Annals of Internal Medicine®

In the Clinic®

Dementia

Prevention and Screening

Diagnosis

Treatment

Alzheimer disease (AD) and other dementia syndromes are becoming more common; an estimated 5.5 million adults aged 65 years or older are living with AD in the United States. It is important for primary care physicians to gain knowledge in this field because most community-dwelling older adults receive their care from them. This article discusses the latest findings in approaches to prevent cognitive decline as well as dementia screening, diagnosis, and treatment. Approaches to address quality of life for persons with dementia and their caregivers are also discussed.

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Dementia is defined as a decline in 2 or more cognitive capacities that causes impairment in function but not alertness or attention. The decline in cognition distinguishes it from lifelong intellectual disability (previously called "mental retardation") and single learning disorders, both of which are present from birth and symptomatic in childhood. That 2 or more cognitive capacities must be impaired distinguishes dementia from amnestic mild cognitive impairment (MCI), amnestic syndrome (previously called Korsakoff syndrome), and single focal brain lesions. The impairment in functional activity also distinguishes it from MCI, although this interpretation is controversial. Intact attention and alertness distinguish it from delirium. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, has recently proposed replacing "dementia" with "neurocognitive disorder" to destigmatize the syndrome. However, opponents point out that the latter term lacks specificity because it includes other categories of cognitive impairment, such as intellectual disability, learning disabilities, and delirium.

Dementia is a syndrome rather than a specific illness; the most common types are Alzheimer disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. One percent to 2% of patients presenting with dementia have a potentially reversible disorder, such as normal-pressure hydrocephalus, medication-induced cognitive impairment, hypothyroidism, or major depression. Although dementia can begin at any age after childhood, it predominantly occurs later in life, with an estimated prevalence of 14% in persons aged 71 years or older, increasing to 37.4% in those aged 90 years or older (1).

Caring for patients with dementia presents a heavy emotional and financial burden for families and society. Patients can be cared for initially in the home, but institutionalization is ultimately required for many—67% die in nursing homes (2). Depending on the methods used to value informal care, the yearly per-person cost attributable to dementia ranged from $41 689 to $56 290 in 2010 (3).

Although most forms of dementia currently have no cure, research findings and accumulated clinical experience support a set of practices that maximize the function and well-being of patients with dementia and their families. This approach incorporates a broad range of practices, including comprehensive diagnostic assessment, optimization of treatment for general medical conditions, attention to patient comfort and quality of life, pharmacotherapy, control of psychiatric symptoms, and education and support of the patient's family.

Prevention and Screening

What medical interventions or health behaviors can help patients prevent dementia or cognitive decline?

Although each type of dementia has several risk factors, data supporting the effectiveness of specific preventive measures to address them are limited.

A recent report on dementia prevention by the Lancet Commission identified 9 potentially modifiable risk factors for dementia and calculated a population-attributable fraction (the percentage reduction in new cases of dementia over a given time if a particular risk factor were to be eliminated) for each. Potentially modifiable risk factors and their population-attributable fractions include the following:

during early life (age <18 years); less education (7.5%); during midlife (age 45 to 65 years): hypertension (2.0%), obesity (0.8%), and hearing loss (9.1%); during later life (age >65 years): smoking (5.5%), depression (4.0%), physical inactivity (2.6%), social isolation (2.3%), and diabetes (1.2%). Although these risk factors are categorized by life stage, it is important to recognize that they are important throughout life (4).

Whether intervening on potentially modifiable risk factors prevents cognitive decline is unclear. In 2017, the National Institute on Aging commissioned the Agency for Healthcare Research and Quality to review evidence for interventions to delay or slow cognitive decline or incident dementia. This systematic review concluded that there was no strong evidence for any intervention to delay or slow cognitive decline or incident dementia, although there was evidence that cognitive training in older adults improves cognitive performance in the specific domain being targeted. In addition, although most of the physical activity intervention studies did not show significant differences between the intervention and control groups in terms of cognitive performance, the pattern of results suggests effectiveness of different types of physical activities, including aerobic and resistance training, and multicomponent physical activity (5). Moreover, FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) found that targeting 4 components simultaneously (nutrition, exercise, cognitive training, and social activity) was effective in improving or maintaining cognitive function in older adults (6). This suggests that targeting several risk factors simultaneously may be more effective in preventing cognitive decline.

More recently, SPRINT-MIND (Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension), which randomly assigned participants aged 50 years or older (mean age, 67.9 years) to intensive (<120 mm Hg) versus standard (<140 mm Hg) blood pressure treatment goals, did not find a statistically significant reduction in risk for probable dementia, the primary outcome (7). However, a secondary analysis found a significant reduction in risk for MCI, raising the possibility of reduced incidence of dementia with longer follow-up.

An important area in which clinicians can make an impact is minimizing or deprescribing medication that may affect cognitive function, particularly benzodiazepines, anticholinergics, barbiturates, and other sedative-hypnotics. Studies have shown that older patients using benzodiazepines or other sedative-hypnotics perform more poorly on cognitive tests than those not using them (8). Deprescribing these medications would be important in optimizing cognitive function.

Although epidemiologic evidence suggests that midlife estrogen use is associated with lower incidence of dementia later in life (9), prospective prevention trials, including the large WHIMS (Women's Health Initiative Memory Study), found that estrogen plus progestin was associated with increased incidence of dementia and other medical complications compared with placebo (10).

WHIMS was a placebo-controlled, randomized controlled trial of estrogen plus progestin (n = 2229) versus placebo (n = 2303) for prevention of dementia in women aged 65 years or older. Use of estrogen for a mean of 4 years was associated with a relative risk of 2.05 (95% CI, 1.21 to 3.48) for dementia during the study period.

In the recent Agency for Healthcare Research and Quality systematic review, omega-3 fatty acids and ginkgo biloba did not prevent Alzheimer dementia and vitamin E showed no benefit in cognitive performance in women. Evidence for vitamin B_{12} plus folic acid was mixed (5).

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Should clinicians screen for dementia?

The U.S. Preventive Services Task Force does not recommend universal screening for dementia (11).

