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Diagnosis and Management of Dementia: Review

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IMPORTANCE Worldwide, 47 million people live with dementia and, by 2050, the number is expected to increase to 131 million.

OBSERVATIONS Dementia is an acquired loss of cognition in multiple cognitive domains sufficiently severe to affect social or occupational function. In the United States, Alzheimer disease, one cause of dementia, affects 5.8 million people. Dementia is commonly associated with more than 1 neuropathology, usually Alzheimer disease with cerebrovascular pathology. Diagnosing dementia requires a history evaluating for cognitive decline and impairment in daily activities, with corroboration from a close friend or family member, in addition to a thorough mental status examination by a clinician to delineate impairments in memory, language, attention, visuospatial cognition such as spatial orientation, executive function, and mood. Brief cognitive impairment screening questionnaires can assist in initiating and organizing the cognitive assessment. However, if the assessment is inconclusive (eg, symptoms present, but normal examination findings), neuropsychological testing can help determine whether dementia is present. Physical examination may help identify the etiology of dementia. For example, focal neurologic abnormalities suggest stroke. Brain neuroimaging may demonstrate structural changes including, but not limited to, focal atrophy, infarcts, and tumor, that may not be identified on physical examination. Additional evaluation with cerebrospinal fluid assays or genetic testing may be considered in atypical dementia cases, such as age of onset younger than 65 years, rapid symptom onset, and/or impairment in multiple cognitive domains but not episodic memory. For treatment, patients may benefit from nonpharmacologic approaches, including cognitively engaging activities such as reading, physical exercise such as walking, and socialization such as family gatherings. Pharmacologic approaches can provide modest symptomatic relief. For Alzheimer disease, this includes an acetylcholinesterase inhibitor such as donepezil for mild to severe dementia, and memantine (used alone or as an add-on therapy) for moderate to severe dementia. Rivastigmine can be used to treat symptomatic Parkinson disease dementia.

CONCLUSIONS AND RELEVANCE Alzheimer disease currently affects 5.8 million persons in the United States and is a common cause of dementia, which is usually accompanied by other neuropathology, often cerebrovascular disease such as brain infarcts. Causes of dementia can be diagnosed by medical history, cognitive and physical examination, laboratory testing, and brain imaging. Management should include both nonpharmacologic and pharmacologic approaches, although efficacy of available treatments remains limited.

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Supplemental content

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Dementia is a common public health problem.[1] Worldwide, approximately 47 million people have dementia, and this number is expected to increase to 131 million by 2050.[1] Reductions in age-adjusted incidence of dementia have occurred in the United States and other developed countries over the last 20 years, perhaps associated with increasing formal educational attainment. However, without improved treatments or preventive therapy, the adverse consequences of dementia will continue to increase.[2]

In the United States, the prevalence of dementia is 15% in people older than 68 years.[3] Alzheimer disease (AD) affects 5.8 million people, and 13.8 million are projected to have the diagnosis of AD by the year 2050.[4] AD is the sixth leading cause of death and the fifth leading cause among people older than 65 years.[5,6] This review summarizes diagnosis and management of dementia, defined as significant cognitive impairment in 2 or more cognitive domains.

Methods

We conducted a literature search in PubMed, using the search terms "dementia and (diagnosis or management)" in the title field. The following inclusion criteria were applied: publication date from

Box 1. Characteristics of Dementia and Mild Cognitive Impairment (MCI)[a]

Dementia

The loss of cognitive abilities must be
- Present in several cognitive domains (often memory with at least 1 other domain such as language, visuospatial, executive, or other)
  and
- Represent a decline from the prior level of function
  and
- Impair functional abilities in day-to-day life (eg, social, occupational, self-care)

The most common form of dementia is a "mixed dementia,"[b] usually a combination of
- A common neurodegenerative disease in aging, most often Alzheimer disease
  and
- VCID

Common neurodegenerative diseases causing dementia include the following, in decreasing order of frequency:[c]
- Alzheimer disease
- Lewy body disease
- Frontotemporal dementia[d]

MCI

The loss of cognitive abilities must be
- Demonstrable on cognitive testing, whether amnestic vs nonamnestic MCI, or single vs multidomain MCI (present in several cognitive domains)[e]
  and
- Not sufficient to significantly impair functional abilities or independence, such that criteria for dementia are *not* met

Abbreviation: VCID, vascular contributions to cognitive impairment and dementia.

[a] Sources: McKhann et al[26] (dementia); Albert et al[27] (MCI).

[b] Mixed dementias have overlapping clinical features and more than 1 pathologic diagnosis.

[c] Other less common neurodegenerative and other diseases not listed but that can be identified during life include vascular dementia, Parkinson disease, Huntington disease, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, Creutzfeldt-Jakob disease, and others; in younger people, consider acute conditions (eg, motor vehicle crash or war-related traumatic brain injury), chronic traumatic encephalopathy (eg, repetitive sports-related head injuries), and multiple sclerosis. Note that for some neurodegenerative diseases causing dementia in older people, there are currently no means to make the diagnosis during life, such as for the TDP-43 (transactive response DNA-binding protein 43) form of frontotemporal dementia and for hippocampal sclerosis.

