Diagnosis and Treatment of Alzheimer's Disease

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Program Audience

Primary care physicians.

Educational Needs Addressed

Alzheimer's disease (AD), the most prevalent dementia, is a neurodegenerative disorder that leads to progressive cognitive impairment and is often accompanied by behavioral symptoms. An estimated 5 million persons in the United States currently have AD. Most cases of AD are diagnosed and managed by community-based physicians, often the primary care provider. As evidence-based therapeutic options expand, it is increasingly important for physicians to achieve an accurate diagnosis, to identify comorbid disorders and other potentially contributing factors, and to offer individualized treatments based on a patient's specific diagnoses, cognitive and behavioral symptoms, and psychosocial needs. Additionally, the aging of the population necessitates patient education about healthy life habits that may decrease the risk of dementia.

Educational Objectives

After participating in this CME activity, primary care physicians should be able to

1. Accurately determine the diagnosis of dementia in patients with memory problems
2. Distinguish AD from other causes of dementia
3. Recognize and treat the cognitive and behavioral impairments in patients with dementia
4. Describe appropriate treatment for the different stages of AD
5. Describe lifestyle habits or modifications that may decrease the likelihood of developing dementia

Alzheimer's disease (AD), the leading cause of dementia, is a devastating degenerative disease of the brain that results in progressive cognitive impairment and functional disability. Dementia prevalence doubles about every 5 years among the elderly [1]. The worldwide prevalence of dementia is estimated at 0.3% to 1% for people aged 60 to 64 years but rises to 42% to 68% for those aged 95 years or older [2]. It is estimated that currently over 5 million people are now living with AD in the United States, and this number is projected to increase to 7.7 million by 2030 [3]. The annual direct and indirect costs of AD and other dementias amount to more than $148 billion annually [3]. AD affects not only patients but also family members and caregivers, who are called on to support a loved one who is gradually becoming more impaired and difficult to care for.

Because AD is frequently diagnosed and most commonly managed by the primary care physician, it is important for primary care physicians to be able to identify dementia in the early stages, distinguish among different dementia types, and institute appropriate therapy for the cognitive and behavioral symptoms and the functional impairment that accompanies dementia. Additionally, given the aging of the population and the looming dementia epidemic, it is important that healthy lifestyle measures that can prevent or postpone dementia be discussed with patients prior to symptom onset.

CASE STUDY
Initial Presentation

A 68-year-old widow is brought in to the clinic by her family for evaluation of memory loss. Her son and daughter-in-law first noticed some mild forgetfulness 2 years ago, but they initially believed it was "just a normal part of getting old." However, over the past 9 months, the memory deficits have significantly worsened and they are concerned.

History

The patient's family states that the patient has difficulty remembering details of conversations and will sometimes repeat stories or ask questions over again, even after they

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Table 1. Diagnostic Criteria for Dementia

1. The development of multiple cognitive deficits manifested by
   a. Memory impairment *and*
   b. At least 1 of the following:
      (1) Language disturbance (aphasia)
      (2) Loss of motor skills (apraxia)
      (3) Difficulties with recognition or complex perceptual skills (agnosia)
      (4) Impairment in planning, organizing, sequencing, or abstracting (executive dysfunction)
2. Cognitive deficits substantially impair social or occupational functioning and represent a substantial decline from a previous level of functioning
3. Cognitive deficits do not occur exclusively during a confusional state (delirium)

Derived from American Psychiatric Association. Diagnostic criteria from DSM-IV. 4th ed. Washington (DC): The Association; 1994.

have been answered. She has recently begun misplacing objects, such as her purse, keys, and eyeglasses. While the family generally feels that she is a safe driver, there have been a few times when she got lost on her way to meet them at a restaurant or store. However, she does not appear to have a problem navigating in familiar neighborhoods. The patient has remained active and still maintains her household, completing light chores without many problems. She typically prepares simple meals without any difficulty, but now she tends to get confused with more complicated recipes and once forgot a pot on the stove until it burned. Basic activities of daily living, such as dressing, bathing, and toileting, are unaffected. Her son is particularly concerned because his mother recently has forgotten appointments with her dentist and friends, whereas in the past she was very careful with her schedule. There is no evidence of depression, agitation, or psychosis (including delusions or hallucinations).

Past medical history is significant only for mild osteoarthritis and childbirth. She has no history of stroke, head trauma, diabetes, or cardiac disease. In addition, there is no family history of dementia or cognitive impairment. She takes only a multivitamin and occasional over-the-counter pain relievers. She has no history of smoking, significant alcohol use, or recreational drug use. She is a high school graduate who was a homemaker and raised 3 children. She enjoys sewing, gardening, and spending time with her grandchildren. After the death of her husband, she has lived alone; she has several friends and meets them regularly to go walking at the local shopping mall for exercise.

