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Dementia

Dementia, or major neurocognitive disorder, is defined as a decline in 1 or more cognitive domains that causes impairment in everyday function. Alzheimer disease is the most common type of dementia in the United States, with an estimated 6.9 million adults who have Alzheimer disease and are 65 years or older. This article discusses the latest findings in preventing cognitive decline. It also discusses dementia screening, diagnosis, treatment, and the quality of life for persons with dementia and their caregivers.

Prevention and Screening

Diagnosis

Treatment

CME/MOC activity available at Annals.org.

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The decline in cognitive function distinguishes dementia from lifelong intellectual disability and single learning disorders, both of which are present from birth and symptomatic in childhood. The impairment in functional activity distinguishes dementia from mild cognitive impairment (MCI). And intact attention and alertness distinguishes dementia from delirium. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* proposed replacing "dementia" with "neurocognitive disorder" to destigmatize the syndrome.

Dementia is a syndrome rather than a specific illness; the most common types of dementia are Alzheimer disease (AD; 60% to 80%), vascular dementia (5% to 10%), dementia with Lewy bodies (5%), and frontotemporal dementia (3%). 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. The prevalence of AD increases with age, with an estimated prevalence of 35% in adults aged 85 and older.

Caring for patients with dementia is an emotional and financial burden for families and society. In the United States, patients can be cared for initially at home, but 70% die in nursing homes. Caregivers of persons with AD provided an estimated 18 billion hours of unpaid care in 1 year that was estimated at $346.6 billion in value (1).

Although most forms of dementia currently have no cure, accelerated progress is being made in developing diagnostic biomarkers and therapeutics for AD. In addition, recent research supports revisions in clinical care that maximize the function and well-being of patients with dementia and their families. These revisions include comprehensive diagnostic assessment, optimization of treatment of 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 discussions about prevention of dementia are infrequent during clinic visits (2), the evidence for dementia prevention is increasing.

The Lancet Commission identified 14 potentially modifiable risk factors for dementia and calculated for each risk factor the percentage reduction in new cases of dementia if a particular risk factor were to be eliminated (3). The risk factors and their percentage reductions follow, organized by the life stages when each risk factor is more likely to be important. For early life, less education was an important risk factor with a percentage reduction of 5%. For ages 18 to 65 years, the following risk factors were important: hearing loss (7%), high low-density lipoprotein cholesterol level (7%), depression (3%), traumatic brain injury (3%), physical inactivity (2%), diabetes (2%), smoking (2%), hypertension (2%), obesity (1%), and excessive alcohol intake (1%). And for ages older than 65 years, the important risk factors were social isolation (5%), air pollution (3%), and vision loss (2%).

Moreover, the FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) found that targeting a combination of nutrition, exercise, cognitive training, and social activity was effective in improving or maintaining cognitive function in older adults. This result suggests that targeting several risk factors

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simultaneously may be more effective in preventing cognitive decline than targeting individual risk factors. There are now global efforts through the World-Wide FINGERS network to reduce the risk for dementia using this approach (4).

Midlife hypertension is associated with increased risk for future cognitive impairment, and there is evidence for lowering blood pressure to prevent cognitive decline (3). The SPRINT-MIND study (Systolic Blood Pressure Intervention Trial-Memory and Cognition in Decreased Hypertension) randomly assigned participants with a mean age of 67.9 years to an intensive blood pressure treatment goal of <120 mm Hg versus a standard goal of <140 mm Hg. This study did not find a statistically significant reduction in risk for probable dementia, the primary outcome (5). However, a secondary analysis found a significant reduction in risk for MCI and a combined end point of MCI or probable dementia.

Another important area is minimizing or deprescribing medication that may affect cognitive function, particularly benzodiazepines, anticholinergics, barbiturates, and other sedative-hypnotics. There is potential harm from each individual medication and from the concurrent use of multiple medications (6).

In addition, hearing loss is a modifiable risk factor with a great potential for preventing cognitive decline (3). In the United States, an estimated 65% of the adults 71 years and older have some degree of hearing loss, yet only 29% use hearing aids (7).

The ACHIEVE study (Aging and Cognitive Health Evaluation in Elders) focused on cognitive decline in adults with ages from 70 to 84 years; 490 were randomly assigned to a hearing intervention and 487 were randomly assigned to a health education control. There was no statistically significant difference between the 2 groups in global cognitive change. However, in a prespecified stratified analysis, higher-risk participants who were older, had higher morbidity, and received the intervention experienced a 48% reduction in cognitive decline (8).

