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Diagnosis and Management of Dementia: A Review

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Abstract

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 US, Alzheimer's disease (AD) affects 5.8 million people. However, dementia is commonly associated with more than one neuropathology, usually AD 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 moderately extended 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 (e.g., symptoms present, but normal examination), neuropsychological testing can help with a diagnosis. 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 should be considered in atypical dementia cases, such as age of onset under 65 years, rapid symptom onset, and/or impairment in multiple cognitive domains but not episodic memory. For treatment, patients benefit from non-pharmacologic 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 AD, 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 is approved for the symptomatic treatment of Parkinson's disease dementia.

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Conclusions and Relevance—AD currently affects 5.8 million persons in the US, and is a common cause of dementia which is usually accompanied by other neuropathology. Causes of dementia can be diagnosed by medical history, cognitive and physical examination, laboratory testing, and brain imaging. Management should include both non-pharmacologic and pharmacologic approaches.

INTRODUCTION

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 (US) 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 US, the prevalence of dementia is 15% in people older than 68 years.[3] Dementia is most commonly attributed to Alzheimer's disease (AD), with over five million people currently affected by AD, and 13.8 million are projected to be affected by the year 2050.[4] AD is the 6th leading cause of death, and the 5th leading cause among persons older than 65 years.[5,6] This review summarizes diagnosis and management of dementia, defined as significant cognitive impairment in two 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: a publication date from 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 five and a half 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 articles of original research, 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 5–10% of people older than 65 years, and 50% of those 85 years old.[7] Non-modifiable 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 cases) and frontotemporal lobar degeneration (in <5% of cases) are less frequent.[19–25]

Definition and Characterization

Dementia is defined by chronic, acquired loss of two 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 Statistical Manual, 5th Edition, have moved away from using the term dementia and have recognized that dementia can be present with impairment in a single domain (i.e. by this definition, a patient with a severe expressive aphasia could be classified as having dementia).[26,27] 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, to pay bills or to take medication. Typically, a person with AD repeats questions and conversations. The memory loss is often accompanied by subjective memory complaints. Difficulty recalling names which 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 testing of cognition, but with maintained daily functions (e.g., 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).[28] MCI can be categorized into "amnestic" MCI, in which reduced performance on memory is the key finding, versus "non-amnestic" MCI, in which reduced cognitive performance is in a non-memory domain such as language. MCI can also be characterized into "single domain" versus "multi-domain" 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 are also present in some conditions including neurodegenerative diseases (such as in early stages of Lewy body disease), cerebrovascular disease (e.g., intermittent small strokes), and psychiatric conditions (e.g., depression, anxiety), and with medications affecting cognition (e.g., opioids), and variability in cognitive test results.

Dementia is a clinical syndrome with variable manifestations (Table 1), which help attribute the cause of dementia and guide management. While research studies have defined a "preclinical" AD,[27,29] 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 look similar (Table 2).[30–34]

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 co-morbid condition with AD, and evidence of cerebrovascular disease does not reduce the

likelihood of AD. However, approximately five percent of people with dementia show evidence of only cerebrovascular disease. After AD, the most common neurodegenerative dementias are Lewy body disease, characterized by chronic REM behavior disorder with early visuospatial impairment and parkinsonism,[21,22,32,33] 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, 34]

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—The 2014 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 age 65 years and older.[35] 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 of the effect of screening on decision making or planning by patients, clinicians, or caregivers.[35] However, report of memory complaints[36–38] or rapidly-progressive cognitive problems over several months may indicate an underlying medical condition that warrants further evaluation with cognitive, laboratory, and other tests.[39–40]

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 complain of forgetfulness, others are unable to recall details of their history and in some instances have anosognosia (i.e., lack of insight into one's disease). One clue that a patient has a memory problem occurs when the person accompanying them provides the medical history. The history should characterize the nature, magnitude, and course of cognitive changes. The nature refers to the cognitive domains affected. Is there loss of episodic memory (e.g., what the patient did that morning, yesterday, and last week), or language abilities (e.g., word finding difficulties with circumlocutions)? The magnitude refers to the severity: does the cognitive loss affect daily functions, such as the patient's ability to manage her own affairs (e.g., does she get lost while driving, not pay her bills, forget to take medications)? Is the course with 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's Disease, head trauma), and use of medications that can impair cognition (e.g., sleep aids and anxiolytics such as benzodiazepines; analgesics such as codeine containing agents; anticholinergics such as tricyclic antidepressants and bladder antimuscarinics).[41,42] 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 (e.g., memory versus 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 <24/30). The MoCA requires about 10 minutes to administer and is useful in early detection of cognitive impairment, including MCI with executive dysfunction.[43] The Mini-Mental State Exam 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.[43–47]

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 and/or temporal regions of the brain while other areas are relatively spared. The examination may demonstrate focal neurologic signs or parkinsonism (e.g., 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 which may be pertinent to rarer causes of dementia (e.g., golden-brown eye discoloration [Kayser-Fleischer rings] of Wilson's disease).

