Managing cognitive impairment in older patients

Evidence-based recommendations for prevention, diagnosis, and management

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These are general recommendations only; specific medical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Alosa Health

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Activity Start Date: April 30, 2026
Activity Termination Date: April 29, 2029

This activity offers CE credit for:

1. Medicine (AMA)
2. Nurses (ANCC)
3. Other

All other attendees will receive a Certificate of Attendance

Activity Overview:

The main goal of the educational program is to help primary care practitioners provide optimal evidence-based care for patients with cognitive impairments related to Alzheimer's disease and related dementias. This document describes the definitions, differential diagnosis, and risk factors for dementia and mild cognitive impairment, provides recommendations about screening and evaluation, summarizes current evidence for both non-pharmacological and pharmacological management of cognitive impairment and behavioral and psychological symptoms of dementia, and reviews best practices for advance care planning.

The educational program includes a written evidence report (print monograph) and several non-CME/CE components:

1. Summary document of top 4-5 key messages
2. "Academic detailing" educational sessions in clinicians' offices with specially trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
3. Patient education information (brochure/tear off sheets)

This program synthesizes current clinical information on this topic into accessible, non-commercial, evidence-based educational material, to be taught interactively to providers by specially trained clinical educators.

Learning Objectives:

Upon completing this activity, participants will be able to:

- Describe the risk factors for dementia and the evidence supporting interventions associated with reduced risk of cognitive impairment.
- Identify patients with cognitive impairment, evaluate for reversible causes, and optimize overall health.
- Recommend treatment of dementia based on severity, and monitor for side effects to determine treatment course.
- Apply appropriate use of biomarker testing in primary care, including when testing is and is not indicated.

- Summarize the current evidence regarding monoclonal antibodies targeting amyloid beta deposition.
- Identify causes of behavioral and psychological symptoms of dementia (BPSD) and prioritize non-pharmacologic management strategies.
- Design a series of conversations to establish and update an advance care plan for patients with dementia and their caregivers.

Financial Support:

There is no commercial support associated with this activity.

Target Audience:

The educational program is designed for primary care providers, including general internal medicine doctors, family practice physicians, nurse practitioners, physician assistants, nurses, and all other clinicians caring for patients with diabetes.

Credit Information:

In support of improving patient care, this activity has been planned and implemented by CME Outfitters, LLC and Alosa Health. CME Outfitters, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Note to Osteopathic Physicians: The AOA automatically recognizes *AMA PRA Category 1 Credit* ™ as AOA Category 2 credit.

Note to Nurse Practitioners: Nurse practitioners can apply for *AMA PRA Category 1 Credit™* through the American Academy of Nurse Practitioners (AANP). AANP will accept *AMA PRA Category 1 Credit™* from Jointly Accredited Organizations. Nurse practitioners can also apply for credit through their state boards. The content of this CNE activity pertains to Pharmacology.

Nurses: This activity is designated for 2.5 nursing contact hours.

California Residents: This continuing nursing education activity was approved by the California Board of Registered Nursing. CME Outfitters LLC's provider number is CEP15510.

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Disclosures:

This material is provided by Alosa Health, a nonprofit organization which accepts no funding from any pharmaceutical company. All individuals including planners, authors, reviewers, academic detailers, staff, etc., who are in a position to control the content of this educational activity have reported no financial relationships related to the content of this activity.

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All identified Conflicts of Interest have been mitigated.