Physical Examination

On initial examination, the patient is a casually dressed, pleasant woman and maintains good eye contact. Her social skills are intact and her mood is euthymic. She is not particularly concerned about her memory problems, and doesn't understand why her family wants her evaluated. During the interview, she repeated herself a few times and had mild word-finding difficulty.

- **What is dementia?**

Dementia refers to disorders of the brain that affect cognition sufficiently to impair the ability to perform usual daily activities. The key symptom of dementia is impairment in memory, associated with deficits in at least 1 other cognitive domain, such as language, skilled motor movements, recognition, or executive functioning (ie, planning, organizing, sequencing, or abstracting) (**Table 1**) [4,5]. These deficits must represent a decline in abilities and be severe enough to interfere substantially with work or usual social activities. Using this definition, memory represents the ability to learn new information and recall this information after an interval of time from 1 or 2 minutes to much longer. Of note, a confusional state or delirium can occur in older persons with infections, metabolic abnormalities, or adverse reactions to medications. This does not necessarily represent a dementia; however, patients with underlying cognitive impairment are more susceptible to delirium. Evaluation for dementia should not be done until after the delirium resolves. Less severe cognitive impairment, particularly characterized by isolated memory deficits not severe enough to interfere substantially with daily activities, is often referred to as *mild cognitive impairment*, sometimes representing an early "preclinical" phase of AD [6] and other dementias. Research is being conducted to further define and identify mild cognitive impairment because early treatment may be able to delay symptom worsening and the diagnosis of dementia [7].

- **What are the causes of dementia?**

The most common dementing illness is AD, but dementia with Lewy bodies (DLB), vascular dementia (VaD), and frontotemporal lobar degeneration (FTLD) are frequently encountered. In a dementia brain bank series, 77% of brains had AD pathology, 26% DLB, 5% FTLD, and 18% VaD. Mixed pathologies were common, causing the total in this study to exceed 100% [8]. The other causes of dementia can usually be distinguished from AD on clinical grounds.

Table 2. Clinical Characteristics of Common Dementias

Diagnosis	Gradual Onset and Progression?	Early Memory Loss?	Prominent Early Behavior Symptoms?	Elementary Neurologic Findings at Onset?	Other Features	Response to Acetylcholinesterase Inhibitors?
Alzheimer's disease	Yes	Yes	No	No	Apathy and delusions are common; general cognitive decline	Yes
Dementia with Lewy bodies	Yes	Yes	Variable	Parkinsonian signs	Fluctuating attention, visual hallucinations	Yes*
Frontotemporal lobar degeneration (FTLD)					Parkinson's symptoms or amyotrophic lateral sclerosis may accompany the FTLD dementia subtypes	No
Frontotemporal dementia	Yes	No	Yes			
Progressive aphasia	Yes	No	No			
Semantic dementia	Yes	No	Yes			
Vascular dementia	Usually, but not always, stepwise	Variable	Variable	Usually signs of focal brain involvement	Stroke risk factors present	Yes*

*Acetylcholinesterase inhibitors are not approved by the U.S. Food and Drug Administration for dementia with Lewy bodies or vascular dementia. Approved use is restricted to mild or moderate Alzheimer's disease, where evidence of efficacy is more compelling.

Alzheimer's Disease

The key clinical feature in AD is the gradual loss of the ability to recall recent events or information, soon accompanied by declines in other cognitive skills (**Table 2**) [9,10]. Cognitive loss generally reflects the malfunction of brain regions more severely affected by intraneuronal neurofibrillary tangles and extracellular neuritic plaques, the characteristic histopathologic changes of AD. Symptom onset is insidious, often recognized only in retrospect. Common early cognitive symptoms in addition to memory loss are loss of visuospatial skills (eg, getting lost and problems with copying geometric figures) and decreased calculation ability. Common early behavioral symptoms include apathy, depression, and delusions, such as delusions of theft or infidelity. Unlike their family members, many patients with AD fail to recognize there is a problem. For some patients, agitation, aggression, and sleep problems complicate the course of the disease. Loss of language abilities usually begins after memory loss and parallels global cognitive decline. Visual or auditory hallucinations occasionally occur but typically not in the early disease course, and elementary motor and sensory functions are preserved until quite late. Life expectancy is reduced in the AD patient compared with a person without dementia. During terminal stages of the disease, patients may be confined to bed and unable to walk, care for themselves, or recognize close family members. They experience complications of limited mobility, including contractures and susceptibility to pressure sores. Eating and even swallowing may be problematic, and the patient often succumbs to infections associated with immobility or to coexisting medical illnesses.