In a systematic review, omega-3 fatty acids and ginkgo biloba did not prevent AD, and vitamin E showed no benefit in cognitive performance in women. Evidence for vitamin B_{12} plus folic acid was mixed (9).

Should clinicians screen for dementia?

The U.S. Preventive Services Task Force does not recommend universal screening for dementia (10).

In a study involving review of the primary care records of 297 patients, 65% of patients who met criteria for dementia did not have dementia documented in their charts, including 20% with advanced dementia (11). In a retrospective Medicare claims data analysis of 81 364 beneficiaries, persons with a diagnosis of AD and related dementia (ADRD) were more likely to miss credit card payments and have subprime credit scores several years before diagnosis compared with demographically similar individuals without the diagnosis of ADRD (12). Another study involving 1461 respondents from the Health and Retirement Study found that persons with an ADRD diagnosis had 4 times greater odds of self-reported difficulties with medication management 1 to 2 years before the diagnosis (13). Therefore, the presence of these types of difficulties in instrumental activities of daily living should prompt screening for cognitive impairment.

Clinicians should consider dementia in the differential diagnosis of adult patients of any age with symptoms of cognitive difficulty, for example, memory or problem solving and any of the following conditions: a decline in the ability to conduct daily activities, unexplained functional decline, deterioration in hygiene, poor adherence to medication regimens, new-onset psychiatric symptoms, or new or repeated hospitalizations. In addition, new-onset

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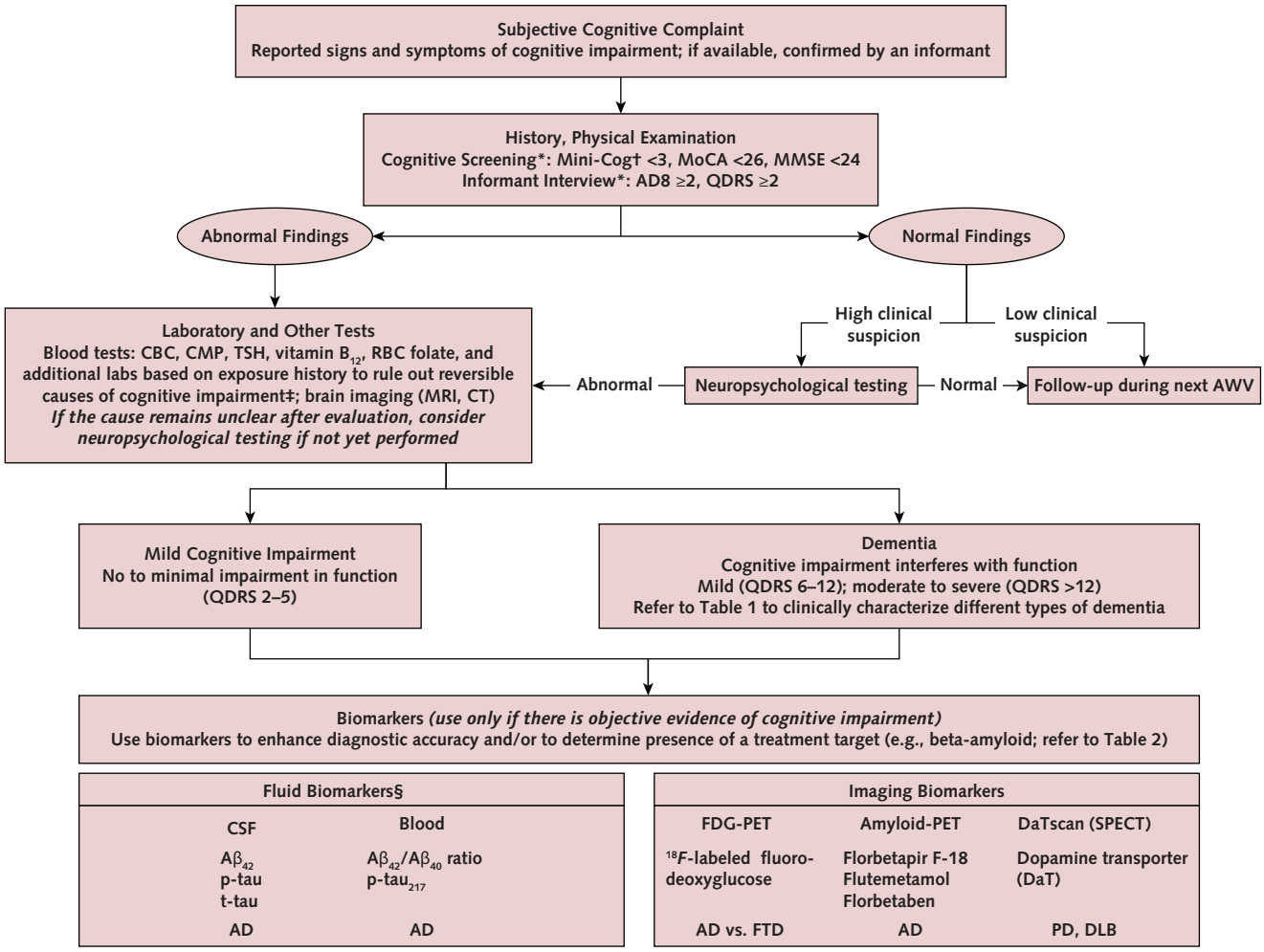
Figure. **Screening and diagnostic algorithm for cognitive impairment.**