In IU-CHOICE (Indiana University Cognitive Health Outcomes Investigation of the Comparative Effectiveness of dementia screening) (ClinicalTrials.gov: NCT01699503), 4005 primary care patients aged 65 years or older were randomly assigned to dementia screening or no screening. Those in the screening group who were identified as having possible dementia were referred to the Collaborative Dementia Care Program for a subsequent diagnostic assessment, counseling, and management. There were no between-group differences in the primary outcomes (health-related quality of life, depression, and anxiety), and there were no differences in the secondary outcomes (health care use and advance care planning) at 12 months. Mortality and serious adverse events also did not differ (12).

However, it is important to distinguish between universal screening and targeted screening or case identification because dementia is prevalent but is often undetected in the primary care setting (13).

In a study involving review of the primary care records of 297 patients, dementia in 65% of those meeting the criteria was not noted on their chart, including 20% with advanced dementia (13). In another study examining the effect of underlying cognitive impairment in hospitalized patients with congestive heart failure (CHF), cognitively impaired patients with CHF had significantly higher 30-day readmission rates than those with other diagnoses. In this study, cognitively impaired patients with CHF who had documented caregiver education had lower readmission rates, suggesting that recognition of cognitive impairment and inclusion of caregivers in the discharge education process may improve outcomes (14).

Therefore, clinicians should consider dementia in the differential diagnosis of adult patients of any age with symptoms of memory difficulty that interfere with daily function, unexplained functional decline, deterioration in hygiene, poor adherence to medication regimens, new-onset psychiatric symptoms, and new or repeated hospitalizations. In some cases, new onset of delirium during an acute illness may also be one of the first signs of underlying dementia.

What methods should clinicians use to look for dementia?

When older patients are being evaluated for dementia, clinicians should use a standardized screening instrument together with a brief history from the patient and a knowledgeable informant. The screening instrument should be easy to use, highly sensitive, widely available, and supported by population data relevant to the patient. The Mini-Mental State Examination (MMSE) (15) has been widely used but is now copyrighted. Alternatives include the Mini-Cog (16), the St. Louis University Mental Status Exam (SLUMS) (17), and the Montreal Cognitive Assessment (MoCA) (18). The Mini-Cog has the benefit of brevity, the SLUMS is most similar to the MMSE (19), and the MoCA has the best sensitivity but lower specificity (20). It is important to note that the MoCA was originally developed for detection of MCI and may be difficult for persons with moderate or advanced dementia. For those whose past cognitive function was measured with the MMSE, a tool is available to link MoCA scores to the corresponding MMSE scores (21).

Prevention and Screening... Use of benzodiazepines, anticholinergics, barbiturates, and other sedative-hypnotics must be minimized in older patients. Screening for dementia in the older population is not recommended, but in some patients a brief history taken from the patient and a knowledgeable informant together with a standardized instrument, such as the Mini-Cog, the SLUMS, or the MoCA, can be used to decide whether a more extensive evaluation is necessary.

CLINICAL BOTTOM LINE

What elements of the history are especially important in evaluating patients with suspected dementia?

Clinicians should use the patient's history to characterize cognitive deficits, generate a differential diagnosis, and determine the cause of the dementia. This is best accomplished by identifying medical, neurologic, and psychiatric signs and symptoms that may provide clues to the cause of the cognitive problems and establishing their order of appearance, severity, and associated features. In the case of cognitive difficulties, it is most important to try to obtain collateral information from a knowledgeable informant because cognitive dysfunction can impair the patient's ability to report accurately. It is often easier to collect this information without the patient present.

When taking the history, the physician must be knowledgeable about the differential diagnosis and natural history of the most common types of dementia (**Table 1**). For example, in classic AD, early symptoms are difficulties with short-term memory, subtle language and visuospatial perceptual problems, and changes in executive function. Significant reductions in efficiency and organizational abilities that the patient may or may not recognize could also occur. Symptoms begin insidiously and progress slowly. The overall level of alertness remains unimpaired. Patients or families may not label these as memory problems but may instead report conversations where the patient has no recollection of previous discussions, increased forgetfulness that causes the patient to lose objects or become confused while shopping, or increased disorganization and decreased efficiency. Symptoms are often first noticed or reported at the time of a life change, such as the death of a spouse, a move into a new residence, a hospitalization, or a vacation in an unfamiliar place. In earlier stages, symptoms are predominantly changes in cognitive function (MCI stage), which then progress to more significantly affect daily function (early/mild stage). In later stages, more assistance is needed in daily activities (middle/moderate stage), with the patient finally requiring assistance in personal care and mobility (advanced/severe stage). Clinical diagnostic criteria for AD are available from the National Institute on Aging and the Alzheimer's Association (see the Box: Clinical Diagnosis of All-Cause Dementia and AD) (22).

Clinicians evaluating a patient with a change in cognition or overall function must consider delirium, which is characterized by acute disturbance in attention and awareness, with additional disturbance in cognition. In contrast to dementia, onset of delirium is usually abrupt, and fluctuations over minutes or hours are common. In addition, unlike dementia, delirium may start to resolve once the underlying cause is treated. Although some patients may be agitated and manifest psychotic symptoms (hyperactive delirium), others are slow and drowsy and seem mildly depressed or withdrawn (hypoactive delirium). Prompt diagnosis of delirium is critical because it usually reflects an underlying systemic condition, such as infection, metabolic derangement, medication effect, or cancer. Such instruments as the 3-Minute Diagnostic Confusion Assessment Method (23), which facilitates rating of the Confusion Assessment Method; the 4 A's Test (24); or the Confusion Assessment Method for the Intensive Care Unit (25) facilitate identification of delirium. It is

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Table 1. **Differential Diagnosis of Cognitive Difficulties**