The routine work-up typically includes a limited number of blood tests (e.g., B12 and TSH) and neuroimaging to identify cortical and hippocampal atrophy (as seen in AD), or neuropathology including potentially treatable causes of dementia (e.g., resectable tumor, or normal pressure hydrocephalus which may be shunted), using brain imaging with either MRI or CT (Box 2).[48–53] Additional evaluation is sometimes warranted. For example, in highly-educated and highly-functioning individuals, a compelling history of cognitive decline (e.g., no longer able to perform a complex task which could easily be done a year ago, such as filling a tax return or working at a cognitively demanding job such as doctor or lawyer), can suggest dementia despite the presence of "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 (e.g., memory, executive function, language, attention, visuospatial abilities) with increased levels of difficulty.[54]

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).

Recent biomedical advances have led to additional tests that may be helpful in the differential diagnosis of dementia, in particular disease biomarkers which are still commonly used in research.[55] For a patient whose presentation is not consistent with AD (commonly called "atypical dementia"; see Supplemental Materials, eTable 1) and for patients in whom diagnostic certainty is low, clinicians may consider specialist referral and additional testing. Functional neuroimaging[56] such as positron emission tomography (PET)[57] 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.[58–59] FDG PET, covered by health insurance for suspected frontotemporal dementia, may differentiate this etiology from AD, facilitating diagnosis of this less common cause of dementia. 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.[60] Amyloid PET can also be used in patients with cognitive impairment who are evaluated for AD or other causes of cognitive decline.[58–59,61] 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 to pre-PET scan. Change in management plans consisted of change in AD medication or other medication therapy, and changes in counseling about safety and future planning.[62] However, there is no evidence that PET scan changes clinical outcomes. Functional neuroimaging with tau radioligands are only appropriate for research purposes.[63]

Cerebrospinal fluid (CSF) testing may be considered to obtain evidence of AD (low amyloid and high tau levels), other neurodegenerative disease (e.g., elevated protein 14–3-3 for Creutzfeldt-Jakob disease) or other etiologies (e.g., positive cultures in infection, oligoclonal bands in demyelination; improved gait after high volume CSF removal in normal pressure hydrocephalus).[64–68] Genetic testing may be reasonable, usually for young patients with a history of first-degree relatives with young-onset dementia (e.g., parents or siblings with dementia in their fourth or fifth decade of life). Rare autosomal dominant forms of dementia (e.g., presenilin gene mutations) warrant genetic counseling to determine whether other family members need to be screened.[69] 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 work-up, such as for amyotrophic lateral sclerosis and medical work-up, such as for cardiac, metabolic, and other etiologies, may be considered with particular attention to ruling out reversible causes of cognitive impairment such as psychiatric disorders (depression) and thyroid dysfunction (see Supplemental Materials, eTable 2).[70]

Management—The overall goals are to reduce suffering caused by the cognitive and accompanying symptoms (e.g., in mood and behavior), while delaying progressive cognitive decline. Both non-pharmacologic and pharmacologic approaches are used to achieve the overall goals.

Non-pharmacologic management: For complex manifestations of dementia, referrals to specialists, such as clinician managers (e.g., geriatric nurse practitioners), social workers, occupational or speech therapists, and others may be helpful. Evidence primarily from observational studies and a few randomized controlled trials suggest potential benefits of select non-pharmacologic approaches in dementia (Box 3). Although data demonstrating benefit are limited, they are inexpensive and generally safe. Cognitive training and activities such as reading and playing cognitively engaging games (e.g., chess, bridge) may help

maintain cognition and function, as shown in randomized trials.[71–73] 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.[74] Because old memories of childhood are preserved the longest, reminiscence therapy, consisting of psychotherapy using the personal history of an individuals' early-life stories and events, may improve psychological well-being.[75]

Physical exercise, both aerobic (e.g., walking, swimming) and non-aerobic/conditioning (e.g., weights), improves cardiovascular health through benefits on blood pressure and stroke risk, and randomized trials suggest these interventions may positively affect cognitive and physical function.[76–78] But, not all randomized trials have shown benefits from exercise for cognition.[79–80] In a randomized clinical trial, a comprehensive sleep education training program reduced night-time awakenings, total time awake at night, and depressive symptoms over 6 months.[81] Social activities may be beneficial, including participating in birthday parties, holidays, support groups with cognitively impaired individuals, and interacting with trained pets (e.g., dog therapy). Eating a brain-healthy diet (e.g., nuts, berries, leafy greens, fish) or a Mediterranean diet is also suggested.[82–85] A randomized clinical trial found that a combined diet, exercise, cognitive training, and vascular risk monitoring intervention improved cognition in people at-risk for cognitive decline.[86] However, patients with moderate-to-severe dementia have difficulty participating in cognitive, physical, and social activities, and activities should be limited when patients can no longer participate safely and productively.

