholinergic activity by pharmacological manipulation may improve memory and cognitive function in these patients. Many clinical trials have suggested that cholinergic enhancers do have a beneficial therapeutic role in the treatment of Alzheimer's disease. The most promising of these new agents will be discussed.

In addition to changes in cholinergic function, patients with Alzheimer's disease may also show changes in the noradrenergic, dopaminergic, serotonergic, and somatostatin neurotransmitter systems. Included among these changes is neuron degeneration.[9] These changes, however, are not as consistent a finding as the cholinergic deficit.[9] Some of these changes are most striking in younger patients with Alzheimer's disease, while others occur only in advanced cases of this disease.[11] Other than the cholinergic deficit, the only neurochemical abnormality that correlates with the severity of dementia is a reduction in cortical somatostatin.[12] Still to be determined is whether changes in these neurotransmitter systems contribute to cognitive impairment and how.[11]

The presence of neurofibrillary tangles and neuritic plaques consisting of a core of excess β-amyloid peptide (28 to 43 amino acids) have been identified early in the course of Alzheimer's disease, and both the presence of neurofibrillary tangles and the density of plaques appear to correlate with the onset of dementia.[13] The β-amyloid peptide is a fragment of amyloid precursor protein, cleaved off excessively as a product of protease activity occurring both at the meningovascular and peripheral level (particularly within platelets); β-amyloid deposition appears in patients with early-stage Alzheimer's disease, young people with Down's syndrome, and up to 80% of the normal elderly over the age of 80 years.[13] Demonstration of the direct toxicity to the neuron caused by β-amyloid peptide, together with the theory of excess activity of proteases allow the supposition that new therapy for Alzheimer's disease may be focused upon developing protease inhibitors and tachykinin neuropeptides to block the neurotoxicity.

Risk Factors

There are dozens of possible risk factors for Alzheimer's disease and, in practical terms, these risk factors may support the overall diagnostic picture in an individual patient. However, the means of modifying risk factors to prevent Alzheimer's disease have not yet been determined.

Although Alzheimer's disease is not an inevitable accompaniment of growing older, age is still the leading risk factor for Alzheimer's disease. The likelihood of developing Alzheimer's disease reportedly doubles every 4.5 years up to the age of 95.[14]

Family history ranks second as a risk factor. Some 40% of patients with Alzheimer's disease have a close relative who also had the disease. It has been suggested that there are two forms of Alzheimer's disease: familial and sporadic, which is assumed to be of other than genetic origin. Both forms seem to be identical in clinical presentation, although familial Alzheimer's disease appears to have an earlier onset.[15] Familial Alzheimer's disease is thought to be an autosomal dominant hereditary disorder, and studies have suggested that a gene on chromosome 21, 19, or 14 may be involved in the development of Alzheimer's disease.[1,15] A connection that may be relevant is that patients with Down's syndrome (chromosome 21 truism) who survive past the age of 40 years experience neuropathologic and neurochemical changes similar to those in patients with Alzheimer's disease.[1,5] These changes include the development of

plaques and tangles, and the loss of choline acetyltransferase in the neocortex and hippocampus in the same distribution as that of typical patients with Alzheimer's disease.[5] Patients with Down's syndrome produce 50% more amyloid B/A-4 protein precursor than individuals without Down's syndrome. Accumulations of amyloid deposits can be found in brains of persons with Down's syndrome in their late teens and early 20s,[1] which might very well represent the earliest structural abnormality yet detected in the brain tissues of patients with Alzheimer's disease or Down's syndrome.[16] However, nongenetic factors also must be important, given that the majority of patients with Alzheimer's disease have no family history of the disease and the concordance in identical twins is only 50%[1]

Epidemiologic studies indicate that head trauma may be a risk factor for Alzheimer's disease.[5] It is possible that the injury leads to loss of neurons[14] or to plaque formation.[1] Interestingly, boxers who become "punch drunk" develop neurofibrillary tangles in the cortex[5,14] besides the parkinsonian-like "dementia pugilista."

Other suggested risk factors include being female,[14] lack of formal education,[1,14] and exposure to aluminum,[17] as well as a whole host of somatic disorders including thyroid disease, diabetes, congestive heart failure, myocardial infarction, and vascular dementia.[1,5,14]

Diagnosis

The key questions to ask when considering the diagnosis of Alzheimer's disease are "Is this patient demented?" and "If so, what is the cause?"[18] The question of whether a patient's mental state is deteriorating must, of course, be judged in context.[19] In this regard, the primary care physician who has taken care of a patient for years and is familiar with his background is in an ideal position to identify dementia. Several studies have shown that family physicians are adept at recognizing dementia, frequently without formal mental status testing, and are quite successful at distinguishing mild to moderate dementia from the normal mental changes of aging.[7] Family physicians should be encouraged to inquire about the activities and functions their elderly patients can perform.