Dementia with Lewy Bodies

DLB is characterized by symptoms associated with both AD and Parkinson's disease. The defining pathologic hallmark is the cortical Lewy body, an intraneuronal inclusion first described in the substantia nigra of patients with Parkinson's disease. In addition, many patients with cortical Lewy bodies have tangles and plaques more typical of AD, although the burden of these changes in DLB is frequently less than with AD. Not surprisingly, DLB shares symptoms and signs suggestive of both Parkinson's disease and AD. The dementia is progressive and characterized by the presence of parkinsonism (especially extrapyramidal rigidity), fluctuating attention, and well-formed visual hallucinations; 2 of these 3 features are required for clinical diagnosis [11]. Disruptive motor behaviors during the rapid eye movement stage of sleep, also known as REM sleep behavior disorder, occurs frequently in patients with DLB and can even be a heralding symptom [11].

Frontotemporal Lobar Degeneration

FTLD refers to syndromes associated with selective atrophy of the frontal and temporal lobes. Cases diagnosed as Pick's disease would fall in the FTLD spectrum. Histopathologic features of FTLD vary but include intracellular inclusions such as Pick bodies or Pick cells, cell loss, or hippocampal sclerosis, and some cases show no distinctive histology [12–14]. The clinical picture is 1 of 3 different presentations: frontotemporal dementia, characterized by behavioral symptoms with alterations in personality and typically disinhibited or socially inappropriate behavior; progressive nonfluent aphasia, characterized by a progressive loss of language abilities with

Table 3. Routine Diagnostic Evaluation for Dementia

- Clinical history from patient and family
  - Memory problems or other cognitive losses affecting daily functioning?
  - Any accompanying psychiatric or behavioral symptoms?
  - How did symptoms start?
  - How did symptoms progress?
- Cognitive testing using 1 or more tests below
  - Mini-Mental State Exam
  - Montreal Cognitive Assessment
  - Comprehensive neuropsychological assessment
- Laboratory screening
  - Vitamin B_{12} level
  - Thyroid-stimulating hormone
  - Complete blood count
  - Comprehensive metabolic panel
  - Consider:
    - Rapid plasma reagin
    - Specific syphilis serologies
    - HIV
- Structural brain imaging with magnetic resonance imaging or computed tomography

a nonfluent aphasia but preserved social skills until late in disease progression; or semantic dementia/progressive fluent aphasia, characterized by loss of recognition of words, objects, and even faces, obsessive preoccupation, and interpersonal interactions characterized by loss of empathy or sympathy [14]. Symptoms commonly begin before age 65 years and associated syndromes, including motor neuron disease or amyotrophic lateral sclerosis and a movement disorder suggestive of Parkinson's disease, may accompany FTLD. Clinical findings that set this dementia apart from AD are marked changes in behavior and early loss of social skills, young age of onset, and preservation of visuospatial skills until late in the disease.

Vascular Dementia

As the term implies, VaD represents dementia attributed to vascular disease of the brain, cerebral infarction (ischemic stroke), or hemorrhagic stroke as documented by history, neurologic examination, or brain imaging findings [15,16]. White matter disease, abnormal signal in the brain white matter seen on magnetic resonance imaging (MRI), without strokes or lacunes (small strokes ≤ 5 mm in diameter), is not a cause of dementia but is commonly seen in patients with AD and normal aging [17]. VaD varies by impairment in multiple areas of neurologic and cognitive function. The course of VaD is variable; cognitive impairment or dementia may begin following a single strategic stroke without sufficient improvement, there may be a stepwise progression with periodic declines following acute strokes followed by stabilization, or a slow and gradual course without noted clinical infarcts until the impairment is severe enough to warrant medical attention. Thought processes are typically slowed, and errors are made when integration of different cognitive abilities is needed. Movement is also slow, and the neurologic examination almost always shows focal increases in tone, focal weakness, and brisk or pathologic reflexes. When caused by discrete infarcts, the clinical assessment reflects the brain areas involved, such as an aphasia following a left hemisphere stroke. The course of dementia can often be substantially stabilized if stroke risk factors such as hypertension or hyperlipidemia are adequately controlled, and stroke prophylaxis (eg, with an antiplatelet agent) is initiated. The main goal of therapy is to reduce stroke risk factors, and management of cognitive and behavioral symptoms is similar to that of AD.