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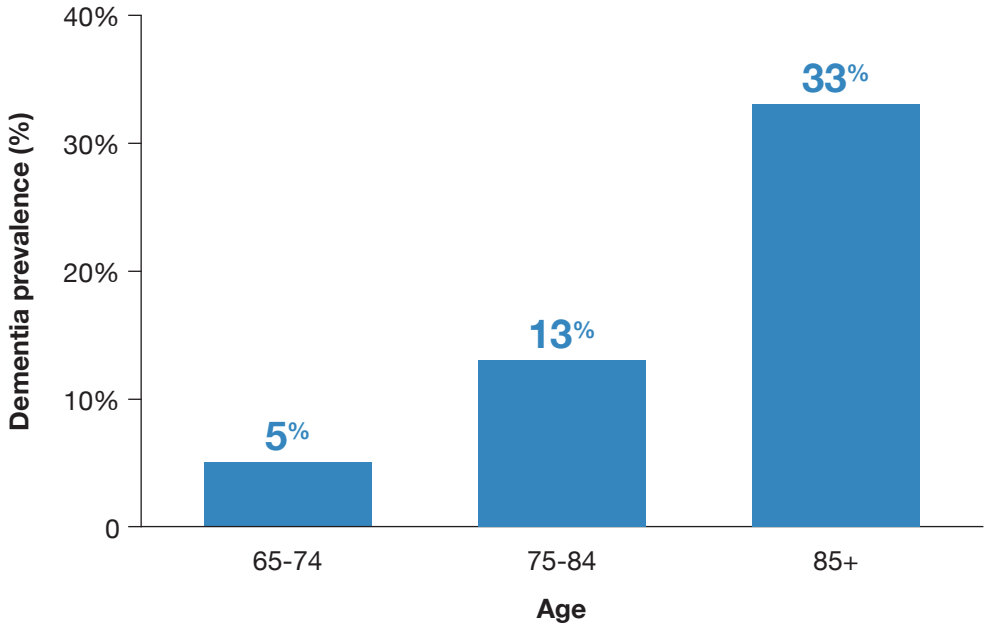
The challenge of Alzheimer's disease and related dementias

As of 2025, an estimated 7.2 million people over age 65 have Alzheimer's disease (AD) in the U.S., with prevalence increasing with age.[1] About 5.1% of adults between ages 65 and 74 have AD, with prevalence rising to 33.4% in people over age 85 (Figure 1).[1] In Pennsylvania, as of 2020, an estimated 282,000 people over age 65 had AD (11.5% of that population).[1] Mild cognitive impairment (MCI), an intermediate stage on the spectrum between normal cognitive aging and dementia, is also common, with an estimated prevalence in the U.S. of 15% to 22% in adults age 65 and older.[2]

Figure 1: Percentage of people in the U.S. with Alzheimer's disease by age group, 2025[1]



Data from the Health and Retirement Study, a nationally representative, population-based longitudinal survey of older U.S. adults (N=10,546) showed a drop in the prevalence of dementia in recent years, from 11.5% in 2000 to 7.7% in 2016.[3] This study also documented a decline in dementia incidence, from 5.0% in 2000-2002 to 3.8% in 2014-2016. Another study found that the age-specific prevalence rates of dementia declined by about two-thirds in the U.S. between 1984 and 2024.[4] Despite the encouraging declines in dementia incidence, the total number of people living with dementia continues to grow due to population aging.[3,4]

Significant racial/ethnic disparities in dementia incidence exist, with an age-adjusted incidence highest among Hispanic persons (20.7 per 1000 person-years) and lowest in White persons (11.5 per 1000 person-years).[5] Racial disparities in dementia risk are a product of complex relationships involving vascular risk factor burden, access to medical care, socioeconomic status, and educational attainment and quality. The COVID-19 pandemic may have exacerbated existing conditions, as it was associated with increased excess mortality for patients with AD and related dementias (ADRD), especially for Asian,

Black, and Hispanic populations.[6] Ultimately, the rise in the total population of older adults will drive a steady increase in the number of people experiencing ADRD in coming decades.

Primary care clinicians must be adept at evaluating older adults for dementia or MCI. They must also be prepared to manage cognitive impairment and related medical issues, maintain patient safety, and support patients and caregivers by linking them with community resources and other health care and social service providers. Given the time constraints under which many primary care providers operate, it is important that they know their own breadth of expertise and "comfort zone" in evaluating and treating dementia or MCI, and seek consultation when necessary.