Clinical Diagnostic Criteria

Although a definitive diagnosis of Alzheimer's disease can be made only by cerebral biopsy or autopsy, highly specific clinical and laboratory criteria allow clinicians to diagnose the condition with 90% accuracy.[5] A working group of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) has outlined criteria for clinical diagnosis,[20] which are summarized in Table 2. The chief diagnostic criteria for Alzheimer's disease in a patient between the ages of 40 and 90 years are slowly progressive memory loss and deterioration in at least two cognitive functions, such as language use, perception, motor skills, learning ability, problem solving, abstract thought, and judgment. The impairment must be both severe enough to interfere with normal activities and not attributable to any other illness. Other associated features may include a family history of dementia, plateaus in disease progression, psychiatric symptoms (for example, alterations in mood, delusions, hallucinations, or catastrophic outbursts), and motor abnormalities or seizures in advanced disease. On the other hand, clinicians should suspect a disorder other than Alzheimer's disease if the clinical picture develops suddenly, or if the patient has clouding of consciousness, focal necrologic findings, or seizures or gait disturbances early in the course of illness.[20]

Relying solely on these clinical criteria, however, has its pitfalls. Alzheimer's disease may overlap or coexist with other dominating illnesses, such as multi-infarct dementia or Parkinson's disease. Alzheimer's disease may also be mimicked clinically by such uncommon necrologic disorders as Pick's disease and Creutzfeldt-Jakob disease.[21]

In addition, a small but significant percentage of systemic diseases can present as dementia.[22] A partial listing of these diseases[22] can be found in Table 3.

Evaluation of Patients

History

A careful history is the most critical part of the initial evaluation. Since patients with Alzheimer's disease are often unaware of their deficits, it is particularly important, if possible, to obtain a corroborating history from a close relative or friend.

First, the family physician should inquire about the patient's most troublesome symptoms and whether these have affected daily activities. It must be kept in mind that occasional forgetfulness not accompanied by other cognitive problems may simply represent age-associated memory impairment and does not necessarily signal dementia.[19,23] Specific questions include whether the patient can take care of his personal needs and household and financial responsibilities, whether he has difficulties driving, whether he becomes easily lost or disoriented, and whether he shows unusual irritability or agitation, or

Table 2. Criteria for Clinical Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition; progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65;
- and absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:
- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques,
  - normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; seizures in advanced disease; and CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:
- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:
- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:
- the clinical criteria for probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:
- familial occurrence;
- onset before age of 65;
- presence of trisomy-21; and
- coexistence of other relevant conditions such as Parkinson's disease.

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even paranoia.[19] Typically, in the early stages of Alzheimer's disease, immediate memory—the ability to repeat back just-learned information—tends to remain intact, but the longer-term retentive memory fails.[24] Seldom-used names of distant acquaintances or phone numbers, for example, are likely to be forgotten. With time, the retentive memory may be so affected that a patient may become unable to remember something learned a minute before.[24] The first signs of language impairment may be difficulties in finding the right word or forgetfulness about names.[24]

The next important point is to clarify the mode of onset, progression, and duration of these symptoms. Alzheimer's disease is a chronic degenerative disease that evolves gradually over many months and years. In contrast, if the symptoms develop over days or weeks, it is more likely depression, a central nervous system infection, or a brain tumor.[25] An underlying infection, or metabolic or toxic cause should be suspected if the patient's consciousness is clouded. A steps decline—that is, periods of sudden deterioration followed by periods of some improvement—suggests vascular (multi-infarct) dementia, particularly in a patient with a history of hypertension or other vascular disease.[23] Other signs associated with multi-infarct dementia include hemiparesis, abnormal gait, weakness, aphasia, and labile emotions. In older patients, depression may accentuate the root of cognitive impairment (so-called pseudodementia), and it is important to look for such clues as disturbed sleep, weight loss, sadness, and negativism. Unlike patients with Alzheimer's disease, depressed patients generally do not try to hide their memory lapses, and they may show distress

Table 3. Diseases That May Present as Dementia

Endocrine	Anemia
Hypothyroidism	Any cause
Hypoglycemia	
Hypercalcemia	Decreased cerebral blood flow
Cushing's disease	Congestive heart failure
	Bradyarrhythmias or tachyarrhythmias
Electrolyte disturbance	Cerebral emboli
Hyponatremia	Coagulopathy
Hyperosmolar states	Cerebral arteriosclerosis
	Cranial arteritis
Metabolic	
Metabolic acidosis	Infections
Metabolic alkalosis	Meningovascular syphilis
Hepatic encephalopathy	General paresis
Uremia	Subacute bacterial endocarditis
Carbon dioxide narcosis	Tuberculosis
	Acquired immunodeficiency syndrome
Nutritional deficiencies	
Thiamine (Wernicke-Korsakoff syndrome)	
Vitamin B_{12}	
Niacin (pellagra)	

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Table 4. Drugs That May Cause Central Nervous System Effects

Unpredictable CNS effects
Glucocorticoids (steroids)
Nonsteroidal antiinflammatory agents
H_2 blockers (cimetidine, ranitidine)
Antihistamines
Decongestants
Predictable CNS effects
Phenothiazines
Barbiturates
Benzodiazepines
Metabolic toxicities
Insulin
Sulfonylureas
Diuretics
Taken incorrectly
Digoxin
Aspirin

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over their forgetfulness.[23] Yet pseudodementia may be a major early presentation of early cognitive loss with severe depression. All such patients need to be treated for depression as part of the evaluation for early Alzheimer's disease.

The family physician must also rule out the possibility that drug side effects may be causing the patient's cognitive defects, especially in an elderly patient on multiple medications. Although most clinicians are aware of such culprits as psychoactive and neuroactive drugs, opiates, and steroids, less obvious causes may include anticholinergic agents, antihypertensive drugs, and digitalis.[19] A partial listing of drugs[26] that may cause central nervous system effects is listed in Table 4. Finally, the history should include questions about other relevant diseases, trauma, surgery, psychiatric disorders, alcohol intake, nutrition, exposure to environmental toxins, and family history of dementia, Down's syndrome, or psychiatric conditions.[19]

Mental Status Testing

Full mental status testing characterizes the extent of cognitive impairment and can be used to confirm the clinician's impression of dementia and to follow the course of the disease. Clinicians should consider administering the test themselves, if possible, so that they can observe the patient's responses and moods while watching for any signs of visual or hearing impairment.[19] A number of multi-scale tests commonly used in the diagnosis, prognosis, and treatment of dementia are listed in Table 5. Five major categories used in the assessment of Alzheimer's disease are: (1) comprehensive dementia assessment and (2) neuropsychologic tests, both used to document the core characteristics of Alzheimer's disease; (3) global staging methods, which measure disease severity; (4) measures of function (eg, activities of daily living) rating the patient's basic ability to function; and (5) assessments of noncognitive behavioral symptoms, which evaluate some of the symptoms of the disease that will give the most trouble to families and caregivers. This list is by no means exhaustive and is intended to provide the major scales and tests most commonly used by clinicians.