[d] Some data suggest this condition is a common cause of dementia in young-onset disease (onset before age 65 years).[28]

[e] Amnestic MCI is defined by neuropsychological test–proven impairment in the memory domain and can be "single-domain amnestic MCI" or "multidomain amnestic MCI"; nonamnestic MCI is defined by impairment in 1 or more cognitive domains other than memory (such as language, executive function, and/or attention), but not in the memory domain, and can be "single-domain nonamnestic MCI" or "multidomain nonamnestic MCI."

November 19, 2013, to June 29, 2019; English language; female or male sex; and "aged, 65 + years" (to exclude studies about less common causes of dementia). Original research studies with sample sizes less than 100 persons were excluded.

Observations

The search yielded 200 articles published in the past 5½ years. We excluded 37 studies with fewer than 100 persons, 52 on topics not relevant to this review, 41 about non-US public policy or practice, 20 about caregivers, 7 about pathology, 5 about medical record documentation or coding, and 11 that were not original research. The remaining 27 original research articles, including 22 observational studies and 5 randomized clinical trials, informed this review.

Risk Factors and Neuropathology

Aging is an important risk factor for all-cause dementia. AD affects 5% to 10% of people older than 65 years and 50% of those aged 85 years.[7] Nonmodifiable risk factors for AD include female sex, black race, Hispanic ethnicity, and genetic factors such as the apolipoprotein E (*APOE*) gene.[8-13] Modifiable risk factors for all-cause dementia include hypertension and diabetes, diet, and limited cognitive, physical, and social activities.[14-18] Pathologically, "mixed dementia" is the most common form of dementia, found in 46% of persons with clinically diagnosed AD and most commonly consisting of AD neurodegeneration and cerebrovascular disease.[19] Other neurodegenerative pathologies such as Lewy body disease (pathologically confirmed in 17% of patients) and frontotemporal lobar degeneration (confirmed in <5% of patients) are less frequent.[19-25]

Definition and Characterization

Dementia is defined by chronic, acquired loss of 2 or more cognitive abilities caused by brain disease or injury (**Box 1**). This definition has been used in clinical practice for decades, although recent changes in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) have recognized that dementia can be present with impairment in a single domain (ie, by this definition, a patient with a severe expressive aphasia could be classified as having dementia).[26,29] Memory requires the recording, storage, and retrieval of information. The most common clinical presentation of AD is a slow onset and gradually progressive loss of memory, typically with inability to learn new information and particularly autobiographical information, such as recent events in ones' life. This is because AD preferentially affects brain networks involved in episodic memory. Examples of episodic memory loss include forgetting appointments or forgetting to pay bills or to take medication. Typically, a person with AD repeats questions and conversations. The memory loss is often accompanied by self-reported memory problems. Difficulty recalling names that are recalled later is common in aging but is not a typical early sign of dementia.

Mild cognitive impairment (MCI) is defined by performance that is lower than normal on objective neuropsychological cognition tests but with maintained daily functions (eg, maintained abilities to function within society such as for daily activities at work, home, and in social settings, and maintained activities of daily living such as for personal care) and therefore not consistent with dementia (Box 1).[27] MCI can be categorized into "amnestic" MCI, in which reduced performance on memory is the key finding, vs "nonamnestic" MCI, in which there is reduced cognitive performance in a nonmemory domain such as language. MCI can also be characterized into "single domain" vs "multidomain" MCI, in which multiple cognitive performance measures are impaired. MCI does not always progress to dementia, and a patient's cognitive status may become normal or fluctuate between MCI, normal cognition, and dementia. Fluctuations in cognition, and

Table 1. Manifestations of Dementia[a]

Area[b]	Earlier-Stage Manifestations		Later-Stage Manifestations	
	Category	Examples	Category	Examples
Cognitive	Short-term memory loss (episodic memory impairment)	Forgetting appointments, to pay bills, recent events (such as family outing in last few weeks)	Memory loss in working memory (the ability to immediately process and store information)	Forgetting how to use household technology (eg, how to use the microwave, dial telephone numbers)
	Word-finding difficulties (anomia) or loss of word meaning (semantic deficits)	Frequent trouble finding exact words to express oneself, word substitutions, imprecise language ("what you eat with" for "fork")	More marked expressive difficulties and eventual loss of language (eg, global aphasia)	Paraphrasic errors while speaking, paucity of words in sentence, lack of initiation of conversations, muteness
Psychological	Apathy	Lack of initiation of thought or actions (eg, not preparing meals)	Delusions	False belief system such as a deceased relative is still alive, caregiver is stealing money
	Depressive symptoms	Hopelessness and loss of purpose in life	Anosognosia	Lack of insight into cognitive problems with attempts to continue to drive or manage money
Behavioral	Withdrawal from social engagement	Inability to participate meaningfully in casual conversations	Aggression	Verbal aggression such as screaming, physical aggression such as throwing things
	Disinhibition	Excesses in speech (eg, echolalia, palilalia) and actions (eg, hyperorality such as eating from others' plate)	Hallucinations	Visual hallucinations such as seeing small people on table; auditory hallucinations such as hearing singing
			Wandering	Walking out of home in middle of night and getting lost
Sleep	Rapid eye movement behavior disorder	Acting out dreams such as running while dreaming one is being chased	Altered sleep-wake cycle	Frequent awakening at night and getting out of bed, sleeping in late in the morning and repeated daytime napping
Physical	Gait impairment	Falls	Repetitive purposeless movements	Fidgeting with buttons on shirt for hours at a time
			Parkinsonism	Stooped posture, short stride, unsteady gait, rigidity
			Seizures	Involuntary repetitive limb jerking while unconscious