Disease	*Characteristics*	*Notes*
Alzheimer disease	Early symptoms include gradual memory loss, preserved level of consciousness, impaired IADL performance, subtle language errors, and worsened visuospatial perception. Middle-stage symptoms include apraxia, disorientation, and impaired judgment. As the illness progresses, aphasia, apraxia, agnosia, and inattention may develop. In the final stages, patients are dependent for IADLs/ADLs and lose the ability to ambulate and swallow.	The presenting symptom to the physician may not relate to cognition. Earliest presenting symptoms may be paranoid delusions or depression, which are only later recognized as part of a dementia syndrome. Neurologic signs, such as falls, tremor, weakness, or reflex abnormalities, are not typical early in the disease. Their presence earlier suggests a diagnosis other than Alzheimer disease.
Vascular dementia	Ideally, loss of function should be correlated temporally with cerebrovascular events. "Stepwise" deterioration may be seen. May be present in patients with "silent" strokes, multiple small strokes, or severe diffuse cerebrovascular disease.	Should be suspected in any patient with cerebrovascular risk factors, even if a neurologic examination does not suggest a stroke.
Dementia with Lewy bodies	Mild parkinsonism; unexplained falls; hallucinations and delusions early in the illness; extreme sensitivity to extrapyramidal side effects of antipsychotic medications; gait difficulties and falls; fluctuating cognition.	May account for up to 20% of total dementia cases. Should be suspected in patients with nonvascular dementia but abnormal neurologic examination.
Frontotemporal dementia	Onset often before age 60 y. Language difficulties are common. Memory often preserved early on. Prominent personality changes, often with behavioral disturbances, such as hyperphagia, worsened impulsivity or aggression, or prominent apathy.	Includes such disorders as progressive supranuclear palsy, primary progressive aphasia, semantic dementia, amyotrophic lateral sclerosis with dementia, and corticobasal degeneration. Functional neuroimaging often demonstrates diminished function in frontal or temporal lobes.
Delirium	Acute onset and fluctuating course of symptoms, inattention, impaired level of consciousness, and disturbance of cognition indicating disorganization of thought (e.g., disorientation, memory impairment, or alteration in language).	Must be excluded to diagnose dementia. Diagnosis is critical because delirium may reflect serious systemic disturbance, such as metabolic abnormalities, medication effects, or infection.
Major depression	Low mood; anhedonia; diminished sense of self-worth; hopelessness; altered appetite, libido, and sleep; increased somatic symptoms; irritability; and wishes for death.	Cognitive impairment may result solely from major depression. Major depression may also be the initial presentation of dementia.
Medications	Common culprits include benzodiazepines, barbiturates, anticholinergics, and other sedative-hypnotics.	Cognitive impairment in patients with dementia may be exacerbated by medications.
Mild cognitive impairment	Evidence of memory impairment in the absence of other cognitive deficits or functional decline.	Many patients progress to dementia (about 12% to 15% per year).
Subdural hematoma	May or may not occur in setting of falls or head injury. Nonspecific headache. Level of consciousness may wax and wane.	Classic presentation is the exception rather than the rule. Neurologic deficits may be minor.
Traumatic brain injury	Clinical features may vary according to site of injury. Personality and mood changes are common.	Postconcussion syndrome may include inattention.
Normal-pressure hydrocephalus	Dementia, gait abnormality (slow, broad-based, impaired turning), and urinary incontinence. Dementia is often associated with psychomotor slowing and apathy.	If suspicion is high, lumbar puncture is performed, with gait monitoring before and after. Ventriculoperitoneal shunting can be curative in some patients.
Vitamin B_{12} deficiency	Insidious onset. May be associated with depression. Neurologic examination may reveal diminished proprioception and vibratory sense, ataxia, and positive Babinski sign.	If serum B_{12} level is in the low-normal range, elevated serum methylmalonic acid and homocysteine levels indicate low intracellular vitamin B_{12} level. Anemia may be absent.
Chronic alcohol use	Chronic alcohol use seems to lead to mild to moderate dementia, which may reverse after a period of abstinence.	This is distinct from Korsakoff syndrome, an isolated loss of short-term memory without global dementia.
Toxins	Aromatic hydrocarbons, solvents, heavy metals, marijuana, opiates, and sedative-hypnotics.	Urine or serum toxicology and heavy metal screens are useful.
Parkinson disease	Features of subcortical dementia, cortical dementia, or both. Free recall may be impaired with preservation of recognition memory. May have impaired visuospatial function.	In contrast to dementia with Lewy bodies, patients with Parkinson disease and dementia typically have motor symptoms of Parkinson disease long before dementia and do not have prominent psychotic symptoms or fluctuating consciousness.
Other causes	Advanced liver or renal disease, brain tumor, chronic CNS infection, CNS vasculitis, Creutzfeldt–Jakob disease, electrolyte abnormalities, HIV-associated dementia, Huntington disease, multiple sclerosis, neurosarcoidosis, neurosyphilis, systemic lupus erythematosus, thyroid disease, Wilson disease.	–

ADL = activity of daily living; CNS = central nervous system; IADL = instrumental activity of daily living.

Clinical Diagnosis of All-Cause Dementia and AD*

All-cause dementia is the presence of cognitive or behavioral (neuropsychiatric) symptoms that:

- Interfere with the ability to function at work or in usual activities
- Represent a decline from previous levels of function
- Are not due to delirium or a major psychiatric disorder
- Are diagnosed through history, clinical examination, and a standardized instrument
- Involve ≥2 cognitive domains

Probable AD:

- Meets criteria for dementia
- Gradual onset
- Progressive cognitive decline
- Cognitive deficits in learning and recall (amnestic) and/or language, visuospatial function, and executive function (nonamnestic)
- Additional factors, including positive family history, cerebral atrophy on neuroimaging, normal electroencephalogram, and lumbar puncture, would be helpful in diagnosis. Biomarkers, such as cerebrospinal fluid amyloid-β 42, amyloid positron emission tomography, and ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography, may increase certainty of AD pathophysiologic process but are not currently recommended for routine use.

*Adapted from reference 22.

important to remember that many older patients report minor cognitive problems, such as mild forgetfulness, difficulty remembering names, and reduced concentration. Patients with memory problems should be screened for dementia, but a complete evaluation should be reserved for those with measurable impairment in memory or other aspects of cognition.

How should clinicians evaluate the physical, mental, and cognitive status of patients with suspected dementia?

