

Diagnosis, Management, and Treatment of Alzheimer Disease

A Guide for the Internist

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Alzheimer disease (AD) is a diagnosis of inclusion based on patient history, physical examination, neuropsychological testing, and laboratory studies; however, there is no definitive diagnostic test for AD. Early recognition of AD allows time to plan for the future and to treat patients before marked deterioration occurs. Effective treatment requires monitoring of symptoms, functional impairment, and safety, and the use of multiple treatment modalities including pharmacotherapy, behavioral management, psychotherapies, psychosocial treatments, and support and education for families. Pharmacotherapeutic agents available for AD only provide symptomatic relief. The cholinesterase inhibitors, tacrine and donepezil, are effective in improving cognition, delaying nursing home placement, and improving behavioral complications in some patients. Other cholinesterase inhibitors are in development, as are other cholinomimetic agents such as muscarinic and nicotinic receptor agonists. Symptomatic treatments are available for the psychiatric manifestations of AD. Anti-inflammatories, antioxidants, neurotrophic factors, and other agents are promising new treatments for the future.

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Alzheimer disease (AD) is one of a group of neurodegenerative disorders that frequently cause dementia. Dementia is characterized by a progressive cognitive decline leading to social or occupational disability occurring in a state of clear consciousness.

Specifically, AD is characterized clinically not only by an impairment in cognition but also by a decline in global function, a deterioration in the ability to perform activities of daily living, and the appearance of behavioral disturbances. When AD was originally described by Alois Alzheimer in 1907,¹ it was considered to be a relatively uncommon disorder. However, subsequent clinical and neuropathological studies identified the characteristic AD pathology of senile plaques and neurofibrillary tangles as the most common cause of dementia in the elderly. With the aging of our population, the management and treatment of AD is likely to become one of the major public health problems facing our society in the next century. Our knowledge of the pathophysiology and natural history of the disease has increased greatly over

the past decade, yet the definitive cause remains unclear and a cure has been elusive. Nevertheless, we now have available effective pharmacological and psychosocial interventions to alleviate the symptoms and suffering of patients with AD and their families. The purpose of this article is to discuss the epidemiology, presentation, diagnosis, and pharmacological management of the disorder.

EPIDEMIOLOGY

The prevalence of dementia in the United States in individuals aged 65 years or older is about 8%, with these rates doubling if those with milder forms of dementia or cognitive impairment are included. Rates of dementia are very much age dependent, doubling every 5 years from 1% to 2% at ages 65 to 70 years, to 30% and higher after the age of 85 years. Alzheimer disease is by far the most common of the dementing disorders in the United

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States, accounting for 65% to 75% of cases.²⁻⁵

COST

The calculated economic cost of the management and treatment of AD is staggering. The combined direct costs, including medical and long-term care and lost productivity, and indirect costs, including resource loss and family care, approach \$100 billion per year.⁶ In addition, there is also the immeasurable emotional cost to families who suffer tremendously watching their affected loved ones slowly lose their identity.

RISK FACTORS

Our knowledge of putative genetic risk factors for AD has increased dramatically over the past decade. There is now evidence that certain types of early-onset, autosomal dominant AD are associated with gene mutations on chromosome 21, chromosome 14, and chromosome 1.⁷⁻⁹ These findings are important for determining pathologic mechanisms but account for only a small proportion (about 2%) of all cases of AD.¹⁰

The presence of the APOE ϵ 4 allele on chromosome 19 has been associated with a considerably greater risk for developing the more common, late-onset form of AD.^{8,11,12} The effect appears to be dose dependent. The presence of a single ϵ 4 allele increases the risk of AD by 2- to 4-fold, whereas possessing the double ϵ 4 allele increases the risk from 4- to 8-fold. It must be remembered that possessing the ϵ 4 allele is neither necessary nor sufficient for the development of AD. Therefore, APOE genotyping is not recommended as a predictive test for AD in asymptomatic individuals.¹³ However, experts disagree on the utility of APOE genotyping as a diagnostic test. It may be useful for confirmation in some patients with dementia when a diagnosis of AD is unclear, although the presence of 1 or 2 copies of the APOE ϵ 4 allele still does not make the diagnosis certain and absence of the ϵ 4 allele does not preclude a diagnosis of AD. APOE genotyping, when used in patients with a clinical diagnosis of

Criteria for Clinical Diagnosis of Probable Alzheimer Disease*

Criteria include

- Dementia established by clinical examination and cognitive test (Mini-Mental State Examination or Blessed Dementia Scale) and confirmed by neuropsychological tests
- Deficits in ≥ 2 areas of cognition
- Progressive worsening of memory and other cognitive function
- No disturbance of consciousness
- Onset between ages 40 and 90 years
- Absence of systemic disorder or brain disease that could account for progressive cognitive deficits

The diagnosis is supported by

- Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
- Impaired activities of daily living
- Altered behavior
- Family history of similar disorders
- Normal lumbar puncture, normal electroencephalogram or nonspecific changes, progressive cerebral atrophy on computed tomography