[a] Note that these manifestations do not occur in all types of dementia; not all examples provided here occur in each individual, and several less common manifestations not listed may occur. This table does not aim to describe the trajectories of conditions within each area but rather to provide examples of manifestations. Variability in individual presentations is common; see text and Table 2 for pathognomonic characteristics of particular dementia etiologies.

[b] Note the range of functional areas affected in dementia, beyond cognition.

variability in cognitive test results, are also present in some conditions including neurodegenerative diseases (such as in early stages of Lewy body disease), cerebrovascular disease (eg, intermittent small strokes), and psychiatric conditions (eg, depression, anxiety), as well as with medications affecting cognition (eg, opioids).

Dementia is a clinical syndrome with variable manifestations (**Table 1**) that help attribute the cause of dementia and guide management. While research studies have defined a "preclinical AD,"[26,30] in clinical care AD is not diagnosed before symptom onset. Differentiating AD from other causes of dementia is easiest in the early stage of illness, as dementias in the late stage have similar manifestations regardless of etiology (**Table 2**).[31-35]

Because mixed dementia is common, the evaluation focuses on identifying conditions likely to contribute to dementia (Box 1 and Table 2). Cerebrovascular disease is the most frequent comorbid condition with AD, and evidence of cerebrovascular disease does not reduce the likelihood of AD. However, approximately 5% of people with dementia show evidence of only cerebrovascular disease. After AD, the most common neurodegenerative dementias are Lewy body disease, characterized by chronic rapid eye movement behavior disorder with early visuospatial impairment and parkinsonism,[21,22,33,34] and frontotemporal dementia, characterized by a behavioral variant (the most common presentation is disinhibition) or less often, a language impairment variant (such as a semantic dementia, in which the meaning of the patient's speech is unclear) (Table 2).[23,35]

Diagnosis and Management

Clinical evaluations, differential diagnosis, and management of dementia most commonly occur in the primary care setting, with appropriate specialist input as needed.

Clinical Evaluation for Diagnosis

In 2014, the US Preventive Services Task Force indicated that there was insufficient evidence to evaluate the balance of benefits and harms for universal screening for cognitive impairment using formal screening instruments in community-dwelling adults 65 years and older.[36] While the task force concluded that adequate evidence existed for some screening tools that have sufficiently high sensitivity and specificity for identifying dementia, there is no published evidence related to the effect of screening on decision making or planning by patients, clinicians, or caregivers.[36] However, report of memory problems[37-39] or rapidly progressive cognitive problems over several months may indicate an underlying medical condition that warrants further evaluation with cognitive, laboratory, and other tests.[40,41]

Evaluation of possible dementia requires a brief medical history and a cognitive and neurologic examination (**Box 2**). The history remains the most important diagnostic tool and should be obtained from both the patient and a close family member or friend. While some patients report forgetfulness, others are unable to recall details of their history or have anosognosia (ie, lack of insight into one's disease). A person accompanying the patient

Table 2. Clinical and Pathologic Characteristics Differentiating Select Causes of Dementia

	Disease[a]			
	Alzheimer Disease	Cerebrovascular Disease[b]	Lewy Body Disease	Frontotemporal Dementia
Pathologic characteristics	Brain atrophy especially of the mesial temporal lobe; histologic hallmarks of neuritic plaques containing β-amyloid and neurofibrillary tangles containing phosphorylated tau	Small, often cystic chronic infarcts (lacunar infarcts), multiple microinfarcts, or large infarcts including intracerebral hemorrhage; age of infarcts may be variable in the same person, including chronic and acute; cerebral vessel pathology such as atherosclerosis and arteriolosclerosis; white matter gliosis; focal brain atrophy	Brain atrophy, often generalized; intraneuronal Lewy body inclusions containing α synuclein, including in the neocortex (as opposed to inclusions restricted to the substantia nigra, as seen in Parkinson disease)	Focal brain atrophy affecting frontal[c] and/or anterior temporal lobes, histologic hallmarks of phosphorylated TDP-43, MAPT, or FUS protein
Onset and course	Slow onset and gradual progression over months or years	Temporal relation between acute vascular event (stroke) and onset of cognitive impairment, within minutes or days; stepwise course	Slow onset and gradual progression over months or years; fluctuations in levels of alertness and cognition	Slow onset and gradual progression over months or years
History, examination, and cognitive features in the early stage[d]	History: Presenting symptom is typically short-term memory loss Examination and/or cognitive testing: Episodic memory impairment accompanied by other subtle cognitive deficits, such as visuospatial problems and anomia	History: Vascular risk factors (eg, hypertension, diabetes) or prior stroke or other vascular events (myocardial infarction) Examination: Focal neurologic deficits consistent with stroke such as unilateral weakness and hyperreflexia, Babinski sign Neuroimaging: Evidence of cerebrovascular disease, such as infarcts or significant white matter changes (unilateral or bilateral) on MRI	History: RBD for years preceding the cognitive impairment; visual and other hallucinations Examination and/or cognitive testing: Marked visuospatial problems with relative preservation of memory; parkinsonism, especially with bradykinesia and rigidity, but also stooped posture and slow and shuffling gait	History: Marked changes in behaviors such as in personality (eg, disinhibition, apathy) Examination and/or cognitive testing: Disinhibition and inappropriate behaviors; in language variant, impaired fluency in speech, semantic paraphrasias; other significant executive or language problems, with relative preservation of memory