During the physical examination, the clinician should look for conditions that can cause or worsen cognitive symptoms (**Table 1**), with an emphasis on vascular and neurologic disease. The examination should include a mental status evaluation that begins with an assessment of the patient's level of alertness, general appearance, and cooperation, which can provide clues to delirium, depression, or nutritional deficiencies. Speech should be evaluated for its content (grammatical or semantic errors) and form (rate, fluency, and volume); the patient's mood and affect should be assessed for depression, anxiety or mania, and risk for suicide; and thought content and perception should be examined for delusions, hallucinations, obsessions, or compulsions. Focal deficits on neurologic examination and changes in speech may be due to cerebrovascular events leading to vascular dementia, and visual hallucinations and parkinsonism may suggest dementia with Lewy bodies. Early presentation of language difficulties or behavioral changes may also suggest frontotemporal dementia (**Table 1**).

The cognitive examination should include a standard instrument, such as the SLUMS, which takes 5 minutes to administer, or the MoCA, which can take 10 minutes. Both tests have strengths and limitations. The MoCA emphasizes executive function and is more sensitive; the SLUMS evaluates orientation, immediate recall, concentration, naming, language function, praxis, and visuospatial perception. It is important to assess for hearing or vision impairments and ensure that the patient has hearing aids and/or glasses because sensory impairments may affect test performance (26). Naming and praxis can be further tested by asking patients to name a series of common and

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uncommon objects and asking them to demonstrate tasks, such as brushing their hair or teeth or slicing bread. Abstract reasoning and judgment should be tested by asking for solutions to real-life problems, such as what to do if one smells smoke in the house, or by having the patient interpret proverbs or similes. Asking the patient to draw a clock and put the hands at 10 minutes past 11:00 is a quick test of visuospatial function, praxis, and planning ability. Also, the patient should be evaluated for corticosensory deficits, such as neglect or left–right confusion.

What laboratory tests are helpful in the evaluation of a patient with cognitive dysfunction?

According to guidelines from the American Academy of Neurology, patients who are evaluated for cognitive problems should have laboratory tests for common medical disorders, with selected additional studies depending on the specific clinical situation (27, 28) (see the Box: Laboratory Studies for Patients Being Evaluated for Cognitive Problems).

When should clinicians order imaging studies and other, more specialized laboratory studies?

Patients with cognitive difficulties for less than 3 years should have a neuroimaging study of the head using computed tomography or magnetic resonance imaging to exclude cerebrovascular disease, hemorrhage, tumor, abscess, Creutzfeldt–Jakob disease, and hydrocephalus. The yield is higher in patients with early onset; rapid progression; focal neurologic deficits; risk factors for cerebrovascular disease; recent falls; central nervous system (CNS) infection; unexplained fluctuation in consciousness; or symptoms atypical of AD, such as early and marked personality change. Routine use of glucose or amyloid positron emission tomography (PET) scanning is not recommended, although these tests may be useful in certain cases, such as to differentiate frontotemporal dementia from AD (29, 30). Recently, results from the IDEAS (Imaging Dementia—Evidence for Amyloid Scanning) study of 11 409 participants examined the potential benefits of amyloid PET imaging in those being assessed for dementia. There was an increase of 63.5% (CI, 62.1% to 64.9%) between the preimaging and postimaging periods in prescription of pharmacotherapy for AD or other dementias and counseling about safety and future planning in those diagnosed with dementia. This was greater than the prespecified target of 30% ($P < 0.001$). The study was not designed to identify whether these changes were associated with improved clinical outcomes (31). Amyloid PET is currently not covered by the Centers for Medicare & Medicaid Services.

Genetic studies are not indicated in the evaluation of dementia unless there is a specific concern about Huntington disease. Current evidence does not support routine testing for the *ApoE4* allele (32). Testing for the autosomal-dominant gene mutations found in patients with familial AD or frontotemporal dementia should be considered only if multiple family members are affected, the clinical picture and work-up support one of these disorders, and the patient is younger than 60 years at onset. Genetic counseling is recommended before genetic testing (32).

Other tests should be reserved for specific situations. Electroencephalography may be useful if delirium, seizures, encephalitis, or Creutzfeldt–Jakob disease is suspected. Lumbar puncture may be indicated in patients younger

Laboratory Studies for Patients Being Evaluated for Cognitive Deficits*

Comprehensive metabolic profile (hyponatremia, hypoglycemia, renal dysfunction, hepatic dysfunction)

Complete blood count (infection, anemia)

Thyroid-stimulating hormone level (thyroid dysfunction)

Vitamin B_{12} level (vitamin B_{12} deficiency)

Patients may also need to have the following tests (some based on exposure history):

- Rapid plasma reagin test (fluorescent treponemal antibody can be checked in cases where concern for neurosyphilis is higher) (syphilis)
- HIV test (HIV-associated dementia)
- Toxicology screen (alcohol, drugs)
- Erythrocyte sedimentation rate (vasculitis)
- Heavy metal screen (arsenic, mercury, aluminum, lithium, lead)
- Thiamine level (thiamine deficiency)
- Paraneoplastic panel (tumor)
- Chest radiography or computed tomography (infection, tumor)
- Urinalysis (infection)

*Adapted from references 27 and 28.

than 55 years and in those with rapidly progressive dementia; those with a positive rapid plasma reagin test result; and those with possible acute or chronic CNS infection, paraneoplastic syndrome, CNS cancer, or immunosuppression. Neuropsychological testing provides the most comprehensive assessment of cognitive function and is particularly useful if the diagnosis of dementia is uncertain (33) or a precise characterization of the patient's cognitive impairment is necessary.

What other disorders should clinicians consider in the assessment of cognitive dysfunction?

Patients with cognitive disturbances should be evaluated for not only the most common disorders that cause dementia but also medications, depression, and MCI. Patients with MCI (34) have cognitive decline with relative preservation of daily function and should be followed closely because 7% to 15% "convert" each year and meet the criteria for dementia; after 5 years, nearly 50% of patients with MCI meet dementia criteria (34).

Diagnosis... Patients who report cognitive and functional decline should be evaluated through a detailed history of medical, neurologic, and psychiatric symptoms from the patient and a knowledgeable informant. They should also have a thorough physical and mental status evaluation and a cognitive examination. Whether to order basic laboratory tests and additional studies, including structural neuroimaging, is dictated by the clinical presentation.