Features consistent with the diagnosis

- Plateaus in the course of progression
- Associated symptoms including depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic outbursts, sexual disorders, or weight loss
- Neurologic signs including increased muscle tone, myoclonus, or gait disorder
- Seizures (in advanced stage)
- Computed tomography normal for age

Features that make the diagnosis uncertain or unlikely

- Sudden, apoplectic onset
- Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination (early in the course)
- Seizures or gait disturbance (at the onset or early in the course)

*From the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association Work Group.¹⁵

AD, may increase the specificity of the diagnosis.¹⁴

Research on other risk factors for AD is relatively new. To date, only age, family history of dementia, and Down syndrome consistently have been shown to be associated with AD. However, high education and ingestion of estrogen, nonsteroidal anti-inflammatory drugs, and vitamin E may be protective. It is likely in the future that risk factor models involving genetic and environmental interactions will emerge.

DIAGNOSTIC PROCESSES AND DIFFERENTIAL DIAGNOSIS

As AD is both a clinical and a neuropathological entity, the definitive diagnosis of AD can be made only with a brain biopsy or an autopsy. One of the major clinical advances in the diagnosis of AD has been the promulgation of diagnostic criteria for possible and probable AD by a select group sponsored by the National Institute of Neurological and Related and Com-

municative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (**Table**).¹⁵ Using these criteria, the clinical diagnosis of AD has been confirmed at autopsy in close to 90% of cases. It has been stated that AD is a diagnosis of exclusion. This is only partially correct. While it is essential for the physician to evaluate other possible causes of memory loss, a positive diagnosis of probable AD can be made based on a characteristic history from a spouse or a knowledgeable informant together with a physical and neurologic examination. The differential diagnosis for AD includes a broad range of other causes of dementia and nondementing metabolic or psychiatric illnesses.

Among the more important nondementing causes of dementia are delirium and depression. Delirium is common in elderly subjects, particularly in inpatient settings and in nursing homes. Unlike delirium in children, which is an acute disorder, delirium in the elderly can be subacute at onset, stretching over weeks or even months, char-

acterized by apathy rather than agitation, and vague paranoid symptoms rather than vivid hallucinations. Thus, delirium in the elderly can often be misdiagnosed. Common causes of delirium include infection (particularly urinary tract infections), hypoglycemia, electrolyte abnormalities (such as those accompanying dehydration), hepatic dysfunction, renal insufficiency, endocrine dysfunction (particularly thyroid abnormalities), and medications (especially anticholinergic agents, benzodiazepines, histamine₂ antagonists, and narcotics), all of which are eminently treatable. Delirium and dementia can coexist. In fact, dementia predisposes to the development of delirium with even modest metabolic insults.

Severe depression in the elderly is often accompanied by complaints of memory loss and the presence of mild cognitive deficits on neuropsychological testing. In depression, the subjective complaints of cognitive impairment often exceed the neuropsychological deficits, and the primary problem seems to be one of motivation or lack of effort. Depression and dementia can coexist, however.

Among the dementing disorders, vascular dementia follows AD as the second most common form.¹⁶ The vascular dementias usually, but not always (eg, Binswanger disease), have a relatively acute onset temporally related to a vascular event such as transient ischemic attack or stroke and have a more fluctuating course than AD. Focal neurologic signs or symptoms usually accompany them. Cerebrovascular changes can also coexist with AD pathology, and this combination can adversely affect the dementing process.¹⁷

Other neurodegenerative disorders that can cause dementia include Parkinson disease, Huntington disease, Pick disease, and dementia with Lewy bodies. Parkinson disease and Huntington disease are characterized by extrapyramidal signs, which usually predate the cognitive decline. Pick disease is one of the frontal lobe dementias and usually presents with behavioral disinhibition, poor insight, and language deficits early in the course of

the illness. Memory and constructional praxis are relatively spared early on. Frontal and temporal lobe atrophy is usually evident on computed tomography. Dementia with Lewy bodies is a progressive dementia characterized by detailed recurrent visual hallucinations, parkinsonism, and fluctuations of alertness and attention.¹⁸ Other common features include frequent falls, syncope, systematized delusions, and neuroleptic sensitivity. Autopsy series findings demonstrate cortical Lewy bodies in 20% to 30% of dementia cases and there may be overlap with AD.¹⁸ A long history of heavy use of alcohol can also cause dementia.

Creutzfeldt-Jakob disease is an example of an infectious cause of dementia caused by prions. Creutzfeldt-Jakob disease is characterized by relatively sudden onset and rapid progression with myoclonic jerks, pyramidal frontal motor signs, visual agnosia, and death within months.

Other neurologic disorders less commonly associated with dementia include normal pressure hydrocephalus, subdural hematoma, brain tumor, posttraumatic brain injury, and posthypoxic damage.