Short tests recommended for use by clinicians include the Mini-Mental State Examination, the Information-Orientation-Concentration scales of the Blessed Dementia Rating Scale, and the Mattis Dementia Rating Scale.[5,19] The overall rate of progression of cognitive decline in patients with Alzheimer's disease appears to be 4.1 Blessed points per year regardless of age of onset, duration of illness, and family history.[28] The widely used Mini-Mental State Examination,[29] shown in Table 6, is a brief screen for identifying deficits in orientation and memory, as well as in verbal, numerical, and spatial ability.[27,30] Its drawbacks are that it may falsely signal dementia in poorly educated patients and that it may miss very mild cases of dementia.[19,27] It is a mini-test—not a global scale. Scores on the Information-Memory-Concentration test reportedly correlate with the number of cortical plaques found at autopsy and with brain CAT

Table 5. Classification of Assessment Measures of Alzheimer's Disease

Category	Assessment Measure
Comprehensive dementia assessments	Blessed (BLS) rating instruments Mini-Mental State Examination (MMSE) Mattis Dementia Rating Scale (DRS) Brief Cognitive Rating Scale (BCRS) Alzheimer's Disease Assessment Scale (ADAS)
Neuropsychologic tests	NYU Computerized Test Battery Memory Assessment Clinics Test Battery SKT
Global staging scales	Global Deterioration Scale (GDS) Clinical Dementia Rating (CDR)
Activities of daily living (ADL)	Katz ADL Scale Physical-Self-Maintenance Scale (PSMS) Instrumental Activities of Daily Living (IADL) Functional Assessment Staging (FAST)
Noncognitive, behavioral assessments	Depression Geriatric Depression Scale Dementia Mood Assessment Scale (DMAS) Cornell Scale for Depression and Dementia Behavioral Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) Dementia Behavior Disturbance (DBD) Scale

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deficiency.[7,31] It shares the same limitations, however, as the Mini-Mental State examination.[19]

Of note is the newly developed Direct Assessment of Functional Status scale, which allows assessment of functional capacities that are typically affected by Alzheimer's disease.[32] A broad spectrum of behaviors within seven functional categories can be measured to help evaluate the progression of the disease as it affects a patient's ability to care for himself and engage in everyday activities. It can be administered in an outpatient setting, and has been found to have excellent test-retest reliabilities.[32]

The NINCDS-ADRDA Work Group has also advocated the use of the Hamilton Depression Scale for severity of depression; the Present State Examination for anxiety, depression, delusions, and hallucinations; and the Hachinski Scale for evaluating the possibility of multi-infarct dementia.[20]

Diagnostic Workup

The next step is to answer the question "Is this Alzheimer's disease?" by means of a complete physical and neurological examination as well as a laboratory assessment. A diagnostic algorithm is provided in the figure.

The differential diagnosis of Alzheimer's disease includes a wide spectrum of vascular, necrologic, infectious, and metabolic disorders. Most important of these are multi-infarct dementia, Parkinson's disease, brain tumor, thyroid disease, neurosyphilis, and other central nervous system infections, and pernicious anemia.[5,20] The human immunodeficiency virus is also a concern, and it is one that will grow as the baby boomers age. Dementia may also be caused by renal or hepatic encephalopathy or by hypoxia or hypercapnia associated with pulmonary disease.[19]

Sensory and motor examination should be normal in the early stages of Alzheimer's disease, except for such nonspecific signs as snout reflex, jaw jerk, rigidity, or myoclonus.[20] Signs of other dominating conditions include tremor, rigidity, and bradykinesia in parkinsonism, myoclonus and rigidity in Creutzfeldt-Jakob disease, flapping tremor in hepatic encephalopathy, writhing movements in Huntington's chorea, focal signs and abnormal gait in multi-infarct dementia, and gait apraxia in normal pressure hydrocephalus.[23]

All patients with suspected Alzheimer's disease should have a chest radiography and an electrocardiogram to rule out the presence of ischemic heart disease, which may result in cerebral ischemia and manifest as dementia.[19] Laboratory screening should include thyroid function tests, serologic testing for syphilis and human immunodeficiency antibodies, and vitamin B_{12} and foliate determinations.[5,19] Also indicated are a complete blood count, electrolyte panel, screening metabolic panel, urinalysis, and an electrocardiogram.[19] Cerebrospinal fluid examination may be helpful if a chronic infection is suspected.[5] The electroencephalogram should be normal or may demonstrate such nonspecific signs as increased slow-wave activity or increased latency of P300 potentials.[20]