Aβ = amyloid-beta; AD = Alzheimer disease; AWV = annual wellness visit; CBC = complete blood count; CMP = comprehensive metabolic panel; CSF = cerebrospinal fluid; CT = computed tomography; DLB = dementia of Lewy bodies; FDG = fluoro-2-deoxy-glucose; FTD = frontotemporal dementia; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; p-tau = phosphorylated-tau; PD = Parkinson disease; PET = positron emission tomography; QDRS = Quick Dementia Rating System; RBC = red blood cell; t-tau = total-tau; SPECT = single-photon emission computed tomography; TSH = thyroid-stimulating hormone.

* Cutoff values for abnormal scores.

† Mini-Cog: Following 3 words, aim for mid-range of pass rates ("banana," "sunrise," "chair").

‡ Rapid plasma reagin test (syphilis; fluorescent treponemal antibody can be checked in cases where concern for neurosyphilis is higher), HIV test, 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 CT (infection, tumor), urinalysis (infection).

§ Different laboratories use different biomarker measures (e.g., different protein ratios and different combination of proteins).

delirium during an acute illness may 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 Mini-Mental State Examination (14) has been widely used but is now copyrighted. Alternatives include the Mini-Cog (15) and the Montreal Cognitive Assessment (MoCA) (16). Compared with the Mini-Mental State Examination, the MoCA has better

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sensitivity for detecting earlier stages of cognitive impairment (17). Note that the MoCA was originally developed for detection of MCI and may be difficult for persons with moderate or advanced dementia. Guidance for the screening and work-up of dementia is presented in the **Figure**.

Prevention and Screening... Multidomain lifestyle intervention and blood pressure control are effective in improving or maintaining cognitive function in older adults. The use of benzodiazepines, anticholinergics, barbiturates, and other sedative-hypnotics should be minimized in older patients. Universal screening for dementia in older adults is not recommended. Targeted screening for dementia in older persons may be warranted when there is a high suspicion of cognitive impairment. A brief history taken from the patient and a knowledgeable informant together with a standardized instrument, such as the Mini-Cog, Mini-Mental State Examination, or the MoCA can be used to decide whether a more extensive evaluation is necessary.

CLINICAL BOTTOM LINE

Diagnosis

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

Clinicians should use the patient's history to characterize cognitive deficits, generate a differential diagnosis, and guide a search for the cause of dementia. This assessment is best accomplished by identifying medical, neurologic, and psychiatric signs and symptoms and establishing their order of appearance, severity, and associated features. In the case of cognitive difficulties, it is most important 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. In addition, it is also important to consider the patient's education, health literacy, and socioeconomic status when developing the diagnosis and when developing a care plan.

To take an effective history, the clinician must know the differential diagnosis of dementia and the natural history of its more common types (**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 that reduce efficiency and organizational abilities, which the patient may or may not recognize. Symptoms begin insidiously and progress slowly. The level of alertness remains unimpaired. Patients or family members report conversations where the patient had no recollection of previous discussions; describe increased forgetfulness that causes the patient to lose objects or become confused while shopping; or describe 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 affect daily function more noticeably. In later stages, more assistance is needed in daily activities, with the patient finally requiring assistance in personal care and mobility. Clinical diagnostic criteria for AD are described in the **Box:** Clinical Diagnosis of All-Cause Dementia and AD (18).