Further Evaluation

The patient's physical examination is within normal limits; specifically, there are no focal abnormalities on neurologic examination and no signs of parkinsonism (tremor, bradykinesia, or rigidity) or localizing signs suggestive of stroke. On mental status examination she scores 24 out of a potential 30 points; she loses 2 points on orientation (missing the exact date and day), 1 point on attention (serial 7s), and 3 points on word recall after a brief delay. She does not benefit from cues or multiple choice on the recall task. She has mild word-finding difficulty but has no problem naming a pencil and watch.

Laboratory tests show a normal complete blood count, comprehensive chemistry panel (including electrolytes, glucose, blood urea nitrogen, creatinine, and liver function tests), thyroid-stimulating hormone level, rapid plasma reagin, and vitamin B_{12} level. Noncontrast head computed tomography (CT) shows no evidence of stroke or masses and only mild generalized cerebral atrophy.

- **What are components of a dementia evaluation?**

When cognitive problems are first identified in a patient, the most important information is the patient's clinical history and evaluation to reveal the pattern of cognitive deficits. Recommended evaluation typically includes a clinical history, physical and neurologic examination, cognitive screening, screening laboratory blood tests, and brain imaging [18] (**Table 3**). Important clinical information includes the mode of onset, initial symptoms, pattern of progression, and accompanying neurologic and behavioral symptoms. Common questions for memory loss may ask if the patient repeats

himself frequently, forgets appointments or phone calls, or misplaces objects. When the memory loss is severe, the patient may forget important events like a family meeting or a death in the family. Identifying behavioral symptoms is important because changes in personality and behavior dominate the initial presentation of FTLD and because such symptoms can often be adequately treated. Successful treatment of behavioral symptoms can improve quality of life for caregivers as well as patients, often more so than treatment of cognitive symptoms.

Screening blood tests for dementia typically include tests for thyroid function, vitamin B_{12} level and tests of electrolytes, glucose, renal and liver function, and a complete blood count [18]. In select populations, a screen for HIV or syphilis is appropriate, and other laboratory tests are warranted in particular clinical settings. Screening tests focus particularly on conditions that can contribute to cognitive dysfunction, even when the primary cause of dementia is likely a degenerative brain disease. Although this screen infrequently identifies a specific cause of dementia, it often uncovers exacerbating conditions, treatment of which may improve cognition, behavior, and function. Additional screening tests may be warranted in atypical cases, such as genetic testing for presenilin-1 mutations (linked to early-onset AD) in a young patient (< 55 years) with a strong family history of dementia.

Structural brain imaging with a noncontrast CT or MRI scan is appropriate in the initial evaluation of dementia [18]. The MRI provides better spatial resolution and may be more specific for certain disorders (eg, recent infarction, inflammatory disorders). Generalized atrophy is common in AD but nonspecific. When assessed at research centers, marked atrophy of the hippocampus or entorhinal cortex may be predictive for the presence of dementia due to AD [19]. Remarkable imaging techniques that are available only as research tools include imaging of the pathologic hallmarks of AD using positron emission tomography (PET) markers [20,21].

To briefly quantify a patient's cognitive dysfunction, a short standardized test is useful; 2 suggestions for this purpose are the Mini-Mental State Examination (MMSE) [22] or the Montreal Cognitive Assessment (MoCA) [23]. The MMSE is older and more widely used but the MoCA accurately measures more areas of cognition and may be more sensitive to early cognitive impairment. Both tests take about 10 minutes to administer. A more exact determination of the pattern of cognitive deficits can be obtained through comprehensive neuropsychological testing, which is especially helpful in cases of very early or questionable dementia.

Additional screening tests not part of the standard evaluation of dementia may increase diagnostic certainty in atypical cases. Functional imaging, such as single photon emission computerized tomography (SPECT) or PET, though not considered diagnostic, can aid in the diagnosis of different dementia types and is most recognized in the differentiation of FTLD from AD [24–26]. Patients with an unusually rapid dementia course, seizures, or decreased consciousness need a lumbar puncture to help rule out infection. Cerebrospinal fluid measurement of tau and β-amyloid$_{1-42}$ concentrations can increase diagnostic certainty of AD and can be used in patients with an atypical presentation due to young age or confounding conditions that adversely affect cognition, such as stroke, trauma, or substance abuse [27].

- **What findings support a diagnosis of AD in this patient?**

The patient has multiple areas of acquired cognitive deficits (memory, language, and visuospatial) resulting in functional impairments (cooking meals, keeping scheduled appointments, getting lost). These symptoms were of gradual onset and progression, and there is no evidence of an acute confusional state. A diagnosis of AD is supported by the results of screening laboratory tests and structural brain imaging, as well as the absence of focal neurologic signs (including parkinsonism), depression, substance abuse, or visual hallucinations. She meets the criteria for dementia (Table 1).