This document covers the definitions, differential diagnosis, and risk factors for dementia and MCI, and provides recommendations about screening and evaluation, with attention to the increasing use of biomarker testing, which is changing the way dementia is diagnosed and categorized. The document also summarizes current evidence for preventing future dementia and managing current dementia with non-pharmacological and pharmacological approaches. Detailed guidance is provided about ways to manage the very common and often challenging behavioral and psychological symptoms of dementia (BPSD).

The spectrum of cognitive impairment

Cognitive function changes with time, and it is necessary to differentiate between normal and abnormal changes. Typically, two types of memory are preserved with aging: semantic (i.e., the ability to recall general facts and concepts, vocabulary, and language) and procedural (i.e., how to perform mental or physical tasks of daily living).[7] Episodic memory (i.e., remembering where objects are and the "what," "where," and "when" of daily life) typically declines with age, together with cognitive skills including processing speed, ability to learn new information, and the ability to multi-task or shift between tasks.[7] However, these normal age-related changes in cognition are generally mild and do not interfere with independence in daily life.[8]

Mild cognitive impairment

MCI is a syndrome in which a person has modest problems with memory, language, or other mental functioning. These problems are severe enough to be noticeable to other people and to be documented on cognitive tests, but not serious enough to interfere with daily life, although greater effort, compensatory strategies, or accommodation may be required.[9] MCI most commonly involves memory problems, but can also affect language, attention, judgment, or other cognitive functions. The extent to which MCI is a consequence of non-neurological factors such as problems with mood, sleep, medications, and general medical illness, as opposed to being a herald of dementia caused by underlying neuropathology, is uncertain in any given patient. A 2018 report found that 15% of patients over 65 with MCI developed dementia within two years.[10] Other clinical studies of older adults with MCI have demonstrated a relatively rapid conversion to a diagnosis of AD (14%-19% per year), with higher risk of conversion in patients with a positive amyloid-β (Aβ) biomarker (22-50% conversion to dementia within two years).[11-13] However, these data also indicate that most patients with MCI do not progress to dementia within these time frames.

Dementia

Dementia involves impairment in cognitive functioning that interferes with a person's ability to carry out usual activities. (Note that the term major neurocognitive disorder (NCD) has replaced the term "dementia" in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, although the term "dementia" is retained as a descriptor for certain sub−types of major NCD and will be used in this document.)

Dementia is diagnosed based on evidence of substantial cognitive decline from a previous level of performance in at least one cognitive domain: (1) memory; (2) language; (3) reasoning, judgment, and handling of complex tasks (i.e., executive dysfunction); (4) higher−order perceptual/motor functioning; (5) personality, behavior, or comportment; and/or (6) social cognition.[9] Dementia is not diagnosed when changes in cognition and function can be accounted for by a reversible physiological condition (e.g., dehydration, urinary tract infection, or drug side effect), an acute confusional state, delirium, or another mental disorder (e.g., depression or schizophrenia). Most dementia follows a progressive course, with a median life expectancy after diagnosis of five to six years, although this varies widely.

AD is the most common but not the only cause of dementia. And, importantly, the types of dementia often overlap, with roughly 46% of cases classified as "mixed" dementia.[14] The cardinal features of the major types of dementia are summarized in Table 1.

Table 1: Major types of dementia[9,15]

Type of dementia	Prevalence*	Clinical features	Comments
Alzheimer's disease (AD)	60−80% of dementia cases	Insidious symptom onset with progression to profound memory loss with one or more of: aphasia, apraxia, agnosia, or impaired executive function.	Symptoms generally begin after age 60. May coexist with vascular dementia.
Vascular dementia (VD)	5%-10% of those with dementia have VD alone, although VD is often involved in other dementia forms	Stepwise rather than gradual deterioration, focal neurological deficits, emotional lability, impaired judgment, early neuropsychiatric symptoms, and/or gait disorders.	Sudden decline usually indicates a stroke, which may be large or small. Progressive subcortical small vessel ischemia can cause slower, stepwise progression.
Dementia with Lewy bodies (DLB)	5%−25% of all dementia cases[16]	Involves any two of the following: visual hallucinations, parkinsonism, and fluctuation in mental state in the absence of delirium. Other features include repeated falls, syncope, autonomic dysfunction, neuroleptic sensitivity, and REM sleep disorder.	Earlier age of onset than either AD or VD. Cognitive impairment affects both memory and ability to carry out complex tasks and can fluctuate within a day, so may be confused with delirium.