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

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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 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. Mood symptoms such as depression and apathy may be commonly observed.	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, and fluctuating cognition.	May account for up to 15% of total dementia cases. Should be suspected in patients with nonvascular dementia but abnormal findings on neurologic examination.
Frontotemporal dementia	Onset often before age 60 years. Prominent personality changes with behavioral disturbances, such as hyperphagia, worsened impulsivity or aggression, or prominent apathy (behavioral variant) or language difficulties (primary progressive aphasia) are common. Memory often preserved early on.	Includes such disorders as behavioral variant frontotemporal dementia, primary progressive aphasia (semantic and nonfluent variant), progressive supranuclear palsy, corticobasal degeneration, and amyotrophic lateral sclerosis with dementia. Functional neuroimaging often demonstrates diminished function in frontal and 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 from major depression. Major depression may also be the initial presentation of dementia.
Mild cognitive impairment	Evidence of cognitive impairment with little or no impairment of function.	Many patients progress to dementia (about 12% to 15% per year).
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 alcohol use, chronic CNS infection, CNS vasculitis, Creutzfeldt–Jakob disease, electrolyte abnormalities, HIV-associated dementia, Huntington disease, medications, multiple sclerosis, neurosarcoidosis, neurosyphilis, normal pressure hydrocephalus, subdural hematoma, systemic lupus erythematosus, thyroid disease, toxins, traumatic brain injury, vitamin B_{12} deficiency, 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 ≥1 cognitive domains.

Probable AD:

- Meets criteria for dementia.
- Has a gradual onset.
- Involves progressive cognitive decline.
- Involves 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-beta$_{42}$, amyloid-PET, and ^{18}F-labeled fluoro-2-deoxyglucose PET, may increase certainty of AD pathophysiologic process but are not currently recommended for routine use.

Alzheimer disease is a progressive neurodegenerative disorder that has characteristic neuropathologic findings. Recently, there has been a greater effort to incorporate biomarkers of AD neuropathology in the diagnosis of AD. However, biomarkers are intended to assist rather than replace clinical evaluation of persons with cognitive impairment and should not be used for clinical purposes in asymptomatic individuals (Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024;20:5143-5169. [PMID: 38934362]).

** Adapted from reference 18.*

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. Several instruments facilitate the identification of delirium, such as the 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) (19), the 4 A's Test (20), or the Confusion Assessment Method for the Intensive Care Unit (21). In addition, the Ultra-Brief Confusion Assessment Method (UB-CAM) is an app-based delirium screening tool that can be administered in less than 2 minutes (22).

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, with an emphasis on vascular and neurologic diseases. The examination should include a mental status evaluation that begins with an assessment of the patient's level of alertness. Focal deficits on neurologic examination and changes in speech may be due to cerebrovascular events leading to vascular dementia. Visual hallucinations and parkinsonism may suggest dementia with Lewy bodies. Early presentation of language difficulties or behavioral disturbances, such as worsened impulsivity or aggression or prominent apathy, may also suggest frontotemporal dementia (Table 1).

Before administering a cognitive examination, it is important to assess whether hearing or vision impairment

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is present and to ensure that the patient who needs them has hearing aids or glasses. It also is important to determine the patient's literacy level and language preference. Moreover, 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. Informant history is important, and a brief screening tool such as AD8 (23) that is filled out by a caregiver can be useful for detecting early-stage dementia. The Quick Dementia Rating System (QDRS), which can be filled out by a caregiver, may be helpful in determining stages of cognitive impairment, such as MCI or mild, moderate, and severe dementia (24).

What imaging studies and other laboratory tests are helpful in evaluating a patient with cognitive dysfunction?

The American Academy of Neurology recommends that patients who are evaluated for cognitive problems should have laboratory tests for common medical disorders, with selected additional studies depending on the situation (25). Patients with cognitive difficulties 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. Biomarkers are rapidly becoming a more important part of the dementia work-up because targeted therapy for AD and other neurodegenerative conditions is becoming available (**Table 2**), but clinical use of biomarkers should be reserved for patients who have evidence of cognitive impairment. Biomarkers may enhance diagnostic accuracy and identify a treatment target, for example, beta-amyloid. Currently available biomarkers include cerebrospinal fluid and blood levels of beta-amyloid and tau proteins as well as an amyloid-positron emission tomography (PET) scan, which can be useful in diagnosing MCI or dementia due to AD (**Figure**). Routine use of glucose PET scanning, for example, using ^{18}F-labeled fluoro-2-deoxyglucose (^{18}F-FDG), is not recommended, although it may help differentiate frontotemporal dementia from AD when this distinction is necessary (26).