- **How should she be treated?**

Treatment of Mild to Moderate AD

The mainstay of pharmacologic treatment is use of acetylcholinesterase inhibitors (AChEIs), approved by the U.S. Food and Drug Administration (FDA) for treatment of dementia due to AD. AChEIs block the breakdown of acetylcholine, the main neurotransmitter whose concentration is decreased in the AD brain. The 3 AChEIs commonly used are donepezil, rivastigmine, and galantamine. Though the AChEIs have similar mechanism of action and side effect profile, the FDA-approved indications differ between the 3 medications (**Table 4**). AChEI treatment can improve cognition, function, and some problematic behaviors [28–31]. Though treatment improves the condition somewhat, it does not stop disease progression, and other treatment interventions are frequently required. Evidence-based estimates are difficult to derive, but patients receiving AChEIs appear to be about 6 months to a year better than they would have been without treatment.

At therapeutic doses, the AChEIs show similar efficacy and side effect profiles. The most frequent side effects are gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhea, and weight loss. Other less frequent side effects are headache, insomnia, dizziness, and muscle

Table 4. Profile of Acetylcholinesterase Inhibitors

Agent	Initial Dose	Dosing Interval	Therapeutic Daily Dose	FDA-Approved Indication
Donepezil	5 mg	Daily	5–10 mg daily	Mild to severe AD
Galantamine	4 mg	Bid	8–12 mg bid	Mild to moderate AD
Galantamine ER	8 mg	Daily	16–24 mg daily	Mild to moderate AD
Rivastigmine	1.5 mg	Bid	6–12 mg bid	Mild to moderate AD and PDD
Rivastigmine patch	4.6 mg	Daily	9.5 mg daily	Mild to moderate AD and PDD

AD = Alzheimer's disease; bid = twice daily; FDA = U.S. Food and Drug Administration; PDD = Parkinson's disease with dementia.

Table 5. Medical Conditions in Which Treatment with Acetylcholinesterase Inhibitors Are Contraindicated or Should Be Used with Caution

Cardiac
Symptomatic bradycardia
Sick sinus syndrome
Heart block greater than first degree
History of congestive heart failure
Unexplained episodes of syncope or presyncope
Pulmonary
Chronic obstructive pulmonary disease
Asthma
Pulmonary conditions requiring regular use of oxygen besides obstructive sleep apnea
Gastrointestinal
Untreated gastrointestinal bleeding in the last 6 mo
Active peptic ulcer disease

cramps. AChEIs are relatively well tolerated if given with food and if dosage elevations occur no more often than monthly. Because of peripheral cholinergic effects, AChEIs are contraindicated or should only be used with caution in certain medical conditions (**Table 5**). Cholinergic deficits are present in DLB and VaD as well as AD. Rivastigmine is the only FDA-approved AChEI [32] for use in Parkinson's disease with dementia, defined as the presence of Parkinson's disease at least 2 years before the onset of dementia. AChEIs are possibly efficacious in VaD [33–35], but use in this condition is not FDA approved. Less is known about AChEIs in patients with FTLD but preliminary evidence suggests that it worsens disinhibition or compulsive acts [36].

Behavioral strategies targeting patients and their caregivers can improve functional and behavioral outcomes in AD [37]. Caregiver education and caregiver respite are important. The Alzheimer's Association (1-800-272-3900; www.alz.org) is a valuable educational resource for all aspects of the disorder. Local support groups provide emotional support as well as practical insight on managing medical, behavioral, social, and legal aspects of the disease. An identification bracelet is a necessary safety measure to assure that lost patients with dementia can safely be returned home. The Safe Return program sponsored by the Alzheimer's Association (www.alz.org/we_can_help_safe_return.asp) offers the Safe Return ID bracelet with a 24-hour emergency response number that immediately contacts the patient's family and activates a support network should a patient become lost. A similar bracelet is available for caregivers.

For many adults, operating a motor vehicle is a key to independent daily living, and the loss of driving privileges is perceived as a loss of autonomy. Complex motor, perceptual, and cognitive skills required for safe driving can be affected even in mild AD [38,39]. Driving skills are better preserved when cognition is only mildly impaired and the presence of dementia is questionable [38,39]. Legal requirements vary by state regarding physician reporting of dementia (confidential reporting to the department of public health is mandated, for example, in California). Guidelines from the Quality Standards Subcommittee of the American Academy of Neurology suggest that recommendation of driving discontinuation should be strongly considered even for mild AD [38]. When dementia is very mild or questionable, evaluation of driving performance by a qualified examiner can help clarify if it is safe for a person to drive. Because impaired driving causes such great risks, the decision not to discontinue driving should be reassessed in 6 months [38].