CLINICAL BOTTOM LINE

Treatment

What should clinicians advise patients and caregivers about general health and hygiene?

In the early stages of dementia, patients may have difficulty comprehending the details of their medical care, organizing care, and keeping track of appointments and medications. The clinician should be alert to these limitations and prepare a care plan that compensates for them. Later

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in the illness, patients may be unable to identify symptoms, such as constipation, dysuria, tooth pain, or diminished visual or auditory acuity, and the clinician should proactively look for these problems.

It is important to attend to general medical and preventive care as conscientiously as in patients without dementia. A stroke or heart attack due to uncontrolled hypertension is likely to impair a patient's function and quality of life as much as the dementia itself, at least in the early and middle stages of the disease. Because poor management of chronic conditions may lead to further cognitive decline, careful attention should be paid to good control of hypertension, diabetes, and cholesterol levels; antiplatelet therapy, when appropriate; and vaccinations. It is also important to individualize treatment goals on the basis of dementia stage and goals of care discussions. For patients with more advanced dementia, it becomes increasingly important to pay attention to nutrition, skin care (particularly of the perineum), toileting schedules, and dental care.

What should clinicians advise about safety issues, such as driving, cooking, and other activities that may require supervision?

Patients with progressive dementia ultimately lose the ability to drive, but predicting when an individual patient should stop driving is difficult, particularly if the restriction significantly burdens the patient or their family. Nonetheless, addressing the issue is imperative because many studies have shown that driving ability becomes impaired in early stages of the disease.

The patient should be asked about recent motor vehicle accidents, near misses, and changes in driving ability. These inquiries should be made in a setting that facilitates an open exchange of information and may necessitate meeting with an informant without the patient present. Patients with early dementia whose driving ability has already deteriorated should be instructed to stop driving immediately. Those with early dementia who have no history of driving problems should undergo a driving evaluation through the local motor vehicle administration or an occupational therapy program at a local hospital. If no impairment in driving is evident and the patient continues to drive, the history should be updated regularly to determine whether the capacity to drive has deteriorated. State laws differ with regard to reporting patients with a diagnosis of dementia to local motor vehicle administrations, and the clinician should be familiar with the applicable regulations. The American Academy of Neurology Evidence-Based Practice Parameter outlines an approach to assessing driving in patients with dementia (35).

In a prospective case–control study using the Washington University Road Test, which has an off-road and an on-road component, 3% of control participants failed the test, 19% of patients with very mild AD failed, and 41% with mild AD failed ($P < 0.001$). Previous driving experience did not protect against failure (36).

A physician recommendation can have beneficial and adverse outcomes. For example, a Canadian study of the results of physicians recommending that patients discontinue driving for various disorders reported a 45% reduction in road crashes (4.76 vs. 2.73 per 1000 patients) ($P < 0.001$), a decrease in return visits to the physician, and an increase in visits to emergency departments for depression (37).

Clinicians should assess other safety issues with the patient and their family on an ongoing basis. Patients with progressive dementia eventually are unable to administer medications; cook; or use power tools, lawnmowers, or firearms. Home safety assessments by an occupational therapist can determine which activities are still safe and which ones need to be limited or supervised. An activity can often be modified to allow safe ongoing participation, such as cooking or gardening with a family member or friend. Wandering from home is common, presents significant safety concerns, and must be assessed regularly.

When should clinicians prescribe acetylcholinesterase inhibitors and memantine?

Acetylcholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, can be prescribed for treatment of symptomatic AD (**Table 2**). These drugs are better tolerated if they are slowly titrated to reach the target dose. Memantine is approved for use in moderate to advanced AD and can be used in conjunction with acetylcholinesterase inhibitors. When the benefit is unclear, use of acetylcholinesterase inhibitors or memantine may be stopped but should be restarted if acute cognitive deterioration occurs. Patients and families may need help in developing realistic expectations for these agents. Adverse effects of acetylcholinesterase inhibitors include nausea, vomiting, diarrhea, bradyarrhythmia, syncope, weight loss, and abnormal dreams. Acetylcholinesterase inhibitors and memantine are not recommended for treatment of MCI.

One study followed 295 community-dwelling patients who had been receiving donepezil for at least 3 months and assessed outcomes at 1 year (38). The primary outcome included standard measures of cognitive ability as determined by the Standardized MMSE and the ability to perform activities of daily living as measured by the Bristol Activities of Daily Living Scale (BADLS). Compared with patients assigned to discontinue use of donepezil, those

Table 2. **Cognitive Agents for Alzheimer Disease**

Agent	*Mechanism of Action*	*Dosage*	*Benefits*	*Side Effects*	*Notes*
Donepezil	Acetylcholinesterase inhibition	Start at 5 mg/d. If tolerated, increase to target dose of 10 mg/d after 1 mo.	Delayed symptom progression in mild, moderate, and advanced Alzheimer disease	Nausea, vomiting, diarrhea, anorexia, bradycardia, syncope	Higher end of the dosing range may be less tolerable; dose >10 mg not recommended
Galantamine	Acetylcholinesterase inhibition	Start at 4 mg twice daily. Target dose total of 24 mg/d; increase by 4 mg twice daily every month until in target range	Delayed symptom progression in mild, moderate, and advanced Alzheimer disease Improvement in caregiver-rated quality of life was observed	Nausea, vomiting, diarrhea, anorexia, bradycardia, syncope	Start extended-release (once-daily) galantamine at 8 mg/d. Increase 8 mg/d every month to target dose of 24 mg/d
Rivastigmine	Acetylcholinesterase inhibition	Start at 1.5 mg twice daily. Target dose range of 6–12 mg/d; increase by 1.5 mg twice daily every month until in target range	Delayed symptom progression in mild, moderate, and advanced Alzheimer disease	Nausea, vomiting, diarrhea, anorexia, bradycardia, syncope	Higher end of the dose range may be less tolerable; start transdermal patch (once-daily) rivastigmine, 4.6 mg/d; if tolerated, increase to target dose of 9.5 mg/d after 1 mo
Memantine	NMDA-receptor antagonism	Start at 5 mg/d. Increase by 5 mg/d every week until target of 10 mg twice daily	Less functional decline, improved cognition, and reduced demands on caregivers in moderate to advanced Alzheimer disease; insufficient evidence to support efficacy for mild Alzheimer disease	Dizziness, confusion, headache, constipation	Generic available; branded drug available only in sustained-release form; available in tablets or solution; start extended-release (once-daily) memantine at 7 mg/d; increase by 7 mg/d every week as tolerated to target dose of 28 mg/d; avoid concomitant use with amantadine