DIAGNOSTIC EVALUATION

A diagnostic evaluation for dementia involves a complete history, neuropsychological examination (eg, the Mini-Mental State Examination [MMSE]),¹⁹ physical examination, and selected laboratory studies and neuroimaging.²⁰ The history should be obtained from a reliable informant. In this regard, attention should be paid to change in cognition and functioning relative to previous performance, mode of onset of impairment (insidious onset is characteristic of AD), progression of illness (slow gradual decline is typical of AD), and duration of impairment (it is important to repeatedly ask if there were any earlier signs that may have indicated a change). One should ask about all cognitive domains and give examples of early signs. For example, when asking about memory impairment, one could ask if the patients have difficulty remembering what day it is,

what they ate for the previous meal, or if they have trouble keeping appointments. Be aware that patients and families often make excuses for memory problems. For the language domain, one could ask if the patients have trouble finding the right word for things or call something by the wrong name, mispronounce words, or if they feel that they have more trouble expressing themselves verbally. For praxis, it would be appropriate to ask if they have trouble figuring out how to use machines that they knew how to use before (microwave, washing machine, or lawn mower) or if they have trouble with any skills (crafts or hobbies) in which they previously engaged. For agnosia, determine if they have trouble recognizing common objects such as a telephone, toaster, or broom. Difficulty with executive functioning manifests as trouble with complex tasks such as preparing a meal or managing finances. In addition to inquiring about cognitive function, it is critical to inquire about the use of prescription and over-the-counter medications, alcohol, and illicit drugs and their temporal relationship to any cognitive changes.

The instrument used most commonly for assessing cognitive function is the MMSE. This instrument is a nonspecific screen for cognitive function and has some limitations. The MMSE is not sensitive for detecting cognitive impairment in individuals with higher levels of education or high levels of premorbid functioning. Conversely, those with low levels of education or minority cultural backgrounds may score low on the test without having impairment. However, the MMSE is especially useful when repeated regularly to follow illness progression.

A complete physical and neurologic examination is indicated. Focal neurologic signs may suggest vascular dementia or some other neurologic disorder, and parkinsonism suggests Parkinson disease or dementia with Lewy bodies disease depending on the time course of symptoms relative to the cognitive impairment. Results of the neurologic examination are usually essentially normal in early AD.

Laboratory evaluation should include tests for complete blood cell counts, electrolytes, blood chemistries, liver functions, thyrotropin levels, vitamin B₁₂ levels, and a serologic test for syphilis. Other tests should be obtained as indicated by the history such as erythrocyte sedimentation rate (autoimmune disease), heavy metal screen (industrial exposure), human immunodeficiency virus (with human immunodeficiency virus risk factors), and toxicology screen (suspected use of illicit drugs). An electroencephalogram reveals nonspecific changes and is rarely indicated except to diagnose Creutzfeldt-Jakob disease, a disease associated with a characteristic periodicity on the electroencephalogram, or hepatic encephalopathy with characteristic triphasic waves.

A neuroimaging study may be obtained in a complete workup to rule out neurologic disease, which may contribute to cognitive decline, but is not required for diagnosis unless warranted by unusual findings. A computed tomographic scan of the head without contrast is usually sufficient to rule out cerebrovascular disease, subdural hematoma, normal pressure hydrocephalus, or brain tumor. Magnetic resonance imaging is more expensive but is better for visualizing small subcortical lacunae and mesial temporal lobe atrophy (in coronal slices). However, there is a tendency to overread vascular changes (periventricular and subcortical white matter hyperintensities) on magnetic resonance imaging. Single proton emission computed tomography may be helpful in atypical, difficult, or early cases. In AD, there is a characteristic hypoperfusion in the temporal and parietal lobes. In vascular dementia, there are more patchy changes. Pick disease is marked by frontal and temporal lobe perfusion defects. Single proton emission computed tomography may be most useful in distinguishing AD from vascular dementia and frontotemporal dementia, but should be used selectively and only as an adjunct to clinical evaluation and computed tomography.²¹ Positron emission tomography has the advantage of greater sensitivity and spatial resolution but at a much

higher price, and while it is a better tool for research purposes, it has limited clinical application. Single proton emission computed tomography is simpler to perform, less expensive, and has greater potential in the clinical setting than positron emission tomography.²²

Detailed neuropsychological testing is also helpful in characterizing the pattern of cognitive impairment. It is also more sensitive than a screening instrument such as the MMSE in detecting early impairment in highly educated individuals. It also provides a quantitative measure, which affords the ability to follow disease progression over time.

If the diagnosis remains unclear after a complete evaluation, there are several options. Repeating the cognitive testing in 6 months will determine if there is progressive cognitive decline during the intervening period. More complete neuropsychological testing may also be helpful. Consultation with a specialist, either a neurologist or geriatric psychiatrist, is warranted.

IMPORTANCE OF EARLY DIAGNOSIS

Early diagnosis of AD is important for many reasons. Patients may present with nonspecific physical complaints that may prompt extensive and costly diagnostic workups and unnecessary treatments. Early recognition allows the possibility of treating with agents that can slow the cognitive decline at a point where there is still minimal impairment. Early diagnosis also allows the patient and the family time to plan for the future such as developing advanced directives and appointing durable power of attorney while competence is not yet an issue. The practitioner can educate the patient and the family regarding disease progression and prognosis, provide support, and monitor judgment and safety issues so that the patient can continue independent or community dwelling as long as possible.