Initial Management

The diagnosis of AD is discussed with the patient and her family. After reviewing the various pharmacologic treatment options, they agree to a trial of an AChEI (donepezil), which is titrated up to a standard dose after 4 weeks. She tolerates the medication well, with only mild gastrointestinal upset for the first few days. The family reports that she appears more interactive and "sharp" after starting the medication.

The family is referred to the local chapter of the Alzheimer's Association for caregiver information and support groups and to a social worker. They are also advised to address legal and financial planning, such as the patient's will and durable power of attorney for health care. A home

safety evaluation is scheduled to assess her living situation. In addition, upon her physician's recommendation, the patient agrees to stop driving, and family members arrange to take her to appointments and on shopping trips.

3-Year Follow-up

Three years later, the patient demonstrates continued gradual cognitive decline. Her MMSE score is now 17 out of a possible 30, and she has more prominent word-finding difficulties on interview. She is still able to perform her basic activities of daily living but she sometimes needs prompting. She is no longer able to perform her instrumental activities of daily living. She has moved in with her son and daughter-in-law, who now handle all her finances, appointments, cooking, and shopping. They are concerned that she is depressed, since she is often tearful and irritable and no longer seems to enjoy activities and visits with family. She is socially withdrawn and has stopped going out with friends. The patient admits to feeling sad but denies feeling hopeless or suicidal, and there are no psychotic symptoms. There is no evidence of abuse or neglect. The family reports that they never leave her alone in the house because she once wandered away, and they are concerned it could happen again.

Although her cognitive deficits have worsened over the past 3 years, the rate and degree of decline are consistent with the original diagnosis of AD. The family is involved with the Alzheimer's Association, and agrees to purchase a Safe Return ID bracelet in case she wanders in the future. Due to the patient's depressive symptoms, the physician suggests a trial of a selective serotonin reuptake inhibitor (SSRI) antidepressant. She is started on a low dose, which is titrated up slowly over the next few months. Her mood and irritability improve noticeably, although she remains somewhat apathetic.

- **What pharmacotherapies are used to manage the behavioral symptoms of dementia?**

Noncognitive symptoms of dementia, such as psychosis, depression, and agitation, are common in AD (**Table 6**). Psychotropic medications are frequently used off-label to address such symptoms when nonpharmacologic treatments (eg, behavioral interventions, psychotherapy, environmental manipulation) have failed or when the situation is urgent, such as in cases where the safety of the patient or others is threatened. In general, the use of medications in the elderly must take into account changes in pharmokinetics and pharmacodynamics. Elderly patients often are on multiple medications, which can lead to significant drug-drug interactions. Patients with dementia may also be more sensitive to adverse effects of medications, such extrapyramidal symptoms from neuroleptics or confusion from anticholinergics. Patients with DLB in particular may not tolerate treatment with neuroleptics.

Table 6. One-Month Prevalence of Behavioral Symptoms in Demented Patients in the Cardiovascular Health Study

Behavioral Symptom	Alzheimer's Disease, %	Other Causes of Dementia, %
Delusions	19	14
Hallucinations	11	10
Agitation or aggression	33	25
Depression	31	35
Anxiety	21	23
Euphoria	4	2
Apathy	36	36
Disinhibition	12	15
Irritability	26	30
Aberrant motor behavior	19	8
Sleep disturbance	26	32
Eating disturbance	18	24

Note: Prevalence based on 362 persons classified as having dementia with informant-based behavioral data from the Neuropsychiatric Inventory. (Adapted with permission from Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 2002;288:1475–83.)

Depressive symptoms are common in AD and other dementia syndromes. The SSRIs appear to be generally well tolerated by patients with AD and may also address other noncognitive symptoms as well [40–43]. Side effect profiles should be taken into account when selecting an agent; antidepressants with significant anticholinergic effects should be avoided, whereas sedating or appetite-stimulating side effects may be favorably exploited in patients with insomnia, anxiety, agitation, or poor appetite.

Antipsychotics have been used for psychosis in dementia as well as for general aggression and agitation. As for antidepressants, antipsychotic agents are not approved specifically for use in dementia by the FDA. Studies have supported the use of both conventional and atypical antipsychotic agents in AD patients, typically for symptoms of psychosis, agitation, and aggression, although effects are modest and significant side effects may occur [44–47]. However, the recent CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease) study found no large clinical benefits to the use of atypical antipsychotic medications (olanzapine, quetiapine, and risperidone) versus placebo [48], and no health economic or effectiveness benefits when compared with placebo [49].