Abbreviations: FUS, fused-in-sarcoma; MAPT, microtubule-associated protein tau; MRI, magnetic resonance imaging; RBD, rapid eye movement behavior disorder; TDP-43, transactive response DNA-binding protein 43.

[a] Diseases are listed in decreasing order of frequency, from left to right (see text for details).

[b] Includes more advanced stage of the syndrome (vascular dementia).

[c] One specific form is Pick disease.

[d] Includes characteristics often present or notably absent.

to a medical appointment who provides the medical history may indicate cognitive impairment.

The history should characterize the nature, magnitude, and course of cognitive changes. "Nature" refers to the cognitive domains affected. Is there loss of episodic memory (eg, what the patient did that morning, yesterday, and last week) or language abilities (eg, word-finding difficulties with circumlocutions)? "Magnitude" refers to severity: does the cognitive loss affect daily functions, such as the patient's ability to manage his or her own affairs (eg, does the patient get lost while driving, not pay bills, forget to take medications)? "Course of cognitive changes" refers to the temporal course of the symptoms, including speed of onset and pattern of progression. Does the course have an insidious onset and a slow progression (as in neurodegeneration) or a rapid onset and fluctuating and stepwise progression (as in cerebrovascular disease)?

The history should focus on medical conditions that could affect cognition including vascular disease risk factors (such as hypertension and diabetes), existing brain conditions (such as stroke, Parkinson disease, head trauma), and use of medications that can impair cognition (eg, sleep aids and anxiolytics such as benzodiazepines; analgesics such as codeine-containing agents; anticholinergics such as tricyclic antidepressants and bladder antimuscarinics).[42,43] A family history might identify young-onset dementia (onset in persons younger than 65 years) in first-degree relatives, suggesting one of the rare inherited genetic forms of dementia.

The cognitive examination identifies the presence, severity, and nature of cognitive impairment (eg, memory vs language) and should consider cultural, linguistic, educational, and other factors such as anxiety and sleep deprivation. One commonly used screening tool is the Montreal Cognitive Assessment (MoCA; range, 0-30; follow-up evaluation to screening recommended if score is <24). The MoCA requires about 10 minutes to administer and is useful in early detection of cognitive impairment, including MCI with executive dysfunction.[44] The Mini-Mental State Examination was developed more than 4 decades ago. It is less sensitive to the presence of MCI and less thoroughly evaluates the domains of executive function, higher-level language skills, and complex visuospatial processing.[44-48]

The neurologic examination evaluates for objective evidence of neurocognitive problems such as aphasia, apraxia, and agnosia. Unusual behaviors, such as disinhibition with hyperorality or hypersexuality, suggest a frontotemporal dementia, which comprises a group of uncommon conditions associated with neuronal loss beginning in the frontal region of the brain, the temporal region, or both, while other areas are relatively spared. The examination may demonstrate focal neurologic signs or parkinsonism (eg, as typically seen in the early stages of Lewy body disease). The routine evaluation also includes physical examination to identify systemic vascular disease and systemic signs that may be pertinent to rarer causes of dementia (eg, the golden-brown eye discoloration [Kayser-Fleischer rings] of Wilson disease).

The routine workup typically includes a limited number of blood tests (eg, measurement of B_{12} and thyrotropin levels) and neuroimaging with either magnetic resonance imaging or computed tomography to identify cortical and hippocampal atrophy (as seen in AD) or neuropathology including potentially treatable causes of dementia (eg, resectable tumor; normal-pressure hydrocephalus, which

may be shunted) (Box 2).[49-54] Additional evaluation is sometimes warranted. For example, in highly educated and highly functioning individuals, a compelling history of cognitive decline (eg, no longer able to perform a complex task that could easily be done a year ago, such as filling out a tax return or working at a cognitively demanding job such as physician or lawyer) can suggest dementia despite "normal" function on a brief, screening cognitive test. In this instance, referral for detailed neuropsychological testing should be considered to assess a broader range of cognitive abilities (eg, memory, executive function, language, attention, visuospatial abilities) with increased levels of difficulty.[55]

If the etiology of dementia is unclear after a brief history and examination, additional history and examination, and select blood, neurologic, and medical tests, should be considered (Box 2).