Unfortunately, AD is frequently not diagnosed at this early stage despite visits to the primary care physician. There are many reasons for this delay in diagnosis. Patients and

families often underreport symptoms, families attribute symptoms to normal aging and compensate for functional impairment, and social skills are maintained, masking any impairment during a short, focused office visit. Even when cognitive testing is performed, individuals with dementia may score in the "normal" range on the MMSE. Results of laboratory tests are normal in AD so a diagnostic workup will not reveal any abnormalities.

There is a need to improve early recognition of AD in the primary care setting and to avoid delays in diagnosis. Practitioners should screen for functional and cognitive decline and any concerns should prompt a full dementia workup.

TREATMENT OF AD IN THE PRIMARY CARE SETTING

The successful treatment of AD involves multiple treatment modalities targeting various aspects of the illness and its consequences for the patient and the family. Again, it is important to stress the necessity for accurate diagnosis of AD and early recognition to provide the best possible treatment. While there is no cure for AD, there are approaches to improving cognition and possibly delaying the progression of the illness, and there are efficacious treatments for the psychiatric and behavioral manifestations. Another important aspect of treatment is helping the patient and the family with the legal aspects, supporting the family through caregiving, and assisting with decisions about long-term care placement. Providing regular appointments for maintenance and surveillance is necessary to meet the goals of minimizing excess disability and ensuring safety and security.

PHARMACOLOGICAL TREATMENT OF AD

There are several conceptual approaches to the treatment of AD. The first approach is to treat symptomatically. This includes treating the cognitive impairment, decline in global function, deterioration in the ability to perform activities of daily living, and behavioral distur-

bances. This approach reflects the current state of treatment. Another approach is to slow disease progression or delay onset of disease. Eventually, it may be possible to be able to prevent the development of AD or even repair neuronal damage after onset of disease. These latter approaches are currently being investigated at a basic science level. The only currently available therapeutic agents are targeted at specific symptoms of AD.

Cognitive Impairment

Cholinesterase Inhibitors.—Alzheimer disease is in part a disorder of cholinergic functioning. Degeneration of basal forebrain cholinergic systems is a hallmark feature of AD and appears to be associated with cognitive deficits, functional impairment, and behavioral disturbances. One strategy for ameliorating the symptoms of AD is to enhance cholinergic neurotransmission. Acetylcholinesterase inhibitors are the best studied and the only currently available agents for the symptomatic treatment of AD. Acetylcholinesterase inhibitors delay the degradation of acetylcholine at the synaptic cleft, thus potentiating cholinergic neurotransmission.

The only 2 agents currently available for the treatment of AD are the cholinesterase inhibitors tacrine and donepezil. Both agents inhibit acetylcholinesterase in a dose-dependent manner. Both are effective in improving performance on a test of cognitive function and global performance in patients with mild to moderate AD.²³⁻²⁹ Cognitive improvements are, on average, modest and may not be clinically relevant in many patients. However, some patients demonstrate a dramatic improvement in cognitive scores that is readily observable in daily functioning. Some cholinesterase inhibitors are also associated with improvement in behavioral symptoms, including depression, psychosis, and agitation, even in the absence of profound cognitive change.³⁰ However, this is based on an open-label study. Cholinesterase inhibitors are also associated with a delay in nursing home placement.³¹ Methodological limitations of this study in-

clude the open-label, nonrandomized, and nonblinded design.

Studies of acetylcholinesterase inhibitors have generally shown an initial improvement in cognitive scores beginning early in the treatment course with a subsequent decline at a rate similar to untreated patients with AD.³² When the medication is stopped, cognitive functioning declines to nontreatment levels. This is consistent with the hypothesis that cholinesterase inhibitors provide symptomatic relief without altering the disease course. The long-term effects or continued benefit of cholinesterase inhibitors will become clearer in clinical practice. One neuroimaging study³³ demonstrated increased regional cerebral blood flow in the parietal lobe, which persisted up to 14 months with continued treatment.

Treatment with tacrine requires a lengthy dose titration beginning with 10 mg orally 4 times daily and increasing by 10 mg 4 times daily every 6 weeks as tolerated to a maximum of 160 mg/d. Only doses of 120 to 160 mg/d are significantly more efficacious than placebo. However, dose titration is frequently limited by adverse effects to the gastrointestinal tract or hepatic transaminase elevations. Transaminase activity (alanine and aspartate aminotransferase) must be monitored weekly until a steady dose has been achieved for 6 weeks, after which monitoring every 3 months is sufficient. If transaminase activity levels rise to more than 5 times the upper limit of normal, treatment with tacrine should be discontinued. Transaminase elevations are usually asymptomatic and reversible and patients may be rechallenged after transaminase normalization (see package insert for details).