Computed tomography scanning or magnetic resonance imaging should be a routine part of the diagnostic workup of the patient with dementia.[33] The computed tomography(CT) scan is invaluable for detecting such potentially treatable conditions as subdural hematoma, brain tumor, hydrocephalus, and vascular lesions. It should be stressed that such disorders do not always produce focal neurologic signs.[23,33] In patients with Alzheimer's disease, CT scans may show evidence of cerebral atrophy, but the findings are general patterns and not diagnostic criteria. Magnetic resonance imaging(MRI) is an even more sensitive scanning technique, allowing the identification of smaller infarcts in the brain.[19,33] Care must be taken, however, to avoid misinterpreting ambiguous findings;the sensitivity of MRI white matter lesions

Table 6. The Mini-Mental State Examination: A Tool for Cognitive Screening of Patients with Suspected Alzheimer's Disease

I. Orientation (Maximum score 10)	
Ask "What is today's date?" Then ask specifically for parts omitted; eg, "Can you also tell me what season it is?"	Date (eg, January 21) ..... 1 ___ Year ..... 2 ___ Month ..... 3 ___ Day (eg, Monday) ..... 4 ___ Season ..... 5 ___
Ask "Can you tell me the name of this hospital?" "What floor are we on?" "What town (or city) are we in?" "What county are we in?" "What state are we in?"	Hospital ..... 6 ___ Floor ..... 7 ___ Town/City ..... 8 ___ County ..... 9 ___ State ..... 10 ___
II. Registration (Maximum score 3)	
Ask the subject if you may test his/her memory. Then say "ball," "flag," "tree," clearly and slowly, about one second for each. After you have said all 3 words, ask subject to repeat them. This first repetition determines the score (0–3), but keep saying them (up to 6 trials) until the subject can repeat all 3 words. If (s)he does not eventually learn all three, recall cannot be meaningfully tested.	"ball" ..... 11 ___ "flag" ..... 12 ___ "tree" ..... 13 ___ Record number of trials: ___
III. Attention and calculation (Maximum score 5)	
Ask the subject to begin at 100 and count backward by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score one point for each correct number.	"93" ..... 14 ___ "86" ..... 15 ___ "79" ..... 16 ___ "72" ..... 17 ___ "65" ..... 18 ___
If the subject cannot or will not perform this task, ask him/her to spell the word "world" backwards (D, L, R, O, W). The score is one point for each correctly placed letter, eg, DLROW = 5; DLORW = 3. Record how the subject spelled "world" backwards: _____ D L R O W	OR Number of correctly-placed letters ..... 19 ___
IV. Recall (Maximum score 3)	
Ask the subject to recall the three words you previously asked him/her to remember (learned in Registration)	"ball" ..... 20 ___ "flag" ..... 21 ___ "tree" ..... 22 ___
V. Language (Maximum score 9)	
Naming: Show the subject a wrist watch and ask "What is this?" Repeat for pencil. Score one point for each item named correctly.	Watch ..... 23 ___ Pencil ..... 24 ___
Repetition: Ask the subject to repeat, "No ifs, ands, or buts." Score one point for correct repetition.	Repetition ..... 25 ___
3-Stage Command: Give the subject a piece of blank paper and say, "Take the paper in your right hand, fold it in half and put it on the floor." Score one point for each action performed correctly.	Takes in right hand ..... 26 ___ Folds in half ..... 27 ___ Puts on floor ..... 28 ___
Reading: On a blank piece of paper, print the sentence "Close your eyes" in letters large enough for the subject to see clearly. Ask subject to read it and do what it says. Score correct only if (s)he actually closes his/her eyes.	Closes eyes ..... 29 ___
Writing: Give the subject a blank piece of paper and ask him/her to write a sentence. It is to be written spontaneously. It must contain a subject and verb and make sense. Correct grammar and punctuation are not necessary	Writes sentence ..... 30 ___
Copying: On a clean piece of paper, draw intersecting pentagons, each side about 1 inch, and ask subject to copy it exactly as it is. All 10 angles must be present and two must intersect to score 1 point. Tremor and rotation are ignored. Eg, 	Draws pentagons ..... 31 ___
Score: Add number of correct responses. In section III, include items 14–18 or item 19, not both. (Maximum total score 30)	Total score ___
Rate subject's level of consciousness: _____(a) coma, (b) stupor, (c) drowsy, (d) alert	