New tests that may help identify the presence of dementia include disease biomarkers still commonly used in research.[56] For a patient whose presentation is not consistent with AD (commonly called "atypical dementia"; see eTable 1 in the Supplement) and for patients in whom diagnostic certainty is low, clinicians may consider specialist referral and additional testing. Functional neuroimaging[57] such as positron emission tomography (PET)[58] can show changes suggestive of AD—usually asymmetric, bilateral temporal-parietal hypometabolism—with routine tracers such as fluorodeoxyglucose (FDG), which has a sensitivity of 91% and a specificity of 85% for AD.[59,60] FDG PET, covered by health insurance for suspected frontotemporal dementia, may differentiate this etiology from AD. For patients with frontotemporal dementia, FDG PET typically shows decreased, asymmetric frontal lobe hypometabolism in the behavioral variant and anterior temporal lobe hypometabolism in the language (semantic) variant.[61]

Amyloid PET can also be used in patients with cognitive impairment who are evaluated for AD or other causes of cognitive decline.[59,60,62] In a recent observational, multisite, longitudinal study of Medicare beneficiaries, amyloid PET results were associated with change in management plans in more than 60% of patients, compared with before PET scanning. Change in management plans consisted of change in AD medication or other medication therapy and changes in counseling about safety and future planning.[63] However, there is no evidence that PET scan results change clinical outcomes. Functional neuroimaging with tau radioligands are only appropriate for research purposes.[64]

Cerebrospinal fluid testing may be considered to obtain evidence of AD (low amyloid and high tau levels), other neurodegenerative disease (eg, elevated protein 14-3-3 for Creutzfeldt-Jakob disease), or other etiologies (eg, positive cultures in infection; oligoclonal bands in demyelination; improved gait after high-volume removal of cerebrospinal fluid in normal-pressure hydrocephalus).[65-69] Genetic testing may be reasonable, usually for young patients with a history of first-degree relatives with young-onset dementia (eg, parents or siblings with dementia in their fourth or fifth decade of life). Rare autosomal dominant forms of dementia (eg, presenilin gene mutations) warrant genetic counseling to determine whether other family members need to be screened.[70] Assessment for the *APOE* genotype is not recommended for routine evaluation of AD because most people with AD dementia do not have either the protective ε2 allele or the ε4 allele (associated with increased risk) and, more importantly, because currently, medical management would not be altered by the test results.[8] Additional neurologic workup, such as for amyotrophic lateral sclerosis, and medical workup, such as for cardiac, metabolic, and other etiologies, may be considered to evaluate for reversible causes of cognitive impairment such as psychiatric disorders (depression) and thyroid dysfunction (eTable 2 in the Supplement).[71]

Box 2. Clinical Evaluation of Suspected Dementia

Dementia is identified based on
- Medical history, including from family, friend, or caregiver, focusing on cognition and function
- Brief outpatient or bedside cognitive examination
- If needed, neuropsychological testing

The etiology of dementia is determined based on
- Medical history
  - Neurologic
  - General medical
  - Family
- Physical examination
  - Neurologic signs (eg, cognitive impairment, focal signs, parkinsonism)
  - Pertinent systemic signs (eg, for vascular and metabolic diseases)
- Neuropsychological testing
- Laboratory testing
  - Thyroid function and vitamin B_{12} level
  - Other tests as indicated, such as for metabolic, infectious, autoimmune, and other etiologies[a]
- Structural brain imaging with CT or MRI
  - AD: generalized or focal cortical atrophy, often asymmetric (hippocampal atrophy)
  - Vascular contributions to cognitive impairment and dementia: brain infarcts or white matter lesions
  - Frontotemporal dementia: frontal lobe or anterior temporal lobe atrophy
  - Other abnormalities such as brain mass (eg, tumor) and hydrocephalus

Referral to a specialist for additional neurologic and medical testing, if specific etiologies suspected
- Neurophysiologic tests: EEG
- Vascular tests: head and neck MRA or CTA
- Cardiac tests: ECG, echocardiography, ambulatory cardiac rhythm monitoring

Abbreviations: AD, Alzheimer disease; CT, computed tomography; CTA, CT angiogram; ECG, electrocardiogram; EEG, electroencephalogram; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging.

[a] Depending on the clinical presentation, consider blood tests (complete blood cell count, erythocyte sedimentation rate, chem 7 panel [includes glucose level, renal and liver function tests, folic acid level], and rapid plasma reagin test).

Management

The overall goals are to reduce suffering caused by the cognitive and accompanying symptoms (eg, in mood and behavior), while delaying progressive cognitive decline. Both nonpharmacologic and pharmacologic approaches may achieve the overall goals.