Testing for the gene mutations found in patients with familial AD or frontotemporal dementia should be considered only if multiple family members are affected, the work-up supports one of these disorders, and the patient is younger than 60 years at onset. Genetic counseling is recommended before genetic testing (27).

Other tests should be reserved for specific situations. An electroencephalogram may be useful if delirium, seizures, encephalitis, or Creutzfeldt–Jakob disease is suspected. Lumbar puncture may be indicated in patients younger 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 central nervous system infection, paraneoplastic syndrome, central nervous system cancer, or immunosuppression. Neuropsychological testing is particularly useful if the diagnosis of dementia is uncertain or if a precise characterization of the patient's cognitive impairment is necessary (28).

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

Patients with cognitive disturbances should be evaluated for the most common disorders that cause dementia (**Table 1**) and for medications, depression, and MCI. Patients with MCI have cognitive decline with relative preservation of daily function and should be followed, because after 5 years nearly 50% of patients with MCI meet dementia criteria (29).

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Table 2. **Cognitive Agents for Treatment of 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 AD	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 AD 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 total 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 AD	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 AD; insufficient evidence to support efficacy for mild AD	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
Lecanemab	Monoclonal antibody against soluble beta-amyloid	Intravenous infusion every 2 weeks Dosing is weight-adjusted at 10 mg/kg of body weight.	Less cognitive decline in mild cognitive impairment and early-stage dementia due to underlying AD pathology	ARIA Asymptomatic, headache, confusion, visual change, dizziness, nausea, gait difficulty, serious ARIA (seizures, status epilepticus, encephalopathy, stupor, focal neurological deficits)	Confirm underlying AD pathology using biomarkers (blood, CSF, amyloid-PET) Obtain ApoE ε4 status to inform risk for ARIA Obtain baseline brain MRI within 1 year of lecanemab administration and prior to the 5th, 7th, and 14th infusions Follow appropriate use recommendations* for monitoring and management of ARIA
Donanemab	Monoclonal antibody against insoluble beta-amyloid present in brain amyloid plaques	Intravenous infusion every 4 weeks Dosing is 700 mg every 4 weeks for the first 3 doses, followed by 1400 mg every 4 weeks. Consider stopping dosing based on reduction of amyloid plaques to minimal levels on amyloid-PET.	Less cognitive decline in mild cognitive impairment and early-stage dementia due to underlying AD pathology	ARIA Asymptomatic, headache, confusion, visual change, dizziness, nausea, gait difficulty, aphasia, weakness, or seizure (3 deaths attributed to ARIA during the phase III trial)	Confirm underlying AD pathology using amyloid-PET Obtain ApoE ε4 status to inform risk of ARIA Obtain baseline brain MRI within 1 year of donanemab administration and prior to the 2nd, 3rd, 4th, and 7th infusions Follow FDA label for monitoring and management of ARIA†

AD = Alzheimer disease; ApoE = apolipoprotein E; ARIA = amyloid-related imaging abnormalities; CSF = cerebrospinal fluid; FDA = U.S. Food and Drug Administration; MRI = magnetic resonance imaging; NMDA = N-methyl-D-aspartic acid; PET = positron emission tomography.
** Reference 36.*
† Reference: www.accessdata.fda.gov/drugsatfda_docs/label/2024/761248s000lbl.pdf.

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Diagnosis... Patients who report cognitive and functional decline should be evaluated with 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 and biomarkers should be guided by the results of this initial evaluation (**Figure**).

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 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 address general medical and preventive care as conscientiously in patients with dementia as in patients without it. Because poor management of chronic conditions may lead to further cognitive decline, careful attention should be paid to good control of hypertension, diabetes, cholesterol levels, pain, anticoagulation for atrial fibrillation, and vaccinations. It is also important to individualize treatment goals based on dementia stage and the goals of care. 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 (30).

What should clinicians advise about issues related to safety?

Patients with progressive dementia eventually lose the ability to drive, but predicting when an individual patient should stop driving is difficult, particularly if the restriction burdens the patient or the patient's family. Nonetheless, addressing the issue early is important 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. States differ with regard to reporting patients with a diagnosis of dementia, and clinicians should be familiar with applicable laws (31). The American Academy of Neurology outlines an approach to assessing driving in patients with dementia (32).

In a prospective case–control study using the Washington University Road

Test, which has off-road and on-road components, 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 (33).