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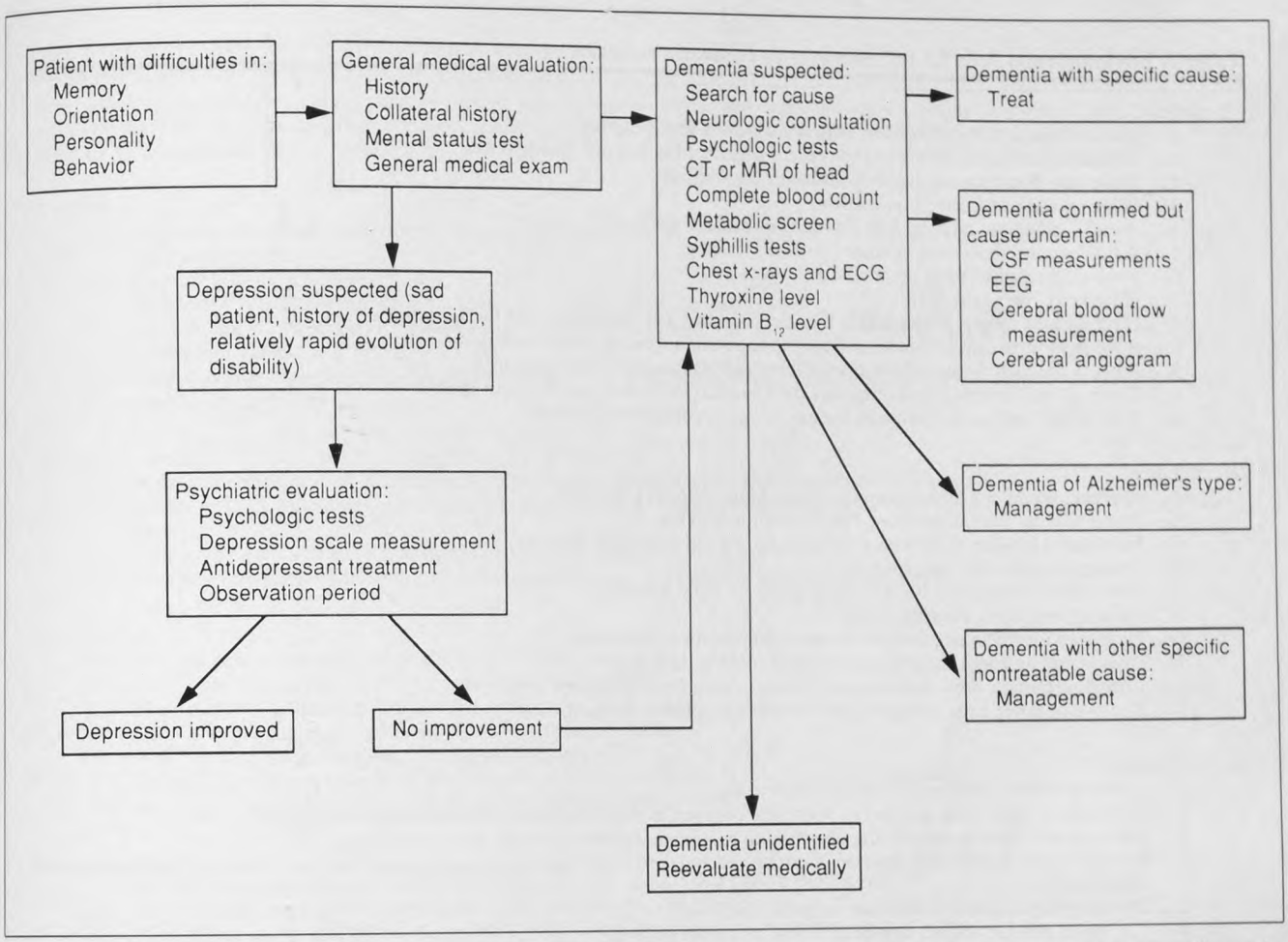

Figure. Algorithm for the diagnostic workup of Alzheimer's disease. Adapted with permission from Kokmen E. Etiology, diagnosis, and management of dementia. Compr Ther 1989; 15:59.

has led to physicians' overdiagnosing of vascular dementia.[19,33]

Management

The management of Alzheimer's disease involves a three-pronged approach. The first of these is nonpharmacologic, or essentially behavioral-supportive, care. Second is a pharmacologic control of associated disruptive behavioral symptoms with neuroleptics, sedatives, and anxiolytics. The third and newest option is the use of medication to maintain memory and cognitive function and to potentially alter the course of the disease.

Family physicians must remember that because a specific disease is labeled terminal or progressive it does not mean it is not treatable. There are a number of chronic conditions, such as diabetes mellitus, congestive heart failure, and degenerative arthritis, for which cures do not exist, and the treatment for these diseases is often symptomatic rather than pathology specific.[26]

Supportive Care

The family physician plays an important role in coordinating supportive care measures with the patient's family. The key to supportive care is to keep the patient socialized and mentally and physically active in a safe but stimulating environment.[5,34] Some environmental aids[35] that should provide the patient with the best possible environment for him to function are listed in Table 7. Patients with Alzheimer's disease cope best in nonstressful, structured, familiar, and constant surroundings. Some memory aids[35] that should be employed are listed in Table 8. A useful suggestion for patient and family may be to post daily schedules, pictures of family members, and signs that point to the location of household objects.[24] Activities that may help preserve cognitive

Table 7. Environmental Aids for the Patient with Alzheimer's Disease

I. Safety
- A. Use combination locks on doors between wards or to the outside.
- B. Dismantle bathroom door locks to prevent patients from locking themselves in.
- C. Make sure floors are not highly polished to prevent falls.
- D. Wipe up spills and urine immediately.
- E. Avoid candles and artificial fruit that can be mistaken for food.
- F. Adjust water temperature in faucets to avoid scalding.
- G. Keep medications locked up at all times.
- H. Have beds low to the floor.
- I. Have padded tongue blades visible in patients' rooms and recreation areas for use in seizures.
- J. Place signs at patient's bedside or doorway to room, indicating special care needs.
- K. Provide adequate light without glare. Older patients usually require extra light.
- L. Teach all staff members and caregivers the Heimlich method to use if patient chokes.
- M. Place bright tape on bottom step because of depth perception problems.

II. Stability
- A. Maintain consistent furniture arrangement. Make changes gradually.
- B. Avoid moving patient from one bed or room to another.
- C. Have items familiar to individual in environment and encourage their use.
- D. Maintain predictable daily routines.
- E. Take history of patient's habits. Use as guide for daily activities.
- F. Develop long-term, consistent staff.
- G. Have staff members establish one-to-one relationships with patients.
- H. Avoid entering room suddenly, especially if room is darkened.
- I. Change dressings, dress and undress patients in own room or private area.
- J. Remove or cover large mirrors if patients become agitated by them.