NMDA = N-*methyl-D-aspartic acid*.

assigned to continue use had a Standardized MMSE score that was higher (indicating better cognitive ability) by 1.9 points (1.4 points is the minimum clinically important difference) (CI, 1.3 to 2.5 points) and a BADLS score that was lower (indicating less impairment) by 3.0 points (3.5 points is the minimum clinically important difference) (CI, 1.8 to 4.3 points). Patients assigned to receive memantine instead of placebo had a Standardized MMSE score that was 1.2 points higher (CI, 0.6 to 1.8 points; P < 0.001) and a BADLS score that was 1.5 points lower (CI, 0.3 to 2.8 points; P = 0.02). The differences between donepezil and memantine were not statistically significant, and addition of memantine to donepezil was not better than either drug alone.

Which other pharmacologic agents are helpful in treating specific types of dementia, and when should clinicians consider prescribing these agents?

The acetylcholinesterase inhibitor rivastigmine has been shown to be effective in improving cognitive performance in patients with mild to moderate Parkinson disease in doses similar to those used in AD, and this benefit is believed to occur with the other acetylcholinesterase inhibitors (39). The data are less clear for dementia with Lewy bodies (40). However, use of these drugs in patients with vascular dementia is not recommended.

Which pharmacologic agents are ineffective in treating specific types of dementia and should be avoided?

The herbal supplement ginkgo biloba does not slow progression of dementia. Also, nonsteroidal anti-inflammatory drugs, estrogen, and ergoloid mesylates should not be prescribed for cognitive decline. Data on whether the widely used food supplements coconut oil and caprylidene can be recommended are inadequate. Recently, the U.S. Food and Drug Administration (FDA) issued a warning against companies selling products that have not been proved to safely and effectively treat the conditions that they claim to, including those that claim to prevent, treat, or cure AD. Physicians play an important role in informing patients about use of these products, which may be ineffective and potentially harmful (41).

When should clinicians prescribe antidepressants in patients with dementia?

Nearly one third of patients have an episode of major depression after onset of dementia (42), but evidence for the efficacy of antidepressants is mixed (43). One explanation is that some symptoms of major depression, such as weight loss and disturbed sleep, may be caused by dementia alone and complicate the diagnosis. Clinicians must therefore have a high index of suspicion for major depression.

What should clinicians advise about nonpharmacologic approaches to sleep problems, behavioral problems, and psychiatric manifestations of dementia?

Psychiatric symptoms, such as depression, anxiety, sleep problems, agitation, hallucinations,

and delusions, are common and often require intervention (44). Various nonpharmacologic approaches are effective and should be tried first unless the symptoms create immediate danger or cause marked distress (45). These approaches emphasize the notion that many emotional and behavioral disturbances can be "decoded," or understood in terms of internal or environmental factors that make them more or less likely to occur. This decoding process should be done using systematic approaches, such as 4-D (Describe, Decode, Devise, Determine) (46) or DICE (Describe, Investigate, Create, Evaluate) (47) (**Table 3**). Decoding involves describing the behavior in detail and noting its characteristics, including time of day, location, antecedent factors, people who are present and absent, proximity to eating or other key activities, and consequences of the behavior. Common examples of environmentally driven behavioral disturbances include agitation when the patient is hungry, tired, under pressure to perform, in pain, or lonely. Common examples in the institutional setting include agitation when personal care is being provided, during shift changes, and in the presence of certain staff members. When patterns are recognized, targeted interventions can be developed, implemented, and refined. Approaching behavioral disturbances this way can often preclude use of psychotropic medications.

Nonpharmacologic interventions were effective in reducing behavioral and psychological symptoms (overall effect size, 0.34 [CI, 0.20 to 0.48]; P < 0.01) and improving caregiver reactions to these behaviors (overall effect size, 0.15 [CI, 0.04 to 0.26]; P = 0.006) (45).

What treatment options manage behavioral disturbances or psychotic symptoms that are refractory to nonpharmacologic approaches, and what are their adverse effects?

Absent a significant risk for harm, psychotic symptoms, such as hallucinations, delusions, and agitated behavior, should first be treated nonpharmacologically (45) because all antipsychotic drugs carry elevated risk for death (48–50). Pharmacotherapy as an adjunct to nonpharmacologic intervention is indicated if symptoms cause significant distress for the patient or create a dangerous situation. Before starting use of antipsychotics, a trial of a selective serotonin reuptake inhibitor, such as citalopram, which has been shown to be effective in reducing agitation in patients with AD, may be warranted (51). However, because of potential dose-dependent QT interval prolongation, the FDA recommends not exceeding 20 mg/d for adults older than 60 years.

When treatment with an antipsychotic medication is being considered, second-generation agents are usually recommended over first-generation agents because of their lower risk for tardive dyskinesia. Overall, the efficacy of these agents is modest (52). Although more evidence supports use of risperidone and olanzapine, similar drugs also are used. These drugs should be prescribed at the lowest possible dose and for the shortest possible time. Ongoing use should be monitored regularly, and attempts should be made to decrease the dose and discontinue use of the drug within 3 months of starting. Antipsychotic medications should not be used to treat sleep disturbances because of their toxicity. The FDA requires black box warnings for second-generation antipsychotics because of increased rates of death and cerebrovascular events. The reasons for these bad outcomes are unclear, but falls, infections, and cardiovascular and cerebrovascular events may contribute. In addition, treatment with antipsychotic medications is associated with metabolic syndrome, weight gain, hyperlipidemia, and diabetes mellitus. Recent evidence supports the effectiveness

Table 3. **Approach for Assessing and Treating Behavioral and Psychiatric Disturbances***