Day care centers and assisted living facilities may also be helpful for either the patient or caregiver, but may not delay nursing home admission.[87] A randomized trial of staff and persons in residential care facilities showed that a clinical protocol for behavioral and psychological symptoms of dementia used by staff, improved patients' behavioral symptoms and staff stress.[86] 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,[88] caregiver education and interventions may improve outcomes for patients with dementia, and inexpensive and useful information is available (See Supplemental Materials, eTable 3). Safety, including for the patient's mental, physical, and financial well-being, should be monitored by the caregiver, with attention to home safety, such as risk of kitchen fires which may be associated with patient burns.[89] 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 modified, including limiting driving to neighborhood and daytime driving to prevent getting lost. While no single test is associated with better driving safety, driving ability should be re-assessed periodically and cessation recommended based on dementia severity, to prevent accidents and injuries.[90] The caregiver can assist in planning for health care and finances as soon as possible in the course of the illness, to determine advanced directives before late-stage dementia.[91] Educating the family on effective communication with a person with dementia, who eventually develop aphasia, is

important. Similarly, family should be educated on promoting psychological health and socially adaptive behaviors (e.g., 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 room visits and institutionalization, and are associated with poor outcomes for patients (e.g., psychological and medical complications) and families.[92,93] Caregiver interventions may prevent patient institutionalization. For example, the family can learn to recognize fear, frustration, and anger (e.g., yelling, lashing out), and address signs of aggression (e.g., by redirecting the patients' attention to something they enjoy), potentially preventing negative outcomes.[94]

An important consideration for families with a member who has dementia, is the high burden of caregiving.[95] This burden may be physical/medical (e.g., 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 (e.g., referrals to social work for additional support), are integral to an effective management plan. A randomized trial demonstrated that delivering caregiver assistance in-person versus by telephone only, both improved care quality and without differences in effectiveness.[96]

Pharmacologic management: Table 3 shows the Food and Drug Administration (FDA) approved drugs for AD dementia. Five drugs, four of which are currently available for prescription, yield modest symptomatic benefit for cognitive symptoms. Acetylcholinesterase inhibitors were the first drugs approved in the US for AD. These drugs inhibit the brain acetylcholinesterase enzyme, thereby promoting relative increases in acetylcholine abundance at the synaptic cleft for cholinergic neurotransmission. In a meta-analysis review of 10 randomized, double blind, placebo controlled trials each with a six month duration of drug exposure, acetylcholinesterase inhibitors were associated with 2.4 points slower decline (95%CI −2.7 to −2.0; $p<0.00001$) in a research measure of cognition spanning 70 points.[97] This 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.[35] 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).[96] 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.[90]

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

about 5 percent of users) may occur (Table 3). Adverse effects may be higher than previously recognized.[98] If encountered, dosage may be lowered (e.g., from 10 mg of donepezil to 5 mg), either temporarily (e.g., days to weeks) before re-escalating more slowly and monitoring for recurrence of adverse effects (family instructed to call clinician if adverse effects). 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.[99] Approximately 5 percent of patients discontinue the drug due to adverse effects. If tolerated, annual brief assessments using the history (e.g., 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 appreciate 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 (e.g., improved ability to function at home). Routine cognitive tests such as the MoCA,[43] can be used to monitor disease course on treatment, and to identify unexpected trends such as rapid decline which would prompt consideration for a medical evaluation (e.g., for systemic infection). However, benefits are typically not seen on such routine tests. Monitoring requires periodic re-evaluation of cognition, function, neuropsychiatric and behavioral symptoms, and medication reconciliation.[100–103]

As neurodegeneration in AD progresses, further cognitive and functional decline invariably occur, and consideration should be given in the moderate-to-severe stages of dementia for adding memantine (Table 3). Memantine can also 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. There are currently no FDA-approved drugs for MCI,[104] and studies of acetylcholinesterase inhibitors failed to show benefit in this population.[105] At this time, more than 100 drugs are being investigated for dementia and cognition, and include potential disease modifying agents.[106–107]