III. Stimulation
- A. Create a cheerful environment using vibrant colors.
- B. Avoid use of light blues and greens with aged patients, as they often have difficulty seeing these colors.
- C. Decorate with visually stimulating objects such as posters, mobiles, pictures, and tropical fish.
- D. Provide large calendars and draw an X through each day to orient patients in time. Large clocks and seasonal decorations also orient patients.
- E. Provide bulletin boards and classes in reality orientation.
- F. Use touch and eye contact as well as words to contact patients.
- G. Encourage visits by family, friends, children, and pets.
- H. Monitor radios, stereos, and TVs for noise levels.
- I. Remove patients from areas of excessive noise and activity.
- J. Introduce reminiscence group therapy in early phases of disease.

IV. Freedom and Mobility
- A. Provide open space so that patients are free to move around.
- B. Avoid light-colored tile floors with dark geometric designs; these confuse patients with faulty perception.
- C. Hand mitts inhibit door opening, tampering with tubes and dressings, and taking other people's property. Can be used instead of restraints.
- D. Place photo and name of patient on door to bedroom.
- E. Paint bathroom and toilet doors in bright colors so that patients can identify them.
- F. Encourage walks as a daily activity.

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function include listening to the radio or looking at newspapers or television, doing chores, attending structured social events, and participating in discussions and reminiscences.[30] Engaging in physical exercise will help the patient maintain body tone. Proper nutrition and personal hygiene must be ensured as well. Supervision of meal preparation may ensure nutrition in patients who are insensitive to time and hunger.

Patients past the earliest stages of Alzheimer's disease should not be allowed to drive, since they will experience disorientation and impairment of judgment and reaction time, in addition to impairment of visual perception.[25,36] A study of 72 patients revealed that 30% had experienced at least one automobile accident since the onset of dementia, and an additional 11% were reported by caregivers to have "caused" accidents, a clear illustration of this potentially serious problem.[36] Patients who are beyond the early stages of the disease should be

Table 8. Memory Aids for the Patient with Alzheimer's Disease

(Note: Many of these aids are appropriate for patients with or without help in the earlier phases of Alzheimer's disease. Later they may have to be done for the patient. Others are appropriately used by caregivers at all phases of the disease. Patients should be encouraged and helped to do as much self-care as possible.)

I. General
- A. Keep pen and white, undecorated paper for reminder notes in same place for easy location. (Use black felt-tipped pen if visual impairment exists.)
- B. Simplify activity schedule.
- C. Place easily read list of important numbers near telephone, most used ones first.
- D. Keep doctor's instructions for taking medication and other health care in visible, consistent place (eg, post on wall or refrigerator door).
- E. Keep checklist near the usual exit door of things to be done before leaving house (eg, put keys in pocket, turn off stove, put out the cat, lock door).

II. Daily Activities
- A. Make a checklist of daily activities with times in large print. Keep in visible and consistent place.
- B. Set alarm clock or a timer as reminder of specific things to be done. Place note by clock or timer reminding of what is to be done.
- C. Arrange to have a friend call at designated times to remind of an appointment.
- D. Establish consistent routines for important activities (eg, put morning medication near pan used to cook morning cereal).

III. Location
- A. Remind person of where he or she is, or is going, and why.
- B. Place signs designating important locations, such as bathroom.
- C. Place pictures designating function on refrigerator, stove, bathroom door.
- D. Keep person's familiar, significant objects in consistent locations.
- E. Post list of major items in each cupboard and drawer.
- F. Arrange for a friend to become familiar with objects in the home to help if they are misplaced.
- G. Attach eye glasses to a chain that the person can wear around the neck.

IV. Wandering
- A. Use identification necklace or necklace with name and address that patient cannot remove.
- B. Attach name and address of patient on strips of cloth that can be put on back of clothing with velcro.
- C. Alert police and neighbors to the person's possible need for assistance in finding the way home.
- D. Keep card in the person's wallet or purse or taped to jacket or hat with directions to home and name and telephone number of responsible person.
- E. Enroll patient in a special registry program where available, eg, the Los Angeles Chapter of ADRDA has instituted a special registry and bracelet program that allows for the registry of persons suffering from chronic memory loss. The patient will wear a bracelet with a code number, his first name, the words "Memory Loss," and a central telephone number. The code will be registered on a computer maintained by ADRDA.
- F. Use structured activity programs to help reduce wandering.
- G. Use buddy system in institutional settings to help patients watch one another.
- H. Use fenced-in yards and buzzer systems to alert staff or caregivers that a patient is wandering.
- I. Establish a protocol for all staff members to use when patient wanders off.
- J. Conduct frequent in-service classes about management of wanderers.

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prevented from traveling alone. For those beyond the early to middle stages, living alone without supervision may be impossible.[25]

Patients may require close supervision to protect them from dangers ranging from falls to medication errors. It may be advisable for the family to secure dangerous or breakable objects. Caregivers must take into account the dangers posed by unstable furniture, breakable objects, rugs that slip, stairs to be negotiated, and matches and gas stoves, as well as hazards posed by bathrooms and electric wiring.[26] Counseling the patient's family is also an important aspect of management. Studies have shown that families value being able to talk with their doctor and benefit from their doctor's understanding, support, and advice.[7]

There is an enormous burden placed on the families of patients with Alzheimer's disease since family members are often the central caregiver. In the past, there have been few interventional programs to help decrease the strain placed on family members. Recently, however,

lectures designed to increase family members' knowledge of the disease and self-help groups that provide social support have become more common.