Disturbance	*Define and Describe*	*Decode (What Causes the Problem?)*	*Devise a Treatment Plan*	*Determine Whether the Treatment Has Worked*
	What occurs, and under what circumstances?	Cognitive impairment, psychiatric symptoms, medical condition, environment?		
Persistent yelling	What is being said, and when is it said? What consequences result from the yelling (to the patient and others)?	Forgetfulness, fear (perhaps from psychotic symptoms), pain, shift changes, noise/other bothersome stimuli, presence/absence of particular people	Treat psychiatric or medical conditions, alter environment or patient placement within it, redirect, reassure, medicate	Monitor frequency of yelling after the intervention
Depressed mood	Describe patient's mood. What time of day is it exhibited? In what environment? Around which people? Are there clear precipitating events?	Frustration with forgetfulness, delirium, major depression, medications, general medical conditions, environment (recent move, departure of a caregiver, some trigger in the milieu)	Provide reassurance or distraction, treat depression (medications, electroconvulsive therapy), treat general medical conditions, adjust medications, improve patient activity regimen, adjust milieu	Monitor/document patient's mood after intervention; monitor/document side effects; identify barriers to implementation of the treatment plan

**Adapted from reference 46.*

and relative safety of nonpharmacologic interventions for neuropsychiatric and behavioral symptoms (45), which reinforces the recommendations to use drugs sparingly for these symptoms. However, head-to-head trials of pharmacologic and nonpharmacologic interventions have not been done.

How can sleep problems be treated?

Clinicians should try nonpharmacologic methods before using medications in patients with dementia who have insomnia because of the potential risks associated with sedative-hypnotics in this population. Careful attention should be paid to sleep environment, caffeine consumption, daytime sleeping, afternoon and evening medications, and other elements of basic sleep hygiene. Meta-analyses do not support the efficacy of any pharmacologic intervention. If necessary, 25 to 50 mg of trazodone can be used with careful monitoring (53).

What other steps should clinicians take to maximize quality of life?

Clinicians should proactively address issues that have the potential to significantly affect quality of life. Examples include working order of sensory aids, such as glasses and hearing aids; dental care; noise, lighting, and temperature; sufficient social and cognitive stimuli; cleanliness; pain levels; and constipation.

When should clinicians consult a dementia specialist?

Clinicians should consider consulting a neurologist, geriatric psychiatrist, geriatrician, or other dementia specialist in patients with atypical features of dementia, such as early onset, early noncognitive neurologic symptoms, rapid progression, early personality changes, or unusual symptom patterns. Consulting a geriatric psychiatrist or dementia specialist should also be considered for evaluation or management of difficult-to-treat neuropsychiatric symptoms, such as depression, psychosis, or behavioral disturbances. These symptoms can endanger the patient and others and reduce quality of life. Consulting a specialist should also be considered if patients require physical restraint. Referral to a neuropsychologist should be considered if it is unclear whether dementia is present and when in-depth documentation of impaired and preserved capacities would benefit the patient.

Treatment of dementia requires a broad clinical approach that ideally includes preventive medicine, psychoeducation, behavioral therapy, safety evaluation, and pharmacotherapy. The clinician should expect to interact with a broad range of professionals, including occupational therapists, social workers, physical therapists, and speech and language pathologists, to provide optimal care.

When should clinicians recommend hospitalization?

During assessment of cognitive impairment, hospitalization should be considered for patients who cannot be evaluated safely or comprehensively as outpatients because of dangerous behavior, unsafe living conditions, compromised nutrition, neglected medical conditions, or lack of cooperation.

Psychiatric hospitalization is sometimes required because of the severity of psychiatric symptoms. For example, hospitalization should be considered for depressed patients who exhibit suicidality, decreased food and fluid intake, delusions, depression, immobility, inability to attend to medical conditions, or need for electroconvulsive therapy. Patients with behavioral disturbances who are a danger to themselves or who cannot be treated safely or successfully as an outpatient because of wandering, violence, calling out, hyperphagia, or a severely disordered sleep–wake cycle should also be hospitalized. Patients with psychotic hallucinations and delusions may require hospitalization if they do not respond to outpatient treatment, require the addition of multiple medications, are in distress or having behavioral disturbances, or present a risk to others. Involuntary commitment may be required in any of these situations.

How can clinicians help families decide to move a patient with dementia into a long-term care facility?

As dementia progresses, moving to an environment that can adequately address the progressive needs of the patient (either an assisted-living facility or a nursing home) is often necessary (54). Some patients may need to move because of inadequate support at home. Generally, a move to a nursing home is prompted by development of physical and cognitive limitations that cannot be managed at home, such as the need for full assistance with transferring, ambulating, toileting, or feeding. Other patients have to move because of unmanageable psychiatric symptoms or high caregiver burden.

Families with ample financial resources may be able to provide many services at home that usually are provided in a facility. Periods of respite care may help families delay placement. Families should be supported and guided through the difficult and painful decision-making process. Families may be advised to proactively investigate facilities

in their region so a good decision can be made quickly—for example, because of a sudden change in functional ability after a medical illness or accident.

What caregiver needs should the clinician address?

Caregiving for a patient with dementia is extremely taxing, both physically and emotionally, and inquiring about caregiver well-being is a critical component of dementia care. Common caregiver symptoms include guilt, anger, grief, fatigue, loneliness, demoralization, and depression. The patient's symptoms and the demands on the caregiver change over time, so the well-being of the caregiver must be assessed at every visit.

Most caregivers benefit from a range of interventions (45) that focus on education about dementia, skills training, and the caregiver's well-being. Many pamphlets, books, and educational Web sites are available from the Alzheimer's Association and other sources. Patient and caregiver safety must be evaluated at each follow-up visit, and caregivers need to be informed about local respite programs and supported in long-term planning.

Caregivers should also be informed of the potential benefits of psychoeducational and other support groups, which are available in most areas. Several large, well-conducted trials have shown that groups that focus on problem solving, communication, management of behavioral disturbances, and emotional support were effective in delaying nursing home placement for up to 1 year, diminishing caregiver and patient depression, and reducing patient agitation and anxiety (45, 55–57).

What are the options for end-of-life care?