Nonpharmacologic Management | For complex manifestations of dementia, referrals to specialists, such as clinician managers (eg, geriatric nurse practitioners), social workers, occupational or speech therapists, and others may be helpful. Evidence primarily from observational

Box 3. Nonpharmacologic Approaches to Dementia

- Cognitively stimulating activities (eg, reading, games)
- Physical exercise (eg, aerobic and anaerobic)
- Social interactions with others (eg, family events)
- Healthy diet such as the Mediterranean diet (eg, high in green leafy vegetables)
- Adequate sleep (eg, uninterrupted sleep and with sufficient number of hours)
- Proper personal hygiene (eg, regular bathing)
- Safety, including inside the home (eg, using kitchen appliances) and outside (eg, driving)
- Medical and advanced care directives (eg, designation of power of attorney)
- Long-term health care planning (eg, for living arrangements in the late stage of dementia)
- Financial planning (eg, for allocation of assets)
- Effective communication (eg, for expressing needs and desires, such as with visual aids)
- Psychological health (eg, participating in personally meaningful activities, such as playing music)

studies and a few randomized clinical trials suggest potential benefits of select nonpharmacologic approaches in dementia (**Box 3**). Although data demonstrating benefit are limited, nonpharmacologic approaches are inexpensive and generally safe. Cognitive training and activities such as reading and playing cognitively engaging games (eg, chess, bridge) may help maintain cognition and function, as shown in randomized trials.[72-74] However, frustration and stress from challenging tasks should be avoided. Music or art therapy, and other experiential approaches, may help maintain cognition or improve quality of life.[75] Because old memories of childhood are preserved the longest, reminiscence therapy, consisting of psychotherapy using the personal history of an individual's early-life stories and events, may improve psychological well-being.[76]

Physical exercise, both aerobic (eg, walking, swimming) and nonaerobic/conditioning (eg, resistance training), improve cardiovascular health through benefits on blood pressure and stroke risk, and randomized trials suggest these interventions may positively affect cognitive and physical function.[77-79] However, some randomized trials showed no effect of exercise on cognition.[80,81] In a randomized clinical trial, a comprehensive sleep education training program reduced nighttime awakenings, total time awake at night, and depressive symptoms over 6 months.[82] Social activities may be beneficial, including participating in birthday parties, holidays, support groups with cognitively impaired individuals, and interacting with trained pets (eg, dog therapy). Eating a brain-healthy diet (eg, nuts, berries, leafy greens, fish) or a Mediterranean diet is also suggested.[83-86] A randomized clinical trial found that an intervention that combined diet, exercise, cognitive training, and vascular risk monitoring improved cognition in people at risk for cognitive decline.[87] However, patients with moderate to severe dementia have difficulty participating in cognitive, physical, and social activities, and activities should be restricted when patients can no longer participate safely and productively.

Day care centers and assisted living facilities may be helpful for either the patient or caregiver but may not delay nursing home admission.[88] A randomized trial of staff and persons in residential care facilities showed that a clinical protocol used by staff for behavioral and psychological symptoms of dementia improved patients' behavioral symptoms and staff stress.[87] In the terminal phase of dementia, palliative care may be helpful.

Clinical attention for the caregiver, often a close relative, is important. While efforts continue to effectively deliver primary care for dementia,[89] caregiver education and interventions may improve outcomes for patients with dementia, and inexpensive and useful information is available (eTable 3 in the Supplement). A caregiver should monitor the patient's mental, physical, and financial well-being, including attention to home safety, such as risk of kitchen fires, which may be associated with patient burns.[90] Other home safety measures include controlling medication intake, limiting access to firearms and other weapons, and monitoring for elder abuse. Safety outside the home includes at work, where the caregiver may facilitate the patient cutting back or stopping work, for instance if managing machinery or making decisions regarding a company's finances. Also, driving may need to be restricted, including limiting driving to the immediate neighborhood and daytime driving to prevent getting lost. While no single test is associated with better driving safety, driving ability should be reassessed periodically and patients with significant dementia should stop driving, to prevent accidents and injuries.[91] The caregiver can assist in planning for health care and finances as soon as possible in the course of the illness, to determine advance directives before late-stage dementia.[92] Educating the family on effective communication with a person with dementia, who may eventually develop aphasia, is important. Similarly, family members should be educated on promoting psychological health and socially adaptive behaviors (eg, simple and clear instructions to encourage cooperation with activities to address physical and mental health needs, without inciting agitation or aggression).

Behavioral problems, such as physical aggression, are a main cause of emergency department visits and institutionalization and are associated with poor outcomes for patients (eg, psychological and medical complications) and families.[93,94] Caregiver interventions may prevent patient institutionalization. For example, the family can learn to recognize fear, frustration, and anger (eg, yelling, lashing out), and address signs of aggression (eg, by redirecting the patient's attention to something they enjoy), potentially preventing negative outcomes.[95]

An important consideration for families with a member who has dementia is the high burden of caregiving.[96] This burden may be physical/medical (eg, neglect of caregiver's own health, with potential medical complications), emotional and psychological (stress, burnout, depression), and/or financial. Prevention, early recognition, and treatment of these issues (eg, referrals to social work for additional support) are integral to an effective management plan. A randomized trial demonstrated that delivering caregiver assistance in person vs only by telephone improved care quality, without differences in effectiveness.[97]

Pharmacologic Management | Table 3 reports the drugs approved by the US Food and Drug Administration for AD dementia. Five drugs, 4 of which are currently available for prescription, yield modest symptomatic benefit for cognitive symptoms. Acetylcholinesterase inhibitors were the first drugs approved in the United States for AD. These drugs inhibit the brain acetylcholinesterase enzyme, thereby promoting relative increases in acetylcholine abundance at the

Table 3. Approved Pharmacologic Treatments for Dementia Attributed to Alzheimer Disease[a]