Type of dementia	Prevalence*	Clinical features	Comments
Frontotemporal dementia (FTD)	<10% of cases of dementia	Onset significantly earlier than AD and VD.[17] Changes in personality (disinhibition, apathy, loss of empathy) and/or language (primary progressive aphasia) typically beginning between ages 45 and 65 years.[18]	Apathy, emotional blunting, and disinhibited behaviors may make it difficult to differentiate from depression or bipolar disorder.
Limbic predominant age-related TDP-43 encephalopathy (LATE)	~33% in persons aged >85 years	More common in persons aged >75 years. Prominent memory deficits with slower progression than classic AD.	Considered when clinical syndrome seems like AD but AD biomarkers (e.g., CSF studies, PET scan) are negative. Also when hippocampal atrophy on MRI is out of proportion to global atrophy.

*Prevalence figures do not sum to 100% because of the wide variability in prevalence estimates and the fact that patients often have more than one type of dementia simultaneously. CSF = cerebrospinal fluid; PET = positron emission tomography; REM = rapid eye movement

Other less common types/causes of dementia include chronic traumatic encephalopathy, Parkinson's disease dementia, prion disease (e.g., Creutzfeldt-Jakob disease), and Huntington's disease.

Cognitive impairment, in some cases reversible, can also be a secondary manifestation of a variety of conditions, including:[9]

- traumatic brain injury
- substance misuse
- medication side effects (including over-the counter and prescribed)
- hypothyroidism (and occasionally hyperthyroidism)
- vitamin B_{12} deficiency
- other severe metabolic derangement
- HIV
- normal pressure hydrocephalus
- delirium

In contrast to dementia, delirium is an acute, reversible mental disorder characterized by impaired attention, disorganized thinking, and a fluctuating or reduced level of consciousness.[9] Delirium generally follows a rapidly waxing and waning course, with a range of hyperactive or hypoactive states. Symptoms include disorientation to time, place, and person; sensory misperceptions; psychomotor agitation or retardation; sleep disturbances; and memory impairment. Although delirium onset is typically sudden, it may take weeks or months for an episode of delirium to resolve.[9]

Establishing the time course by obtaining collateral information about cognitive function prior to the acute presentation is critical to distinguish delirium from dementia. Delirium is often caused by reversible medical conditions such as infection (including urinary tract and respiratory), pain, drug intoxication or

withdrawal, seizures, head trauma, and metabolic disturbances such as hypoxia, hypoglycemia, fluid/electrolyte disturbance, and hepatic, cardiac or renal impairment. Management of the precipitating medical problem will often resolve the delirium.

Although delirium is distinct from dementia, patients with dementia are at higher risk of developing delirium (i.e., delirium superimposed on dementia). Delirium may also herald the onset of MCI, and emerging research suggests that delirium itself is a risk factor for dementia.[19] Patients with delirium may not return to their prior level of functioning and may subsequently experience a steady progression of cognitive dysfunction. Because delirium may involve hallucinations, it can complicate a diagnosis of dementia, particularly dementia with Lewy bodies.