Medical management should address common causes of cognitive impairment and dementia, including polypharmacy which affects a third of persons older than 60 years.[108–109] Special considerations may be appropriate for patients with medical comorbidities (e.g., 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 anti-thrombotics 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 120mmHg, to a pressure between 120–140mmHg) did not reduce risk of dementia, but did reduce the combined rate of MCI or probable dementia in a *post-hoc* analysis.[110]

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%).[111] Approved treatments do not exist for these non-cognitive manifestations in the setting of dementia. For depression, a low dose antidepressant can be tried such as with a selective serotonin-reuptake inhibitor (e.g., escitalopram). Management of agitation and aggression can be challenging. Conventional antipsychotics such as haloperidol, should be avoided.[112] 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.[113] Specifically, death, cardiac effects such as heart failure, and stroke, have resulted in a black box warning. Therefore, antipsychotics should only be used in controlled environments (e.g., under close medical supervision) and for a limited time only (e.g., a few weeks) when all other non-pharmacologic approaches have failed or the patient's behavior poses a substantial threat to themselves or others.[112]

CONCLUSIONS

AD currently affects 5.8 million persons in the US, and is a common cause of dementia which is usually accompanied by other neuropathology. The cause of dementia can be diagnosed by medical history, cognitive and physical examination, laboratory testing, and brain imaging. Management should include both non-pharmacologic approaches with cognitive, physical, and social activities, and pharmacologic approaches such as with an acetylcholinesterase inhibitor for AD, although efficacy of treatments remains limited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.
Characteristics of dementia and mild cognitive impairment

Dementia[27]

The loss of cognitive abilities must be:

- Present in several cognitive domains (often memory with at least one 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 (e.g., social, occupational, self-care)

The most common form of dementia is a "mixed dementia",* usually a combination of a:

- Common neurodegenerative disease in aging, most often Alzheimer's disease (AD), and
- Vascular contributions to cognitive impairment and dementia (VCID)

Common neurodegenerative diseases causing dementia include the following, in decreasing order of frequency:**

- AD
- Lewy body disease
- Frontotemporal dementia ***

Mild cognitive impairment (MCI)[28]

The loss of cognitive abilities must be:

- Demonstrable on cognitive testing, whether amnestic versus non-amnestic MCI, or single versus multi-domain MCI (present in several cognitive domains),**** and
- Not sufficient to significantly impair functional abilities or independence, such that criteria for dementia are NOT met

* Mixed dementias have overlapping clinical features and more than one pathologic diagnosis.

** Other less common neurodegenerative and other diseases are not listed 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 (e.g., motor vehicle accident or war-related traumatic brain injury), chronic traumatic encephalopathy (e.g., 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 Transactive response DNA-binding Protein 43 (TDP-43) form of frontotemporal dementia and for hippocampal sclerosis.

*** Some data suggest this condition is a common cause of dementia in young-onset cases (onset before age 65 years).[114]

**** Amnestic MCI is defined by neuropsychological test proven impairment in the memory domain, and can be "single domain amnestic MCI" or "multi-domain amnestic MCI"; non-amnestic MCI is defined by impairment in one 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 non-amnestic MCI" or "multi-domain non-amnestic MCI".

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 history
  - ➢ General medical history
  - ➢ Family history
- Physical examination
  - ➢ Neurologic signs (e.g., cognitive impairment, focal signs, parkinsonism, other)
  - ➢ Pertinent systemic signs (e.g., for vascular and metabolic diseases)
- Neuropsychological testing
- Laboratory testing
  - ➢ Thyroid function and vitamin B12 level
  - ➢ Other tests as indicated, such as for metabolic, infectious, autoimmune, and other etiologies *
- 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 (e.g., tumor) and hydrocephalus
- Referral to a specialist, for additional neurologic and medical testing, if specific etiologies suspected
  - ➢ Brain tests: electroencephalogram [EEG]
  - ➢ Vascular tests: head and neck magnetic resonance angiogram (MRA) or computed tomography angiogram (CTA)
  - ➢ Cardiac tests: electrocardiogram [ECG], echocardiography, ambulatory cardiac rhythm monitoring

* Depending on the clinical presentation, consider blood tests for a CBC, ESR, chem 7 which includes a glucose level, renal and liver function tests, folic acid, and a RPR.

Box 3.

Non-pharmacologic approaches to dementia

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

Table 1.