Donepezil has replaced tacrine as the first choice "cognitive enhancer" owing to ease of administration, less titration, greater tolerability, relative lack of hepatotoxic side effects, and absence of monitoring requirements. Donepezil is selective for acetylcholinesterase and is longer acting than tacrine. It is metabolized via the hepatic cytochrome P450 system and is highly plasma protein bound. Donepezil is administered in once-daily dosing and requires less ex-

tensive titration. Dosing is initiated at 5 mg/d and may be increased to 10 mg/d in 1 month. It is well tolerated and the most common adverse effect is gastrointestinal tract distress (nausea, vomiting, and diarrhea).

Other cholinesterase inhibitors are in development and are expected to reach the market soon. Metrifonate is a prodrug for the long-acting cholinesterase inhibitor, 2,2-dichlorovinyl dimethyl phosphate. Its pharmacokinetic profile permits once-daily dosing. Early studies demonstrate improvement in cognitive scores and global function compared with placebo, with few adverse effects.³⁴⁻³⁶ Rivastigmine is a central nervous system-selective, pseudo-irreversible, carbonate-selective cholinesterase inhibitor.³⁷ Dosing is 2 or 3 times daily and extensive titration is required. It is well tolerated at the lower doses with predominantly adverse effects on the gastrointestinal tract. Heptylphysostigmine is a derivative of physostigmine with a long duration of inhibition.³⁸ Several other agents are also in development.

Other Cholinergic Agents.— Another strategy targeting the cholinergic system is specific cholinergic receptor agonists. Muscarinic acetylcholine postsynaptic m1 receptors are relatively intact in AD, while the m2 presynaptic receptors are decreased. Agents that target the postsynaptic m1 receptors are being developed. There is some evidence suggesting that these agents may also slow disease progression, but most have not been well tolerated at therapeutic doses. Xanomeline is a selective m1 and m4 agonist that has demonstrated moderate efficacy in improving cognitive performance, but even greater efficacy in decreasing psychotic symptoms and agitation.³⁹ However, adverse events to xanomeline were associated with high discontinuation rates primarily because of adverse effects on the gastrointestinal tract and syncope. Other cholinergic agonists in development include milameline, SB202026, AF 102B, and ENS-163. Stimulation of presynaptic nicotinic receptors increases the release of acetylcholine and may be associ-

ated with cognitive improvement in selected domains. Therefore, nicotinic acetylcholine receptor agonists also appear promising.

Disease-Altering Treatment Strategies

One target for disease-altering treatments is apoptosis or programmed cell death. Mechanisms that are implicated in neuronal degeneration are the inflammatory response and oxidative stress. The inflammatory response contributes to cell death in part by triggering release of free radicals. An accumulation of free radicals in turn damages cell membranes and triggers the neurodegenerative cascade. In addition, components of the inflammatory response are found in association with senile plaque formation. Anti-inflammatory agents may be protective against AD; in epidemiological studies, the use of anti-inflammatory drugs is associated with a decreased risk of AD. Prednisone is currently under investigation for the treatment of AD.⁴⁰ Antioxidants may also be protective against cell death. In one clinical trial,⁴¹ alpha-tocopherol (vitamin E) and selegiline hydrochloride (L-deprenyl), a selective monoamine oxidase–type B inhibitor that acts as an antioxidant, demonstrated efficacy in delaying adverse events. Methodological limitations of this study include poor randomization whereby baseline scores on the MMSE were higher in the placebo group, requiring adjustment for this in the analysis. Chelating agents may also work via an antioxidant mechanism. Other monoamine oxidases are currently under investigation.

Neurotropic factors may have a modulating effect on neuronal structural integrity and neurotransmitter function. Estrogen acts as a neurotropic factor and may be protective in decreasing the incidence or delaying the onset of AD and enhancing response to cholinesterase inhibitors.^{42,43} It is currently being investigated as a treatment for AD. Other neurotrophic factors under investigation include nerve growth factor and other agents that enhance its effect.⁴⁴

Other treatment strategies involve blocking the abnormal phos-

phorylation of tau proteins, preventing amyloid deposition, blocking amyloid toxicity, and lowering APOE $\epsilon 4$ levels. Ganglioside GM1 and phosphatidylserine have membrane effects that may interfere with the disease process. Other potential treatment under investigation include ergot alkaloids (ergoloid mesylates and nicergoline⁴⁵), nootropics (piracetam, oxiracetam, pramiracetam, and aniracetam), and vinca alkaloids. These agents have multiple putative mechanisms of action including cholinergic and dopaminergic properties, as well as effects on protein processing and cellular metabolism. However, studies to date involving these agents have shown them to be generally ineffective.

FUNCTIONAL IMPAIRMENT

Alzheimer disease is associated with a gradual decline in global functioning. Instrumental activities of daily living are the first to deteriorate. These include managing finances, shopping, cooking, cleaning, and maintaining an independent lifestyle. Basic activities of daily living include bathing, toileting, dressing, and feeding oneself. Eventually, patients with AD become unable to perform even these basic tasks. Functional impairment often prompts changes in levels of care from independent living to more active involvement of family to living with a family member or assisted living, and often eventually to skilled care or a nursing home.