Risk factors for dementia

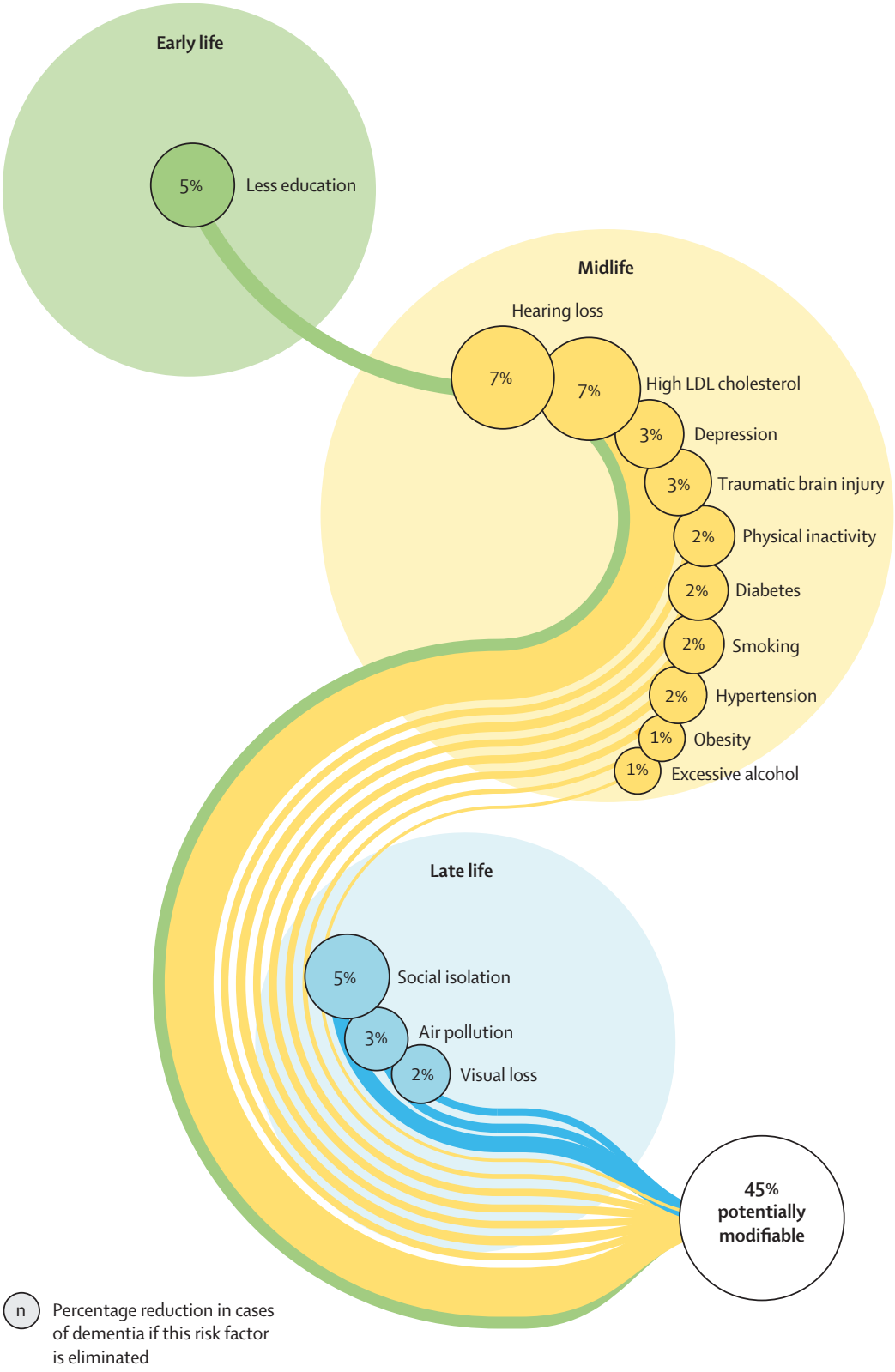
Many conditions and diseases increase the risk of cognitive impairment and dementia. Genetic, environmental, and lifestyle risk factors play interrelated roles. Non−modifiable risk factors for dementia include:

- older age
- family history
- female sex
- Down syndrome
- lower IQ
- genetic factors

Potentially modifiable risk factors for dementia have increasingly drawn attention, though limited evidence exists for the efficacy of specific interventions that address these risk factors. A 2024 Lancet Commission systematic review and meta-analysis of largely observational studies estimated that about 45% of dementia is attributable to a combination of modifiable risk factors; however, this study did not assess the effectiveness of modifying any specific one of them.[20] These modifiable risk factors include:

- education only to ages 11 or 12 (i.e., limited educational attainment)
- midlife
  - hearing loss
  - high LDL cholesterol
  - depression
  - traumatic brain injury
  - physical activity level
  - diabetes
  - smoking
  - hypertension
  - obesity
  - excessive alcohol
- later life
  - social isolation
  - visual loss
  - air pollution

Figure 2. Life course of modifiable risk factors for dementia[20]



Recent research shows that younger birth cohorts have lower age-specific rates of dementia than older cohorts, suggesting that changes in lifetime exposure to potentially modifiable risk factors has decreased dementia risk over time.[4]

A 2022 cross-sectional study similarly found that one-third of ADRD cases were associated with a combination of these risk factors.[21] However, the authors found that the modifiable risk factors associated with the largest proportion of ADRD in the U.S. may have shifted from physical inactivity, depression, and smoking to midlife obesity, physical inactivity, and low education. The study also found that the proportion of ADRD associated with these modifiable factors was relatively higher in men vs. women and among Black Americans, American Indians and Alaska Natives, and Hispanics compared with Asians, Whites, and non-Hispanics.

Despite the identification of risk factors contributing to dementia risk, a 2017 systematic review of prospective trials and quasi-experimental observational studies from the Agency for Healthcare Research and Quality found that interventions aimed at preventing or delaying the onset of cognitive impairment or ADRD by targeting these risk factors had little to no benefit.[22] The lack of strong evidence for such interventions may be related to the logistically and ethically difficult nature of conducting long-term randomized controlled trials that evaluate individual interventions for specific risk factors, as well as the challenge of targeting such interventions at the appropriate periods during the life course.

Observational studies and prospective cohort studies have provided some evidence for associations between individual risk factor modification and the incidence of ADRD. For example, an analysis of data from the U.K. Whitehall II study found that multimorbidity (defined as presence of ≥ 2 chronic diseases), particularly when present earlier in life, was associated with subsequent risk of dementia (when present at age 55, hazard ratio [HR] 2.4; 95% CI: 1.80-3.3).[23] A 2023 study followed a cohort of patients with normal cognition for 10 years and found that those who adopted healthy lifestyle habits, including a healthy diet, regular exercise, active social contact, active cognitive activity, and absence of smoking and alcohol had slower memory decline.[24]

The following sections summarize the evidence base for specific modifiable risk factors, much of which is drawn from observational data (and thus subject to confounding).

Hearing loss

Hearing loss is common in older adults. A population-based study of 3,285 adults found steady increases in prevalence with age: 11% between ages 44-54; 25% between ages 55-64; and 43% between ages 65-84.[25] Hearing loss was associated with a greater risk of dementia in a meta-analysis of three studies (relative risk [RR] 1.94; 95% CI: 1.38-2.73).[26] A 2023 analysis of a representative sample of older adults in the U.S. found that the prevalence of dementia was 1.61 times greater in patients with moderate to severe hearing loss compared to normal hearing.[27] Another 2023 meta-analysis found that use of restorative devices for those with hearing loss was associated with a 19% decrease in risk of long-term cognitive decline.[28]

The impact of a hearing intervention was evaluated in the **ACHIEVE** randomized trial of adults age 70-84 with untreated hearing loss and without substantial cognitive impairment.[29] Participants were randomized to a program of audiological counselling and provision of hearing aids (N=490) or a control intervention of health education (N=487) and followed for 3 years. In the primary analysis 3-year cognitive change (in SD units) was not significantly different between the hearing intervention and health education control groups, but a prespecified sensitivity analysis evaluating a sub-population of the study participants at high risk for

cognitive decline showed a significant difference in the effect of the hearing intervention. In the subgroup of participants at high risk for cognitive decline, the decline on a measure of global cognition was less in the intervention group (-0.211 SD; 95% CI: -0.349 to -0.073) compared to the control group (-0.402 SD; 95% CI: 0.-536 to -0.267) (P=0.027).

This study and other evidence support the notion that a key factor in addressing hearing loss is not only providing hearing aids, but ensuring optimal adherence to hearing aids through appropriate calibration and audiological consultation.