Clinicians should continually assess other safety issues. 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 often can be modified to allow safe participation, for example, 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. Adverse effects of acetylcholinesterase inhibitors include nausea, vomiting, diarrhea, bradyarrhythmia, syncope, weight loss, and abnormal dreams. 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.

When should clinicians prescribe monoclonal antibodies for the management of AD?

Clarity AD enrolled study participants with MCI or mild dementia due to AD and evidence of beta-amyloid accumulation by amyloid-PET imaging or cerebrospinal fluid testing. The study randomly assigned 898 participants to lecanemab, which is a monoclonal antibody targeting soluble beta-amyloid, and 897 to placebo. The primary outcome was a change from baseline to 18 months in the Clinical Dementia Rating–Sum of Boxes score (range, 0 to 18 points), and the score was significantly different between the lecanemab and placebo groups, favoring lecanemab (−0.45 [95% CI, −0.67 to −0.23]; P < 0.001). However, a greater proportion of participants in the lecanemab group than in the placebo group experienced amyloid-related imaging abnormalities (ARIA) on magnetic resonance imaging for both cerebral micro- and macrohemorrhages or superficial siderosis (17.3% vs. 9.0%) and cerebral edema or effusions (12.6% vs. 1.7%). The risk for ARIA was higher in apolipoprotein E ε4 gene carriers, especially in homozygous persons (34).

Donanemab is a monoclonal antibody against insoluble brain beta-amyloid. The TRAILBLAZER-ALZ 2 trial enrolled study participants with MCI or mild dementia due to AD and biomarker evidence of beta-amyloid accumulation on amyloid-PET imaging. The study randomly assigned 860 participants to donanemab and 876 to placebo. The primary outcome was change from baseline to 76 weeks in score for the integrated Alzheimer Disease Rating Scale (range, 0 to 144 points). The score was significantly different between the donanemab and placebo groups, favoring donanemab (2.92 [CI, 1.51 to 4.33]; P < 0.001). A greater proportion of participants in the donanemab group experienced ARIA on magnetic resonance imaging for both cerebral microhemorrhages and hemosiderin deposits (31.4% vs. 13.6%) and cerebral edema or effusions (24% vs. 2.1%). Three study participants from the donanemab group had ARIA and subsequently died (35).

Eligibility for both lecanemab and donanemab should be determined by biomarker confirmation of brain beta-amyloid in individuals who have MCI or

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an early dementia stage. Details of the proposed inclusion and exclusion criteria for lecanemab are available through the Appropriate Use Recommendations (36). Due to the increased risk for bleeding, persons receiving anticoagulation are excluded, and recommendations preclude the administration of thrombolytics once lecanemab is started (36). As many candidates for lecanemab are older adults who may need urgent intervention with thrombolytics and anticoagulants for ischemic stroke, myocardial infarction, or pulmonary embolism (37), providers need to carefully counsel patients about the benefits versus harms of lecanemab before starting treatment (38).

When should clinicians consider prescribing other pharmacologic agents in treating specific types of dementia?

The acetylcholinesterase inhibitor rivastigmine is 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 other acetylcholinesterase inhibitors (39). The data are less clear for dementia with Lewy bodies (40). Although the benefit is most likely small, acetylcholinesterase inhibitors may be tried for patients with vascular dementia (41).

Which pharmacologic agents are ineffective in treating dementia?

The herbal supplement ginkgo biloba does not slow progression of dementia. Nonsteroidal anti-inflammatory drugs, estrogen, and ergoloid mesylates should not be prescribed for cognitive decline. Data on whether the food supplements coconut oil and caprylidene can be recommended are inadequate. The U.S. Food and Drug Administration has warned companies against selling products that claim to, but have not been proven to, safely and effectively treat medical conditions, including products that claim to prevent, treat, or cure AD. Physicians play an important role in informing patients about the use of these products (42).

When should clinicians prescribe antidepressants in patients with dementia?

Nearly one third of patients have an episode of major depression after onset of dementia (43), but evidence for the efficacy of antidepressants is mixed (44). 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. In addition, in patients with dementia who have depressive symptoms without the diagnosis of major depressive disorder, there is evidence that nonpharmacologic interventions such as exercise combined with social interaction and cognitive stimulation may be helpful (45).

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. Various nonpharmacologic approaches are effective and should be tried first unless the symptoms create immediate danger or cause marked distress (46). 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. Decoding should be done using systematic approaches, such as 4-D (Describe, Decode, Devise, Determine) (47) or DICE (Describe, Investigate, Create, Evaluate) (48) (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.