	Acetylcholinesterase Inhibitors			Memantine (NMDA Receptor Antagonist)	Memantine + Donepezil (Combination Drug)
	Donepezil	Rivastigmine	Galantamine		
Stage indicated	All stages of dementia	Mild to moderate[b]	Mild to moderate	Moderate to severe	Moderate to severe
Dosage titration and target	Tablet or orally disintegrating tablet: starting dose is 5 mg once daily for 6 wk; if tolerated, increase to 10 mg once daily (typical target dose); if tolerated and needed, may increase to 23 mg once daily[c]	Capsule: starting dose is 1.5 mg twice daily for 2 wk; if tolerated, increase to 3 mg twice daily for 2 wk, then 4.5 mg twice daily for 2 wk, then 6 mg twice daily (maximum recommended dose, 6 mg twice daily) Transdermal patch: starting dose is 4.6 mg/24 h once daily for 4 wk; if tolerated, increase to 9.5 mg/24 h for ≥4 wk; if tolerated and needed, increase to 13.3 mg/24 h (recommended effective dose, 9.5-13.3 mg/24 h)	Extended-release capsule: starting dose is 8 mg once daily for 4 wk; if tolerated, increase to 16 mg once daily for ≥4 wk; if tolerated and needed, increase to 24 mg once daily (recommended target dose range, 16-24 mg once daily) Immediate-release tablet or oral solution: starting dose is 4 mg twice daily for 4 wk; if tolerated, increase to 8 mg twice daily for ≥4 wk; if tolerated and needed, increase to 12 mg twice daily (recommended target dose range, 8-12 mg twice daily)	Extended-release capsule: starting dose is 7 mg once daily for 1 wk; if tolerated, may increase to 14 mg once daily, then 21 mg once daily, and then 28 mg once daily, at a minimum of 1-wk intervals (recommended target dose, 28 mg once daily) Tablet or oral solution: starting dose is 5 mg once daily for 1 wk; if tolerated, may increase to 5 mg twice daily, then 5 mg in AM and 10 mg in PM, and then 10 mg twice daily, at a minimum of 1-wk intervals (recommended target dose, 10 mg twice daily)	Capsule: target dose is 28 mg memantine extended-release with 10 mg donepezil, once daily in the evening For patients with severe renal impairment, maximum dose is 14 mg memantine extended-release with 10 mg donepezil once daily
Advantages	Among drugs listed, donepezil has been available for the longest time and, with prescriber familiarity, remains commonly used; available as generic drug and covered by most health insurance plans	Also available as a skin patch application, which is a good option when a patient has barriers to using an oral route of administration; also indicated for mild to moderate dementia associated with Parkinson disease	The most recent option for use in mild to moderate stage	May be used in combination with one of the acetylcholinesterase inhibitors or as monotherapy	Single-pill combination is best for patients already exposed to 1 or both of these individual drugs in the past and who have not experienced adverse effects
Adverse effects	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, vivid dreams, insomnia; use with caution in patients with peptic ulcer disease, respiratory disease, seizure disorder, and urinary tract obstruction; contraindicated in patients with bradycardia	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, vivid dreams, insomnia; use with caution in patients with peptic ulcer disease, respiratory disease, seizure disorder, and urinary tract obstruction; contraindicated in patients with bradycardia Patch formulation can cause local skin irritation and reactions	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, vivid dreams, insomnia; use with caution in patients with peptic ulcer disease, respiratory disease, seizure disorder, and urinary tract obstruction; contraindicated in patients with bradycardia	Headache, constipation, confusion, and dizziness; use with caution in patients with cardiovascular disease, seizure disorder, and severe hepatic and renal impairment	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, vivid dreams, insomnia; use with caution in patients with peptic ulcer disease, respiratory disease, seizure disorder, and urinary tract obstruction; contraindicated in patients with bradycardia Headache, constipation, confusion, and dizziness; use with caution in patients with cardiovascular disease, seizure disorder, and severe hepatic and renal impairment

Abbreviation: NMDA, *N*-methyl-D-aspartic acid

[a] Approved by the US Food and Drug Administration; refer to current, established sources of data (eg, https://www.pdr.net/drug-summary) for most up-to-date prescribing information, including for indications, dosages, adverse effects, risks, and contraindications; note that tacrine, another anticholinesterase inhibitor, was the first drug approved for Alzheimer disease in the United States but is no longer in use because of related toxicity.

[b] A transdermal patch formulation is also approved for the severe stage of dementia.