Hypertension

The harmful effects of hypertension on cognitive function were recognized as early as the 1960s, when a study of psychomotor speed among air traffic controllers and pilots demonstrated reduced performance in patients with hypertension.[30] Hypertension has also been associated with reduced abstract reasoning (executive dysfunction), slowing of mental processing speed, and, less frequently, memory deficits.[31]

Although AD and vascular dementia have traditionally been considered distinct entities, these conditions often coexist.[32] In an analysis of 4,629 patients with AD, 80% showed evidence of vascular pathology and 32% had a diagnosed cerebrovascular disease; some patients had both conditions.[33] Hypertension disrupts the structure and function of cerebral blood vessels, leads to ischemic damage of regions critical for cognitive function, and may promote Alzheimer pathology.[34]

Consistent evidence shows an association between hypertension in midlife and altered cognitive function in both midlife and late life.[34] The association of blood pressure (BP) in late life with cognition is less clear. The inconsistent results across studies, especially in older age, may reflect differences in the cognitive domains assessed, differences in study design, and differences in characteristics of the study populations that may confound the hypertension-cognition association.

Although observational studies show a cumulative effect of hypertension on cerebrovascular damage, evidence from clinical trials that antihypertensive treatment improves cognition is suggestive but not conclusive. The 2019 Systolic Blood Pressure Intervention Trial (**SPRINT-MIND**) tested the effect of more intensive BP control on cognitive outcomes in persons without diabetes or preexisting stroke.[35] The trial randomized 9,361 participants to systolic BP goals of either <120 mm Hg or <140 mm Hg. After a median follow-up of 5.1 years there was a small difference in the rate of newly-diagnosed dementia (146 cases in the intensive group vs. 176 cases in the standard group; HR 0.83; 95% CI: 0.67-1.04), which misses the conventional definition of statistical significance. The treatment group did show statistically significant results in secondary outcomes: the rate of developing mild cognitive impairment was modestly but significantly lower in the intensive group (14.6 vs. 18.3 cases per 1,000 person years; HR 0.81; 95% CI: 0.69-0.95), and the combined rate of mild cognitive impairment or probable dementia was also significantly lower in intensive group (20.2 vs 24.1 cases per 1000 person-years; HR 0.85; 95% CI: 0.74–0.97).[35]

By contrast, a 2021 Cochrane review found no high-certainty trial evidence for the effect of hypertension treatment on dementia and cognitive impairment.[36] The studies included in the review provided what the Cochrane authors considered low-certainty evidence that treatment of hypertension leads to less cognitive impairment but this difference was not seen as clinically significant.

Vaccination status

Some evidence suggests that vaccinations, particularly those for herpes zoster, may have a potentially protective role against the development of MCI or dementia.

A 2025 study in a cohort of 282,557 individuals in Wales with no record of cognitive impairment prior to September 1, 2013 found that vaccination with live-attenuated herpes zoster vaccine (Zostavax) was associated with a 3.1% decrease in the occurrence of newly-diagnosed MCI during the 9 years of study (95% CI: 1.0% - 6.2%).[37] Receipt of the live-attenuated herpes zoster vaccine was also associated with a 29.5% reduction in deaths due to dementia during the study period (95% CI: 0.6% to 62.9%). The reduction in subsequent dementia diagnosis among eligible cohorts receiving the live attenuated herpes zoster vaccine was confirmed in two separate cohorts, one in Australia and one in Canada.[38,39]

However, the live attenuated herpes zoster vaccine is no longer recommended on the adult vaccination schedule in favor of the recombinant zoster vaccine (Shingrix). A 2026 retrospective matched cohort study in 65,800 individuals vaccinated with two doses of the recombinant zoster vaccine matched to 263,200 unvaccinated individuals found a significantly reduced risk of dementia associated with zoster vaccination (adjusted HR 0.49; 95% CI: 0.46-0.51).[40]

Less robust analysis suggests that vaccination with other recommended vaccines may change cognitive impairment risk. A 2025 meta-analysis of 21 observational studies (N=104,031) evaluating the association of adult vaccinations with dementia risk found risk reductions with the following vaccinations:[41]