Manifestations of dementia *

AREA**	EARLIER-STAGE MANIFESTATIONS	*EXAMPLES* OF EARLIER-STAGE MANIFESTATIONS	LATER-STAGE MANIFESTATIONS	*EXAMPLES* OF LATER-STAGE MANIFESTATIONS
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 (e.g., how to use the microwave, dial phone numbers, etc.)
	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 (e.g., 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 (e.g., not preparing meals)	Delusions	False belief system such as a deceased relative is still alive, the 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 (e.g., echolalia, palilalia) and actions (e.g., hyperorality such as eating off 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 (RBD)	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

* 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 provide examples of manifestations. Variability in individual presentations is common; see text and Table 2 for pathognomonic characteristics of particular dementia etiologies

** Note the range of functional areas affected in dementia, beyond cognition

Table 2.

Clinical and pathologic characteristics differentiating select causes of dementia

	DISEASE*			
	Alzheimer's disease (AD)	**Cerebrovascular Disease*** **	**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**** and/or anterior temporal lobes, histologic hallmarks of phosphorylated Transactive response DNA-binding Protein 43 (TDP-43), microtubule-associated protein tau (MAPT), or fused-in-sarcoma (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, EXAM, AND COGNITIVE FEATURES IN THE *EARLY* STAGE **	History: presenting symptoms is typically short-term memory loss Exam and/or cognitive testing: episodic memory impairment accompanied by other subtle cognitive deficits, such as visuospatial problems and anomia	History: vascular risk factors (e.g., hypertension, diabetes) or prior stroke or other vascular events (myocardial infarction) Exam: 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 magnetic resonance imaging (MRI)	History: Rapid Eye Movement (REM) Behavior Disorder (RBD) for years preceding the cognitive impairment; visual and other hallucinations Exam 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 (e.g., disinhibition, apathy) Exam and/or cognitive testing documenting disinhibition and inappropriate behaviors; in language variant, impaired fluency in speech, semantic paraphrasias; other significant executive or language problems, with relative preservation of memory

*Diseases are listed in decreasing order of frequency, from left to right (see text for details)

**Includes characteristics often present or notably absent

***Includes more advanced stage of the syndrome, of "vascular dementia"

****One specific form is "Pick's disease"

Table 3.

Approved* pharmacologic treatments for dementia attributed to AD

	Acetylcholinesterase inhibitors			NMDA** receptor antagonist	Combination drugs
	Donepezil	**Rivastigmine**	**Galantamine**	**Memantine**	**Memantine and donepezil**
STAGE INDICATED	All stages of dementia	Mild-to moderate***	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 weeks; if tolerated, increase to 10 mg once daily (typical target dose); if tolerated and needed, may increase to 23 mg once daily (note: 23 mg dose available as brand-name tablet only).	**Capsule:** starting dose is 1.5 mg twice daily for two weeks; if tolerated, increase to 3 mg twice daily for 2 weeks, then 4.5 mg twice daily for 2 weeks, then 6 mg twice daily. Maximum recommended dose: 6 mg twice daily. **Transdermal patch:** starting dose is 4.6 mg/24 hours patch once daily for 4 weeks; if tolerated, increase to 9.5 mg/24 hours for ≥4 weeks; if tolerated and needed, increase to 13.3 mg/24 hours. Recommended effective dose: 9.5 to 13.3 mg/24 hours patch.	**Extended-release capsule**: starting dose is 8 mg once daily for 4 weeks; if tolerated, increase to 16 mg once daily for ≥4 weeks; if tolerated and needed, increase to 24 mg once daily. Recommended target dose range: 16 to 24 mg once daily. **Immediate-release tablet or oral solution**: starting dose is 4 mg twice daily for 4 weeks; if tolerated, increase to 8 mg twice daily for ≥4 weeks; if tolerated and needed, increase to 12 mg twice daily. Recommended target dose range: 8 to 12 mg twice daily.	**Extended-release capsule:** starting dose is 7 mg once daily for one week; if tolerated, may increase to 14 mg once daily, then 21mg once daily, and then 28 mg once daily, at a minimum of 1 week intervals. Recommended target dose: 28 mg once daily. **Tablet or oral solution:** starting dose is 5 mg once daily for one week; 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 week 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, this 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 for 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.	Singe pill combination is best for patients already exposed to one 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 bradycardia. Patch formulation (for rivastigmine) can cause local skin irritation and reactions.			Headache, constipation, confusion and dizziness; use with caution in patients with cardiovascular disease, seizure disorder, and severe hepatic and renal impairment.	(see both cells to the left).

* Approved by the US Food and Drug Administration (FDA); refer to current, established sources of data (e.g., www.pdr.net/drug-summary) for most-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 AD in the US, but is no longer in use because of related toxicity

** NMDA: N-Methyl-D-Aspartic acid

*** Note that a transdermal patch formulation is also approved for the severe stage of dementia