Nonpharmacologic interventions for neuropsychiatric and behavioral symptoms are as effective as pharmacologic interventions (49) and carry less risk for harm, which reinforces recommendations about using antipsychotic drugs sparingly for these symptoms.

What treatment options are available for behavioral disturbances or psychotic symptoms that are refractory to nonpharmacologic approaches?

A trial of a selective serotonin reuptake inhibitor, such as citalopram, may be warranted (50). However, because of potential dose-dependent QT interval prolongation, the Food and Drug

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 47.*

Administration recommends not exceeding 20 mg/d for adults older than 60 years.

Antipsychotics are widely used but are indicated only if symptoms cause significant distress for the patient or create a dangerous situation, because all antipsychotic drugs carry an elevated risk for death. Second-generation agents are usually recommended over first-generation agents because of their lower risk for tardive dyskinesia. The efficacy of these agents is modest (51). Although more evidence supports use of risperidone and olanzapine, similar drugs also are used. Brexpiprazole is not more effective than older drugs and is more expensive (52). 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 the drug within 3 months of starting. Antipsychotic medications should not be used to treat sleep disturbances.

How can sleep problems be treated?

Disrupted sleep need not be treated unless it is interfering with care or causing distress. Nonpharmacologic methods such as increasing physical activity during the day can minimize sleep disturbance in patients with dementia (53). 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 (54).

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

Clinicians should proactively address routine issues that have the potential to significantly affect quality of life. Examples include making sure glasses and hearing aids work; promoting routine dental care; paying attention to noise, lighting, and ambient temperature; providing sufficient social and cognitive stimuli; promoting cleanliness; and treating pain and constipation (55).

When should clinicians consult a dementia specialist?

Clinicians should consider consulting a neurologist, geriatric psychiatrist, geriatrician, or other dementia specialist in cases of 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 be considered for the evaluation or management of difficult-to-treat neuropsychiatric symptoms, such as depression, psychosis, or behavioral disturbances. Consulting a specialist should also be considered if a patient requires physical restraint. Referral to a neuropsychologist should be considered if it is unclear whether dementia is present or 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. To provide optimal care, the clinician

should expect to interact with a broad range of professionals, including occupational therapists, social workers, physical therapists, and speech and language pathologists (55).

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

As dementia progresses, it is often necessary to move the patient to an assisted-living facility or a nursing home that can address the progressive needs of the patient (56). A move to a nursing home is usually prompted by the 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 must move because of unmanageable psychiatric symptoms or a high burden on the caregiver.

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

Most caregivers benefit from a range of interventions (57) that focus on education about dementia, skills training, and the caregiver's well-being. User-friendly resources are available from the Alzheimer's Association and other organizations. In addition, patients and caregivers may benefit from referrals to trained health care professionals such as social workers, psychologists, nurses, and occupational therapists (10). Caregivers need to be informed about local respite programs and supported in long-term planning. Caregivers should also be informed about support groups, which are available in most areas. Support groups that focus on problem solving, communication, management of behavioral disturbances, and emotional support delay nursing home placement for up to 1 year, diminish caregiver and patient depression, and reduce patient agitation and anxiety (58).

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

In one observational study, 81% of patients were considered for surgery or hospitalization, with decisions ultimately made by surrogates (59). Because full incapacitation is inevitable for every person with progressive dementia who lives long enough to experience the full course of the disease, advance directives maximize the likelihood that the person's surrogate will be aware of the person's wishes for end-of-life care, but recent recommendations support the importance of surrogates' using a best-interest criterion in making end-of-life decisions for a decisionally incapacitated person (60). Physician support of the people making these decisions and awareness of advance directives are central to these decisions.

Observational studies suggest that persons with dementia receiving hospice care have improved quality of life and are more likely to be treated for pain (61, 62). Experts recommend that clinicians consider discontinuing medications that have minimal short-term benefit, such as cholesterol-lowering agents (59). Decreased food intake is common in advanced dementia. Most experts recommend hand-feeding rather than tube-feeding and the avoidance of antimicrobials for asymptomatic bacteriuria (63).