In addition to the risk of adverse events well known to occur with use of these agents (eg, extrapyramidal symptoms, sedation, anticholinergic effects, neuroleptic malignant syndrome, tardive dyskinesia), there is evidence that antipsychotic medication use is associated with a significantly higher risk of death in the elderly. In April 2005, the FDA issued a public health advisory regarding the association of atypical antipsychotic use with increased mortality in elderly patients with dementia in 15 of 17 placebo-controlled trials utilizing olanzapine, aripiprazole, risperidone, or quetiapine [50]. Specifically, there was approximately 1.6- to 1.7-fold increase in mortality compared with placebo-treated subjects; most deaths were due to cardiac events or infections. As a result, black box warnings were added to the labeling for all of the atypical antipsychotics. An independent meta-analysis of 15 trials of atypical antipsychotics also found an association with an increased risk for death (odds ratio, 1.54; 95% CI, 1.06–2.23) compared with placebo [51]. The use of conventional antipsychotics, however, may also be associated with higher risk in elderly patients with dementia. A retrospective study of 22,890 elderly patients [52] found that conventional agents were associated in the short term with a higher risk of death than atypical antipsychotics. This result, and the adverse effects associated with conventional neuroleptics, suggests that despite the black box warnings on atypical agent labels, substituting older antipsychotics may not be safer.

Clinicians should carefully consider the risk-benefit ratio of utilizing pharmacologic treatments for patients with dementia, use the lowest possible effective dose, and make periodic attempts to taper patients off of medications. More studies looking at the safety and efficacy of psychotropic medications for the noncognitive symptoms of patients with AD are clearly needed to guide the selection of treatment.

5-Year Follow-up

Approximately 7 years after the onset of memory problems, the patient remains on an AChEI and SSRI. She is still able to perform most of her basic activities of daily living but requires regular prompts for hygiene and needs assistance picking out appropriate clothing for the occasion and weather. She frequently accuses people of stealing from her, causing significant distress in the family. When the family leaves the house even briefly, she locks the doors, fearful that outsiders will come in and steal things. Sometimes she is so anxious about the possibility of theft that she stays awake most of the night, which keeps the rest of the family up. However, she is not aggressive and there are no hallucinations.

On interview, her speech is empty, with prominent word-finding difficulties. She can only answer simple questions. Her MMSE score is now 11 out of 30 points. She appears withdrawn but denies feeling sad or suicidal. Her daughter-in-law, who spends the most time providing care for her mother-in-law, appears tired and distressed. It is suggested that the family look into adult day care centers or other respite care alternatives, in addition to caregiver support groups and eventual consideration of long-term care placement. Memantine is started and titrated up to a standard dose over 4 weeks. The patient tolerates it well, and at follow-up the family reports that she is calmer and more interactive than before, although her significant cognitive and functional problems remain.

- **How should patients with more severe AD be managed?**

The principles for treatment of mild to moderate AD discussed above also apply to the more advanced stages. Of the 3 commonly used AChEIs, only donepezil is approved by the FDA for patients with advanced dementia, though small studies with the other AChEIs suggest potential benefit [53,54].

Memantine has FDA approval for use in moderate to severe AD (roughly corresponding to MMSE scores of 5–17). Memantine is an uncompetitive antagonist of the N-methyl-D aspartate (NMDA) class of glutamate receptors. NMDA receptors play a crucial role in learning and memory, but sustained receptor activation is implicated in processes leading to programmed cell death (apoptosis) [55]. In clinical trials, memantine compared with placebo [56] or memantine plus donepezil compared with donepezil alone [57] provided modest improvement in global severity, cognition, behavior and functional activities, and it decreased care-giving burden. The side effect profile of memantine is favorable, and there are few interactions with other medications. Memantine is contraindicated in patients with renal failure, and dosage should be titrated more slowly in patients with renal insufficiency.