Effective treatment for functional decline is the same as for cognitive impairment. The cholinesterase inhibitors have been shown to delay outcomes of functional decline and are the only currently available treatment.

PSYCHIATRIC MANIFESTATIONS OF AD

Psychiatric manifestations are common in AD and occur in almost all patients at some point in their illness. Behavioral disturbance is the most common symptom and occurs in up to 90% of patients with dementia.⁴⁶ Behavioral disturbance, especially agitation and wan-

dering, is associated with greater cognitive impairment, is the symptom most likely to emerge during the course of treatment, and is the most persistent.⁴⁷ It is the symptom that is the most troubling to families and caregivers and is the most common reason for institutionalization in long-term care facilities and for referral to specialists. Psychosis is the next most common psychiatric manifestation and includes delusions, most commonly paranoid and misidentification delusions, and hallucinations, with visual more common than auditory hallucinations. Delusions are associated with greater cognitive and functional impairment and show moderate persistence over time.⁴⁷ Psychosis may also be associated with more rapid cognitive decline. Depressive symptoms are present in up to 86% of patients with AD, with about 10% to 20% having a diagnosable depressive disorder.⁴⁸ Depressive symptoms are less likely to emerge during the course of AD than psychosis and behavioral disturbance, and are the least persistent.⁴⁷ Comorbid depression is associated with greater cognitive impairment, greater level of disability, and higher rates of institutionalization, mortality, and functional impairment.⁴⁹

Effective treatment of the psychiatric manifestations of AD can improve quality of life for patients and their families, decrease caregiver burden, decrease health care utilization, and delay institutionalization. Treatment can also significantly decrease the risk of harm to the patients and their caretakers.

Nonpharmacological treatment approaches should be attempted first before pharmacological treatments. Environmental manipulation or simple behavioral techniques may be helpful. In this regard, creating a safe and consistent environment with moderate stimulation, contrasting colors, and pictures for directions and signs may be useful. A structured routine and consistent environment as free from change as possible also can help eliminate confusion. Additionally, it may be desirable to provide familiar personal objects such as pictures and mementos, as well as cues for orientation like calendars and clocks. Com-

munication should be clear and simple. Behavioral interventions such as validation and not correcting misstatements can ease anxiety. Patients should be encouraged to be active participants in their care and in decision making. Emotion-oriented psychotherapy, supportive psychotherapy, interpersonal psychotherapy, and reminiscence therapy may be beneficial in individual cases. Stimulation-oriented therapy such as music, art, and pet therapy and exercise may be helpful for others.

Because the psychopathology changes over the natural course of the illness, treatments must be monitored and periodically reevaluated for continued appropriateness. Since depressive symptoms are not persistent over time, short-term antidepressant treatment is probably indicated. Psychotic symptoms are moderately persistent and long-term antipsychotic use is associated with significant morbidity and adverse effects, so antipsychotics should be tapered if possible. Because behavior disturbance is more persistent, long-term treatment is likely necessary.

TREATMENT OF DEPRESSION IN AD

Recognition of depression in AD may be complicated by an overlap of symptoms between the 2 disorders and failure to meet strict criteria for a depressive disorder. Any patient with dementia with significant depressive symptoms such as sleep, appetite, or energy disturbance, depressed mood or irritability, anhedonia, social withdrawal, excessive guilt, a passive death wish or suicidal ideation, or agitation should be considered for treatment of depression even if failing to meet criteria for a depressive disorder.⁵⁰

There are limited data on the treatment of depression in AD,^{51,52} so treatment strategies are extrapolated from the treatment of depression in elderly patients without dementia. In general, starting doses are half those normally used in adults and titration is at smaller increments and slower, to allow for the decreased rate of metabolism. Effective doses in patients with AD may

be lower than in adults or may be the same as in younger patients.

Selective serotonin reuptake inhibitors (SSRIs) are first-line agents because they are the best tolerated, do not have cognitive adverse effects, and may even improve cognitive function independent of antidepressant effects.⁵³ The choice of an SSRI is dependent on pharmacokinetics and adverse-effect profiles.⁵⁴ Sertraline has few interactions with the cytochrome P450 system and little anticholinergic activity, so it is a good first choice SSRI for the patient with AD. Fluoxetine, with its long half-life and active metabolite, make it less desirable in the elderly unless noncompliance is a problem; the long half-life allows for adequate levels to be maintained even when doses are missed. Paroxetine is the most anticholinergic of the SSRIs and, theoretically, may have more adverse effects on cognition. Fluvoxamine has a relatively short half-life and the twice-daily dosing may impair compliance. The starting dose of SSRI therapy should be half that normally used in adults (ie, 25 mg of sertraline or 10 mg of fluoxetine). The most common adverse effects with the SSRIs are transient headache, nausea and vomiting, diarrhea, anxiety, restlessness, psychomotor agitation, insomnia, and lethargy.