Treatment... Treatment requires a broad approach that addresses comfort and quality of life, cognitive enhancement, stabilization of psychiatric symptoms, and caregiver well-being. Patients who need pharmacologic treatment can be treated with acetylcholinesterase inhibitors, and memantine can be added for patients with moderate to severe disease. Shared decision making to balance benefits versus harms is important when considering monoclonal antibodies directed against beta-amyloid. In addition, it is important to identify psychiatric symptoms and to treat them with either behavioral interventions or medications; to minimize risk factors for cerebrovascular disease; and to treat other conditions that could reduce cognition. Moreover, it is important to address safety issues, regularly monitor the caregiver's well-being, and suggest referral to support groups and other psycho-educational activities.

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 MedlinePlus in English and other languages

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

www.alz.org/alzheimers-dementia/what-is-dementia
www.alz.org/alzheimer-demencia/que-es-la-demencia
Information on symptoms, diagnosis, causes, and treatment from the Alzheimer's Association in English and Spanish.

www.caregiver.org
Information for caregivers from the Family Caregiver Alliance.

Information for Health Professionals

www.uspreventiveservicestaskforce.org/uspstf/recommendation/cognitive-impairment-in-older-adults-screening
Recommendation statement on screening for cognitive impairment in older adults from the U.S. Preventive Services Task Force.

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

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

www.aan.com/Guidelines/home/GuidelineDetail/396
Practice guideline on assessment and management of driving risk in 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 daily life. Alzheimer disease and vascular dementia are 2 common types. Dementia can begin at any age but commonly develops later in life. Symptoms usually start slowly and worsen over time.

What Are the Symptoms of Dementia?

Many dementia symptoms occur in normal individuals, so it is difficult to know when to pay attention to a symptom. You should be concerned if a symptom causes more difficulty, worsens with time, and is accompanied by other symptoms. You may first notice symptoms when there is a life change, such as a spouse's death or a hospitalization. Symptoms include:

- Forgetfulness that may cause the person to lose objects
- Not remembering conversations
- Trouble finding the right words
- Difficulty with familiar activities, like cooking or making a phone call
- Feeling disoriented while walking or driving
- Changes in personality, such as becoming confused, suspicious, or fearful

Can I Prevent Dementia?

Some lifestyles may prevent a future decline in mental function, including:

- Staying physically active
- Eating a healthy diet
- Participating in social events
- Doing activities that occupy the mind, like puzzles or hobbies
- Quitting smoking
- Controlling blood pressure, blood sugar, and cholesterol

How Is Dementia Diagnosed?

If you suspect that you or someone you know has dementia, a health care provider can help. They will ask about symptoms, take a medical history, and conduct a physical examination. They may want to speak with someone who knows the person well. The provider will evaluate mental status, speech, and mood and administer screening tests that assess memory and language.

There is no specific test for dementia, but laboratory tests or brain imaging may be necessary to rule out other conditions that cause similar symptoms.

How Is Dementia Treated?

Treatment focuses on controlling symptoms and avoiding harm. Regular checkups maximize function and well-being. These include hearing and vision checks, deciding whether to stop medicines that might worsen symptoms, and ensuring that vaccinations are up-to-date and chronic diseases are controlled. Checkups also monitor for anxiety, depression, agitation, sleep disturbances, and hallucinations.

People with dementia should have a calm and predictable environment. They should get enough rest, eat well, brush their teeth, and stay clean. Patients and caregivers should discuss the patient's values and wishes soon after the diagnosis because progression of symptoms will make later discussions more difficult. It is also important to plan how care will change as symptoms progress. The provider can help by arranging a home safety assessment to evaluate whether the patient is able to safely cook, keep track of medicines, and do other activities independently. They can also arrange a driving assessment to determine if it is safe for the patient to continue driving.

Newer medicines are available for dementia, but they are only mildly effective and have side effects. Talk with a provider about what is best for your situation.

For Caregivers

Caregivers play an important role for people with dementia. The provider will talk more with the caregiver and less with the patient as symptoms progress and patients become less able to function independently. Eventually, it may be necessary to discuss whether the patient should go to an assisted living facility or a nursing home.

Many caregivers experience guilt, anger, loneliness, and depression. If you feel tired, sad, or stressed, talk with your provider, who can help you stay healthy, identify whether additional assistance is available, and connect you with support groups.

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 make sure my wishes for future care are recognized and followed?
- Will I need to go to an assisted living facility or a nursing home?
- Are there things I should start or stop doing now?
- Do I need to see a specialist?
- Are there support groups for me and my caregivers?

For More Information

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Alzheimer's Association
www.alz.org/alzheimers-dementia/what-is-dementia
www.alz.org/alzheimer-demencia/que-es-la-demencia

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

Family Caregiver Alliance
www.caregiver.org

Patient Information