[c] The 23-mg dose is available as brand-name tablet only.

synaptic cleft for cholinergic neurotransmission. In a meta-analysis review of 10 randomized, double-blind, placebo-controlled trials, each with a 6-month duration of drug exposure, acetylcholinesterase inhibitors were associated with 2.4-points slower decline (95% CI, −2.7 to −2.0; $P < .001$) for a cognition outcome with range 0 to 70.[98] This improvement is equivalent to about 6 months of decline from natural history studies of AD dementia, but the magnitude of the clinically relevant benefit is uncertain.[36] Also, modest improvements were observed in activities of daily living and behaviors. The efficacy of anticholinesterase inhibitors is similar among the individual drugs (donepezil, rivastigmine, galantamine).[97] Given the modest benefits and known risks, clinicians should engage in shared decision-making regarding the initiation of an acetylcholinesterase inhibitor for the symptomatic treatment of AD dementia.[91]

Each drug shown in Table 3 is available for use orally, and 1 (rivastigmine) is also available for transdermal use. A slow-titration dosing regimen over 4 to 8 weeks is recommended to reach the target dose and minimize adverse effects for all of the drugs. Some drugs are prescribed at different maintenance doses depending on effects or adverse effects. For example, donepezil maintenance can be at 5 mg (eg, if higher dose is associated with poor tolerability), 10 mg (typical target), or 23 mg (rarely used), once daily. Despite

a slow titration, adverse effects, such as gastrointestinal adverse effects (eg, nausea, vomiting, and diarrhea in about 5% of users), may occur (Table 3). Rates of adverse effects may be higher than previously recognized.[99] If adverse effects are encountered, dosage may be lowered (eg, from 10 mg of donepezil to 5 mg) temporarily (eg, days to weeks) before reescalating more slowly and monitoring for recurrence of adverse effects (family instructed to call clinician if adverse effects occur). Alternatively, the drug can be discontinued and a different drug can be prescribed even in the same class (another acetylcholinesterase inhibitor), given that adverse effects vary among same-class drugs.[100] Approximately 5% of patients discontinue the drug because of adverse effects. If the drug is tolerated, annual or semi-annual brief assessments using the history (eg, progression of cognitive problems, new cognitive problems, functional status) and a brief cognitive test can be used in the absence of new problems. Often, clinicians cannot discern a benefit and must rely on caregiver reports. A good response to a drug would result in the caregiver noticing a slight improvement in day-to-day life (eg, improved ability to function at home). Routine cognitive tests such as the MoCA[44] can be used to monitor disease course during treatment to identify unexpected trends such as rapid decline, which would prompt consideration for a medical evaluation (eg, for systemic infection). However, benefits are typically not seen on such routine tests. Monitoring requires periodic reevaluation of cognition, function, neuropsychiatric and behavioral symptoms, and medication reconciliation.[101-104]

As neurodegeneration in AD progresses, further cognitive and functional decline invariably occur. Memantine may be considered for patients with moderate to severe dementia (Table 3). Memantine also can be used as a first-line drug, for instance when a patient with moderate dementia presents for a first evaluation but is not taking any medication for cognition. Another use is for patients who cannot tolerate an acetylcholinesterase inhibitor. Adverse effects of memantine include headaches and constipation.

Aside from AD, few other dementia etiologies have approved pharmacologic treatments for cognitive symptoms, and no disease-specific treatments exist for Lewy body disease or frontotemporal dementia. In addition to AD, rivastigmine has also received approval for Parkinson disease dementia. Currently, no drugs are approved by the US Food and Drug Administration for MCI,[105] and studies of acetylcholinesterase inhibitors failed to show benefit in this population.[106] At this time, more than 100 drugs are being investigated for dementia and cognition, including potential disease-modifying agents.[107,108]

Medical management should address common causes of cognitive impairment and dementia, including polypharmacy, which affects one-third of persons older than 60 years.[109,110] Special considerations may be appropriate for patients with medical comorbidities (eg, kidney dysfunction). Another approach in dementia management is reducing brain ischemia and stroke risk by treating vascular risk factors (hypertension, diabetes, hyperlipidemia) and consideration of the risk-benefit ratio for antithrombotics and anticoagulants (if prior stroke or atrial fibrillation are present). A recent randomized clinical trial of dementia prevention showed that intensive blood pressure lowering in persons with hypertension (comparing a target systolic blood pressure below 120 mm Hg with a pressure between 120-140 mm Hg) did not reduce risk of dementia but did reduce the combined rate of MCI or probable dementia in a post hoc analysis.[111]

Dementia is often accompanied by neuropsychiatric and behavioral problems. About 95% of patients have at least mild symptoms, most commonly apathy (83%) and depression (63%).[112] Approved treatments do not exist for these noncognitive manifestations in the setting of dementia. For depression, a low-dose antidepressant can be tried, such as a selective serotonin reuptake inhibitor (eg, escitalopram). Management of agitation and aggression can be challenging. Conventional antipsychotics, such as haloperidol, should be avoided.[113] Newer-generation "atypical" antipsychotics such as risperidone and quetiapine fumarate should be avoided if possible, given their association with serious risks, especially in older patients[114]; death, and cardiac effects such as heart failure and stroke, have resulted in a black box warning. Therefore, antipsychotics should only be used in controlled environments (eg, under close medical supervision) and for a limited time only (eg, a few weeks) when all other nonpharmacologic approaches have failed or the patient's behavior poses a substantial threat to the patient or others.[113]

Conclusions

Alzheimer disease currently affects 5.8 million persons in the United States and is a common cause of dementia, which is usually accompanied by other neuropathology, often cerebrovascular disease such as brain infarcts. Causes of dementia can be diagnosed by medical history, cognitive and physical examination, laboratory testing, and brain imaging. Management should include both nonpharmacologic and pharmacologic approaches, although efficacy of available treatments remains limited.

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