Prevention and Future Treatment

The 2 areas of greatest research interest for AD are prevention and the development of disease-modifying treatment. In the realm of prevention there is a focus on beneficial nutrients and diet, medications that decrease the risk of AD, beneficial exercise, and other lifestyle factors. Beneficial nutrients for prevention or postponement of disease onset include polyphenols, compounds found in fruits and vegetables, and other food products such as turmeric and fish oil. Evidence primarily from epidemiologic studies suggest fish oil, a source of omega-3 fatty acids, seems to be protective against AD, and protective against death following a heart attack based on placebo-controlled studies [58–62]. The polyphenols, including catechins from green tea, resveratrol from wine, and many others, are powerful antioxidants

that seem to protect consumers from many diseases including AD [63]. Curcumin, derived from turmeric, also has a number of protective mechanisms that may help prevent AD [64]. The Mediterranean diet, which represents a healthy pattern of eating, seems to be a particularly healthy diet for the prevention of AD, heart disease, cancer, and other cardiovascular disorders [65,66]. **Table 7** lists the more and less healthy components of the Mediterranean diet; a diet pattern associated with better health and longevity would be predominantly composed of the healthy components with minimal consumption of less healthy components.

There 2 main types of medications currently FDA-approved for other conditions that seem to decrease the risk of getting AD: statins and nonsteriodal anti-inflammatory drugs (NSAIDs). Statins seem particularly protective. Users of statins have been found to have a decreased risk of AD and to be significantly less likely to have AD pathology at autopsy [37,67,68]. A large amount of epidemiologic data support that use of NSAIDs prior to age 65 years is associated with a lower risk of AD [69,70]. Despite promising epidemiologic, animal, and cell culture evidence for benefit, there are few prospective controlled studies of nutrients or pharmaceuticals for prevention, and the few that exists are generally too small for meaningful information. Though these medicines seem promising, they should only be used for their approved indication until definitive studies showing efficacy in dementia have been completed. Currently, some large well-designed studies looking at these compounds are now underway.

Lifestyle factors including regular moderate exercise [71,72], social connectedness [73,74], and mental activity such as gardening or hobbies [75] are also associated with a lower risk of dementia development. A healthy diet, exercise, and mental activity currently seem to be the most reliable and cost-effective means of AD prevention or postponement of symptoms. The optimal time for a healthy lifestyle to prevent dementia is not known but is probably decades before the usual onset of symptoms and perhaps lifelong.

A number of newly developed medications are currently being investigated for their ability to alter the pathology of AD and significantly alter the course of the disease. The pathologic hallmarks of AD are amyloid plaques formed of aggregated β-amyloid$_{1\text{-}42}$ and hyperphosphorylated tau protein that form neurofibrillary tangles. The main targets for treatment development are the modulation of β-amyloid formation, aggregation, and the clearance of it from the brain. Drugs aimed at decreasing the formation of β-amyloid include inhibitors or modulators of gamma secretase activity, such as tarenflurbil (also known as R-flurbiprofen) [76], and statins which modulate enzymes that can form β-amyloid. Tramiprosate is a medicine being studied to prevent aggregation of β-amyloid [77], and different passive and active immunization strategies are being employed to promote β-amyloid removal from the brain.

Table 7. Mediterranean Diet Components

Healthy components
Fish
Fruits
Vegetables
Nuts
Grains
Cereal*
Legumes
Olive oil is primary oil used
Moderate wine consumption (1–2 glasses daily)
Less healthy components
Dairy products
Eggs
Rare use of red meat (≤ 1/mo)
Poultry
Saturated oil

*Cereal is loosely defined as cereal flakes, flour, pasta, bread, and rice. Most of these cereals should be derived from whole grain.

CONCLUSION

AD is a common disease and its frequency is expected to greatly increase with the aging of the population. Treatment of AD needs healthy lifestyle habits before the onset of AD symptoms, patient and caregiver education after the disease begins, and medications to treat the cognitive and behavioral symptoms. In the future, there will likely be more effective medications to treat and stabilize AD, and possibly there will be medications to prevent AD in susceptible people.

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CME EVALUATION: Diagnosis and Treatment of Alzheimer's Disease

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. The routine diagnostic evaluation for a patient with symptoms of dementia include
   A. Clinical history of symptom onset, characterization of symptoms, and progression
   B. Laboratory tests to evaluate for common metabolic or thyroid disorders
   C. A cognitive screening test
   D. All of the above

2. Visual hallucinations early in the disease are characteristic of what type of dementia?
   A. Alzheimer's disease (AD)
   B. Dementia with Lewy bodies
   C. Frontotemporal dementia
   D. Vascular dementia

3. FDA-approved treatment options for moderate to severe AD include
   A. Donepezil
   B. Memantine
   C. Galantamine ER
   D. Both A and B

4. Acetylcholinesterase inhibitor dosing titration should occur no sooner than
   A. Monthly
   B. Weekly
   C. Daily
   D. Based on patient's tolerance of medication

5. Lifestyle factors associated with a lower risk of AD include
   A. Healthy diet rich in fruits, vegetables, legumes, and grain
   B. Regular exercise
   C. Cognitive stimulation
   D. All of the above

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