Several atypical antidepressants are available. Venlafaxine inhibits both serotonin and norepinephrine reuptake without having anticholinergic adverse effects. Most common adverse effects are nausea, anxiety, insomnia, dizziness, constipation, and sweating.⁵⁵ Bupropion has an atypical and not well-understood mechanism of action.⁵⁶ It is a weak norepinephrine uptake inhibitor but is a stronger inhibitor of dopamine uptake. The dopaminergic effect may be beneficial in some patients and may be stimulating and particularly effective for apathy. Bupropion is generally well tolerated with most common adverse effects being insomnia, anxiety, headache, tremor, nausea, dry mouth, and constipation as well as a dose-related increase in risk of seizures. Mirtazapine is an α_2 -antagonist and serotonin type 2 and type 3 (5HT₂ and 5HT₃)

receptor antagonist and may be effective in treating refractory patients. However, it is sedating and causes weight gain in some patients.⁵⁷ Nefazodone is a serotonin reuptake inhibitor and 5HT_{2A} receptor antagonist. It is administered in twice-daily dosing and the most common adverse effects are lethargy, dizziness, and dry mouth.⁵⁸

Tricyclic antidepressants should be used only if better tolerated agents are ineffective or in depression severe enough to warrant inpatient psychiatric hospitalization. Tertiary tricyclic antidepressants (imipramine and amitriptyline) should never be used in patients with AD because of the anticholinergic effects. Nortriptyline is the tricyclic antidepressant of choice because of fewer anticholinergic effects. Serum levels and electrocardiogram should be monitored at steady state before each dose increase with target levels of 50 to 150 ng/mL. Adverse effects include orthostatic hypotension, which places patients at risk for falls and hip fractures, cardiac conduction delays, and anticholinergic effects such as urinary retention, constipation, cognitive impairment, and delirium.

Specific target symptoms should be identified and monitored through the course of treatment to determine treatment response and to guide dose titration. Cognition should also be monitored with a simple instrument such as the MMSE. Treatment should be reevaluated periodically as depressive symptoms may decrease with natural disease progression. If symptoms are adequately controlled and there is no history of recurrent major depression, consider tapering the antidepressant in 6 months. Be prepared to reinstitute treatment if any depressive symptoms reemerge.

TREATMENT OF PSYCHOSIS IN AD

Choice of antipsychotic is determined by the adverse-effect profile. The low-potency agents, such as chlorpromazine, have significant anticholinergic adverse effects while the high-potency agents, such as haloperidol, have significant extrapyramidal adverse effects causing parkin-

sonism; both can predispose to falls. The newer atypical agents (risperidone, olanzapine, quetiapine, and clozapine) or midpotency agents such as perphenazine are preferred because of fewer adverse effects.

Haloperidol has demonstrated efficacy for psychosis and behavioral disturbance in dementia and was considered the criterion standard agent. However, its use is limited by extrapyramidal adverse effects even at relatively low doses, and it also causes cognitive deterioration.⁵⁹

Risperidone has demonstrated efficacy in psychosis and agitation in AD.⁶⁰ Even relatively low doses can produce the disabling extrapyramidal syndrome in older patients. Other potential adverse effects include postural hypotension and sedation. Olanzapine and quetiapine, the newest atypical antipsychotic agents, have not yet been well studied in this population. Clozapine has demonstrated efficacy in elderly patients with psychosis but, owing to the risk of agranulocytosis and need for weekly blood monitoring, it is not a first-line agent in AD. It should be reserved for patients who develop significant extrapyramidal syndrome or who remain refractory to other antipsychotics. Clozapine is a low-potency agent and is associated with orthostatic hypotension and sedation.

There are no data on the long-term benefits of antipsychotics although the long-term risks are well understood. Antipsychotic use should be reevaluated periodically (every 3-6 months) to determine continued necessity. Dose tapering should be attempted if symptoms are under adequate control. If symptoms reemerge during drug taper, an effective dose should be reinstituted. The most serious long-term risk is tardive dyskinesia, which occurs at a much higher rate in elderly patients. Estimates of the risk of tardive dyskinesia in the elderly begin at 29% in the first year and increase to 40% after 10 years of antipsychotic exposure.⁶¹ The Omnibus Reconciliation Act regulations for nursing home care require frequent reevaluation of continued use of antipsychotics and other psychotropic medications. Dose reductions should be attempted at least twice per year to determine continued necessity.