Patients with Alzheimer's disease and their families require ongoing counseling from their primary care physician, starting when the disease is first suspected and continuing as the reality of progressive dementia and increased dependence touches the family. Families who choose to provide care for patients throughout the course of the disease require access to support groups, good clinical information about the probable course of the disease, effective management strategies, and nonjudgmental recommendations as to when to seek outside help and nursing home placement. The Alzheimer's Disease and Related Disorders Association (ADRDA) (1-800-272-3900) and the Area Agency on Aging (AAA) offer support groups and relevant literature to educate families. The family physician may need to provide personal counseling and support of the caregiver(s) to prevent caregiver disease (backache, exhaustion, headache, peptic reflux, and other somatic complaints) and psychological problems (depression, anxiety, sleep disorders, substance abuse).[37] Texts such as *The Michigan Long-Term Care Reader* review the legal, economic, and social interventions needed to provide a protected environment for patients with Alzheimer's disease.[38]

Adult day-care centers and respite care centers may help the patient and relieve the family's burden as well. The ADRDA can provide the family with information on such programs, as well as family support groups. Social workers may be able to provide referrals to nursing, physical therapy, and homemaking services. Timely use of outside-the-home day care or respite care can reduce caregiver deterioration that could arise as a result of depression, medical illness, or "burnout."

There is now a movement to open special-care units within nursing homes for the care of patients with Alzheimer's disease or related dementia. These programs take into account the security and safety measures, mental and physical stimulation, and demanding physical care required by patients with dementia, and provide staff who are trained to care for these patients.[39] Guidelines for such facilities vary greatly. Although some states have developed licensing regulations, it is difficult to assess the appropriateness of care in absolute terms since experts still disagree about precisely what good care for patients with dementia should include. It is hoped that long-term studies will be initiated to resolve these issues.

Treatment of Psychiatric Symptoms

Depression. Depression may accompany Alzheimer's disease and can contribute to cognitive decline. When treating depression, however, the physician should be especially careful to prescribe antidepressant drugs without anticholinergic activity (eg, trazodone or fluoxetine) to avoid further compromising cognitive function.[30] The risks of falls as a result of orthostatic hypotension and the possibility of cardiovascular toxicity must also be kept in mind when tricyclic antidepressants are prescribed. The best approach is to start with a low dose, use divided doses, and gradually increase the dose until the patient responds.[30] As a general rule, the dose should be about half that usually prescribed for younger adults.[2] The motto is "start low, go slow."[30]

Agitation. As many as one third of patients with Alzheimer's disease who have delusions, hallucinations, or aggressive agitation may improve when treated with a neuroleptic agent. However, these drugs should be used only to control potentially dangerous behavior and not to manage insomnia, fidgeting, and uncooperativeness.[34] Clinicians should prescribe low doses of these agents and should try periodically to decrease the dose or discontinue the medication altogether. Caution is in order, since neuroleptics, like tricyclic antidepressants, carry the risk of anticholinergic side effects and orthostatic hypotension, and in addition, may cause extrapyramidal reactions such as bradykinesia, rigidity, and tremor. The higher potency neuroleptics, such as haloperidol and fluphenazine, have been recommended for use in patients with Alzheimer's disease.[22,24] Propranolol, carbamazepine, and fluoxetine have also been applied in the treatment of aggressive agitation in patients with dementia, but their value in this setting is unproven.[34,40] All neuroleptics are restricted in their use in nursing home centers under Omnibus Budget Reconciliation Act regulations. Nonsedating anxiolytics such as an azaperone (eg, buspirone) appear promising, and their use at low doses is not restricted.

Less severely agitated patients with Alzheimer's disease sometimes may be helped by a short course of benzodiazepines (eg, temazepam, triazolam), but these drugs should not be used for more than a week at a time.[2,34] Behavioral plans to have the patient exercise adequately during the day also can aid sleeping. If the patient continues to experience difficulty sleeping, low doses of hydroxyzine or haloperidol may be appropriate.

Treatment of Cognitive Impairment

Pharmacologic agents may play a useful but, to date, limited role in the overall treatment of cognitive impairment in Alzheimer's disease. Nonetheless, these agents may provide limited but positive benefits to both patients and their family members. A partial list of some of the

Table 9. Some Drugs of Potential Benefit in Improving Cognitive Function or Slowing the Progression of Alzheimer's Disease

Augmenting acetylcholine	Vascular system
Cholinesterase inhibitors	Vasodilators†
Physostigmine	Ergoloid mesylates
Tetrahydroaminocridine	Nicergoline
Velnacrine maleate	Captopril
Increasing precursors	Calcium channel blockers
Lecithin	Nimodipine
Nootropics*	Miscellaneous
Piracetam	Monoamine oxidase β inhibitors
Oxiracetam	Selegiline (deprenyl)
	Nerve growth factor
	Cell membrane stabilizers
	Phosphatidylserine

** These are drugs otherwise affecting neuron function.*
† Nominally vasodilators, the mechanism of action in treating Alzheimer's disease may be different.
Modified with permission from Cooper JK. Drug treatment of Alzheimer's disease. Arch Intern Med 1991; 151:24–59. Copyright 1991, American Medical Association.

therapies[34] can been found in Table 9. At present, there is no one drug that can be used to successfully treat all of the symptoms associated with this debilitating disease. While some improvement in cognitive function has been demonstrated with several agents, it is clear that research into developing an effective pharmacologic agent is only in the initial stages.

Vasodilators. The use of vasodilators in Alzheimer's disease originated from the now discarded notion that dementia was caused by "hardening of the arteries."[2] The ergoloid mesylate compound Hydergine LC, formerly classified as a cerebral vasodilator, is now termed a *metabolic enhancer,* although how this action pertains to the treatment of dementia is uncertain. It is currently the only FDA-approved drug for treatment of Alzheimer's disease, but it appears to be an ineffective treatment.[41] Another ergot drug, nicergoline, reduced disorientation in nearly a third of patients in a multicenter, double-blind placebo trial, but this drug is not available in the United States.[34] Nimodipine, a calcium channel blocker selective for the brain vasculature, is now being studied in patients with Alzheimer's disease[34]; such therapy has the potential to improve local oxygenation, although its present cost may limit its use.