In 1 observational study, 81% of patients were considered for surgery or hospitalization, with decisions ultimately made by surrogates (58). Because full incapacitation is inevitable for every person with progressive dementia who lives long enough to experience the full course of the disease, early advance directives maximize the likelihood that the person's wishes for end-of-life care will be carried out. Physician support of the people making these decisions and awareness of advance directives is central to this decision-making process.

Observational studies also suggest that persons with dementia receiving hospice care have improved quality of life and are more likely to be treated for pain (59, 60). Experts recommend that clinicians consider discontinuing medications that have no short-term benefit, such as cholesterol-lowering agents (58). Decreased food intake is common in advanced dementia. Hand-feeding rather than tube-feeding is recommended by most experts, as is avoidance of antimicrobials for asymptomatic bacteriuria (61). However, the latter can be difficult to ascertain in noncommunicative patients with end-stage dementia.

Treatment... A broad approach that addresses comfort and quality of life, cognitive enhancement, stabilization of psychiatric symptoms, and caregiver well-being needs to be adopted. Patients with AD can be treated with acetylcholinesterase inhibitors, and memantine can be added for patients with moderate to severe AD. When the benefit is unclear, use of the drug may be stopped but may be restarted if acute cognitive deterioration occurs. It is important to identify and treat psychiatric symptoms, such as depression, psychosis, anxiety, and behavioral disturbances, with both behavioral and pharmacologic treatment to minimize risk factors for cerebrovascular disease and to treat any other conditions that could reduce cognition. Attending to safety issues, regularly monitoring the caregiver's well-being, and suggesting referral to support groups and other psychoeducational activities are also important.

CLINICAL BOTTOM LINE

In the Clinic
Tool Kit

Dementia

Patient Information

https://medlineplus.gov/dementia.html

https://medlineplus.gov/languages/dementia.html
Information on dementia from the National Institutes of Health's MedlinePlus in English and other languages.

www.alz.org/alzheimers-dementia/what-is-dementia
Symptoms, diagnosis, causes, and treatment information from the Alzheimer's Association.

www.nia.nih.gov/health/alzheimers
Patient information on Alzheimer disease and related dementias from the National Institute on Aging.

www.caregiver.org
Information for caregivers from the National Center on Caregiving.

Information for Health Professionals

www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/cognitive-impairment-in-older-adults-screening
2014 guideline from the U.S. Preventive Services Task Force on screening for cognitive impairment in older adults.

www.nia.nih.gov/health/alzheimers-dementia-resources-for-professionals
Alzheimer disease and dementia resources from the National Institute on Aging.

www.alz.org/professionals/healthcare-professionals
Resources and information on Alzheimer disease and dementia patient care from the Alzheimer's Association.

www.aan.com/Guidelines/home/GuidelineDetail/42
Practice guidelines for diagnosis and management of dementia from the American Academy of Neurology (updates in progress).

www.aan.com/Guidelines/home/GuidelineDetail/396
Practice guideline on assessment and management of driving risk in patients with dementia from the American Academy of Neurology.

WHAT YOU SHOULD KNOW ABOUT DEMENTIA

What Is Dementia?

Dementia is a decline in mental function that interferes with your daily life. There are different types of dementia, with Alzheimer disease and vascular dementia among the most common. Although dementia can begin at any age after childhood, it most commonly develops later in life. Symptoms usually start slowly and worsen over time.

What Are the Symptoms?

You may first notice symptoms at the time of a life change, such as a spouse's death, a hospitalization, or a vacation in an unfamiliar place. Symptoms include:

- Increased forgetfulness that may cause you to lose objects
- Not remembering previous conversations
- Trouble finding the right words
- Difficulty with familiar activities, like preparing a meal or making a phone call
- Feeling disoriented while out walking or driving
- Personality changes, such as becoming very confused, suspicious, or fearful

Can It Be Prevented?

Evidence shows that certain lifestyle changes may prevent a decline in mental function later in life. These include:

- Staying physically active
- Eating a healthy diet
- Staying social
- Doing activities that keep your mind busy, like puzzles
- Quitting smoking
- Controlling blood pressure, blood sugar, and cholesterol

How Is It Diagnosed?

There is no specific test for dementia. If your health care provider suspects you have dementia, they will ask questions about your symptoms and take a detailed medical history. They will also want to speak with a family member or friend who knows you well. Your provider will administer:

- A physical examination that also addresses mental status, speech, and mood
- Short screening tests that assess memory and language

You could also have laboratory tests or brain imaging to rule out other medical conditions that cause similar symptoms.

How Is It Treated?

Because dementia is progressive, treatment focuses on controlling your symptoms and avoiding harm. Regular medical checkups will maximize your function and well-being. These will include hearing and vision checks; reviewing medications that might make your symptoms worse; and ensuring that your vaccines are up-to-date and chronic diseases, like diabetes, are controlled. You will also be monitored for anxiety, depression, agitation, sleep disturbances, and hallucinations.

You and your caregivers should create a calm, predictable environment. Get enough rest, eat well, brush your teeth, and stay clean. Discuss your values and wishes with your caregivers early so they can make the best health care decisions for you if you become unable to do so. Having a care plan in place to address limitations caused by dementia is also important. Your provider may suggest a home safety assessment or a driving assessment. These will evaluate whether you are still able to cook, drive, keep track of medications, and do other activities independently.

Medicines are available to treat dementia symptoms. However, they are only mildly effective and have side effects. Talk with your provider about what is best for you.

Questions for My Doctor

- How do I know whether my memory loss is dementia?
- How can I manage my symptoms?
- Will medicine help me? Does it have side effects?
- How can I document my wishes to ensure they are followed?
- Will I need to go to an assisted living facility or a nursing home?
- Are there things I should stop doing now?
- Do I need to see a specialist?
- Are there support groups for me or my caregivers?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

Alzheimer's Association
www.alz.org/alzheimers-dementia/what-is-dementia

National Institute on Aging
www.nia.nih.gov/health/what-dementia-symptoms-types-and-diagnosis

Advance Care Planning
www.nia.nih.gov/health/advance-care-planning-healthcare-directives
https://polst.org

Patient Information