TREATMENT OF AGITATION IN AD

The diagnostic evaluation of agitated behavior should begin with a thorough medical evaluation to search for a treatable cause such as urinary tract infection, fracture, decubitus, constipation, or reaction to a medication or drug interaction. The underlying medical problem should be treated or the offending medication discontinued. Once a physical illness has been ruled out, the underlying psychopathology should be determined and treated appropriately.⁶² Agitation may be associated with underlying depression, anxiety, psychosis, or delirium. If there is no underlying problem and the agitation is an isolated disturbance, antipsychotics are the most effective treatments. In a meta-analysis of antipsychotic trials,⁶³ antipsychotics were significantly more effective than placebo in reducing agitation, but there was a modest effect size, with only 18% of patients benefiting from antipsychotics over placebo. No antipsychotic was better than any other. Other treatment strategies for which there is limited evidence of efficacy include buspirone, carbamazepine, valproate, trazodone, propranolol, and lithium. Benzodiazepines are generally not useful for agitation and may produce paradoxical reactions (increased agitation and disinhibition) and cause sedation, falls, ataxia, amnesia, and delirium. Cholinergic agents such as the cholinesterase inhibitors and cholinergic agonists may also be effective for the behavioral disturbances. Theoretically, the behavioral complications may be due in part to altered cholinergic function, explaining why cholinomimetics can improve behavior. There is evidence that the cholinesterase inhibitors such as donepezil, tacrine, and metrifonate and the muscarinic agonist xanomeline can improve psychosis and behavioral disturbance in AD.^{30,39}

TREATMENT OF INSOMNIA IN AD

Insomnia or sleep-wake cycle disturbance is common in AD and occurs in up to 20% to 40% of patients. This can cause significant distress to family caregivers who are

awakened at night and may have to be vigilant to prevent wandering away from home or self-injury of the patient. Insomnia often occurs concurrently with other symptoms. Treatment of insomnia and sleep-wake cycle disturbance is not well studied in AD. Effective strategies include trazodone and zolpidem administered at bedtime. Chloral hydrate and benzodiazepines should only be used for short-term treatment. The benzodiazepine triazolam should be avoided due to amnesia. Diphenhydramine should be avoided because of anticholinergic effects.

CAREGIVER DISTRESS

Treatment of a patient with AD invariably also involves treatment of the family, especially the primary caregiver. The emotional, physical, and often financial stresses associated with caring for a relative with AD are enormous. Thus, it should come as no surprise that up to 50% of caregivers suffer from "caregiver burnout." This may take the form of depression, anxiety, isolation, substance abuse, or physical illness. Individual and family counseling and support as well as involvement in support groups can avoid or delay nursing home placement by almost 1 year.⁶⁴ These family intervention strategies are most effective in the early to middle stages of the illness, again reinforcing the need for early illness recognition. Respite services can also provide a source of relief to family members so that they can have some time for taking care of themselves and renewing social relationships with others. The Alzheimer's Association is an excellent source of information on local services such as support groups and respite care. Families should be referred to their local chapter for additional support.

CONCLUSIONS

Alzheimer disease is the most common cause of dementia and will affect a growing number of people as the US population ages. It is now clear that AD is both diagnosable and treatable. Because most patients with AD are treated in the primary care

setting, it is important for primary care practitioners to be able to accurately diagnose and effectively treat AD. The primary care practitioner has multiple roles in the treatment of AD. The primary care practitioner must accurately diagnose AD and distinguish it from depression, delirium, and other causes of dementia. This practitioner must also be prepared to treat the cognitive impairment, treat the behavioral disturbances, refer to a specialist when there is uncertain diagnosis or difficult-to-manage psychiatric manifestations, provide education and support to the patient and their family, help maintain safety in the community, and address long-term care issues.

Early recognition is important to begin pharmacological therapy at the point in the illness when it can be most effective and to provide education about progression of the illness, help families and patients anticipate the course of the illness, and discuss planning for the future. Alzheimer disease is a diagnosis of inclusion based on history and clinical presentation. A full laboratory and neuroimaging workup is not necessary in every case to rule out other causes of dementia.

Cognitive impairment may improve in the short-term with the cholinesterase inhibitors tacrine and donepezil. New cholinesterase inhibitors such as metrifonate and cholinergic agents such as specific muscarinic and nicotinic agonists will be available soon. Vitamin E and selegiline may slow disease progression. Other disease-altering strategies are currently being investigated including estrogen, nonsteroidal anti-inflammatory drugs, and neurotrophic factors.

Behavioral disturbances including depression, psychosis, and agitation are common in AD and are treatable with antidepressants, antipsychotics, and other psychotropic medications, as well as with acetylcholinesterase inhibitors. The natural course of behavior disturbance changes with progression of the illness, so patients require repeated regular reassessment of treatment and alteration as appropriate.

Treatment of a patient with AD also involves treatment of the fam-

ily. This includes providing education and support, referral to the Alzheimer's Association and other support networks, evaluating caregiver burnout, helping assess and maintain safety in the community, and helping families deal with the legal issues and with long-term care when and if appropriate.

Primary care physicians are not alone in treating patients and their families with dementia and AD. Specialists should be consulted in atypical or complex cases.⁵⁰ Neurologic consultation is important for patients with parkinsonism, focal neurologic signs and atypical presentations, or course of illness. Geriatric psychiatrists should be consulted for difficult-to-treat behavioral or psychiatric manifestations. Psychologists can provide behavior management, family counseling, and functional evaluations. Neuropsychologists can help clarify uncertainties in diagnosis and ascertain cognitive and functional impairment. Other supports include social workers, attorneys, community support agencies, area councils on aging, and the Alzheimer's Association.

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