Cholinergic enhancers. The cholinergic enhancers represent the first real therapeutic option for treating memory loss and cognitive dysfunction for patients with Alzheimer's disease. They should be considered the first rational therapy for Alzheimer's disease, since they address a known underlying neurochemical abnormality. The most successful cholinergic enhancers to date have been the cholinesterase inhibitors, which block the enzyme that degrades acetylcholine. The prototype cholinesterase inhibitor is physostigmine. Long-term trials have shown that physostigmine is significantly better than placebo in improving memory, though not other cognitive functions.[42,43] A short-term study found that improvements in memory correlated with increases in central cholinergic activity,[43] thereby supporting the contribution of the cholinergic deficit to memory loss. Thus, these studies pioneered the clinical applicability of long-term cholinesterase inhibition in the management of patients with Alzheimer's disease. The half-life of physostigmine in plasma is 30 minutes, necessitating oral dosing every 2 hours to achieve steady-state levels[44,45]—not a realistic regimen.

As a result, enthusiasm greeted a report that a longer-acting cholinesterase inhibitor, tetrahydroaminoacridine (THA, or tacrine), significantly improved clinical and psychological performance in patients with Alzheimer's disease.[46] The results of this small study were challenged, however, when it was subsequently reported that with longer treatment deterioration of initially improved memory occurred.[47] Larger studies have been completed since. In 6-week and 8-week clinical trials of tacrine administered to patients with moderate to severe Alzheimer's disease, tacrine was found to improve cognitive test scores but not clinical function.[48,49] Patients may exhibit improved mental status testing scores for memory, but show no improvement in assessments of activities of daily living and instrumental activities of daily living. Dosing of tacrine in protocols has ranged from 40 to 160 mg/d, in three to four divided doses with meals.[48,49] Concern about hepatotoxicity and elevation of transaminases has precluded recommendation of the higher levels (150 to 200 mg/d) originally tested by Summers et al.[46,48–50] The Tacrine Collaborative Study Group reported in 1992 that the lower doses of tacrine (40 to 80 mg/d) administered for 6 weeks showed marginal improvement over placebo in terms of functional scales,[49] while the Canadian double-blind crossover multicenter study, administering up to 100 mg/d, reported no clinically significant improvement over an 8-week trial.[48] The FDA approved tacrine to treat mild to moderate Alzheimer's disease in 1993.

Another cholinesterase inhibitor currently under clinical investigation for its effect on memory and cognition is velnacrine maleate. This new cholinesterase inhibitor has been shown to be as effective as tacrine in reversing scopolamine-induced dementia in animal models.[51] Clinical studies are currently under way investigating the effect of velnacrine maleate on memory and cognition in patients with Alzheimer's disease.[52]

The pharmacokinetic profile of velnacrine maleate indicates that it is quickly absorbed in both young and elderly subjects after oral administration, reaching peak plasma concentrations in 0.9 to 1.7 hours[53]; its bioavail-

ability is not changed by food, an important practical issue with a drug that must be taken on a long-term basis.[54] In elderly patients, velnacrine has a 2- to 3-hour half-life; between 11% and 30% of a given dose is excreted unchanged in the urine, and the drug is eliminated quickly over all dosage ranges.[53,55]

Other agents. Numerous theories as to the pathophysiologic origins of Alzheimer's disease have been posed, and, over the years, many drugs have been tested in animal studies and a few have reached preliminary human studies. Lecithin, ergoloid mesylates, and vasodilators are among the oldest agents tried in double-blind crossover human studies, but none have resulted in statistically significant improvement in patients with Alzheimer's disease. Recent studies with L-deprenyl, a monoamine-oxidase inhibitory drug used successfully to treat Parkinson's disease, show no measureable impact on cognitive or behavior function in patients with Alzheimer's disease.[56] Current research has focused on inhibiting the formation of neurofibrillary tangles at a biochemical level. To date, no drug has been uniformly successful.

Conclusions

Until the underlying causes of nerve cell degeneration in Alzheimer's disease can be unraveled and therapeutically targeted, management can aspire only to symptom control, rather than disease reversal. At present, this can be accomplished by a variety of behavioral, environmental, and perhaps in the near future, pharmacologic intervention. Cholinesterase inhibitors such as velnacrine maleate and tacrine show some promise as a strategy for slowing the memory loss and cognitive impairment of this disabling disease and may produce modest improvement in selected patients.

There is a clear need for further investigation of the functional and cognitive rates of decline during the course of Alzheimer's disease in order to realistically plan for the growing demands on medical and social resources, to enable physicians to better inform patients and their families of the disease's expected course, to facilitate the recruitment of patients at definable stages for clinical studies, and to apply drug therapy in a clinically and economically appropriate manner.[57,58]

To better care for their patients, family physicians will want to be aware of ongoing clinical trials in which their patients may participate. This information can be obtained from the local chapters of their ADRDA. Furthermore, family physicians will need to develop diagnostic skills to identify patients with early disease, as the most profound impact of these newer agents may occur early on in the course of Alzheimer's disease. Until now physicians have been admonished not to rush to the diagnosis of Alzheimer's disease, as there was no specific recommendation for therapy and treatment. This trend may soon be reversed.

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