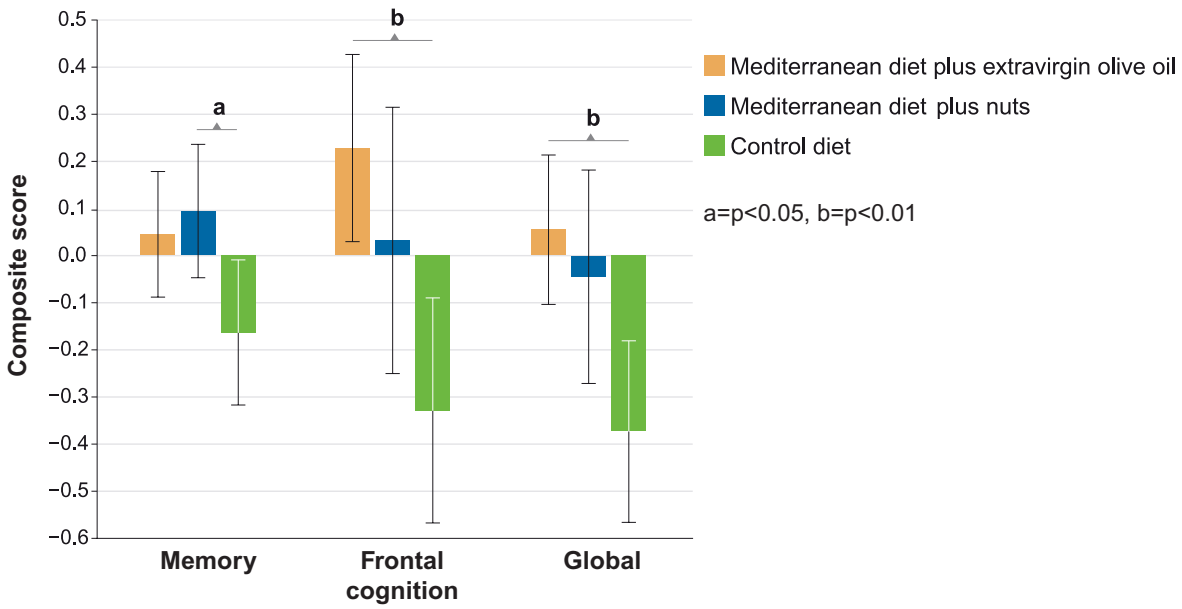
- influenza (RR 0.87; 95% CI: 0.77–0.99)
- pneumococcal (RR 0.64; 95% CI: 0.47–0.87)
- tetanus, diphtheria, pertussis (Tdap) (RR 0.67; 95% CI: 0.54–0.83)

Food and dietary factors

Some clinical trial data show protective effects against cognitive decline for olive oil, nuts, and a Mediterranean diet.[42] Adherence to a Mediterranean-style diet may be associated with slower cognitive decline in patients diagnosed with MCI. Some of these findings are based on observational studies.[43-45] For example, a retrospective study of 482 patients with MCI followed for a mean of 4.3 years found that patients with the highest level of adherence to a Mediterranean diet had a 48% lower risk of developing AD in the study period than those with the lowest level of dietary adherence.[43] A 2023 prospective cohort study with a follow up period of 9 years found lower all-cause dementia risk (HR 0.77; 95% CI: 0.64-0.91) with adherence to a Mediterranean diet.[46]

The **PREDIMED** trial of 447 cognitively healthy people were randomized to three dietary groups (Mediterranean diet plus olive oil; Mediterranean diet plus nuts; and a control diet) and were followed for a median of 4.1 years (Figure 3).[47] It found improvements in memory and frontal cognition in the two intervention groups, compared to declines in cognitive functioning in the control group.

Figure 3: Improvements in cognition with Mediterranean diet[47]



The low-salt Dietary Approaches to Stop Hypertension (DASH) diet has also been associated with reduced risk of dementia in observational studies. A 2026 cohort study in 159,347 community-dwelling men and women evaluated six dietary patterns and found that higher adherence to the DASH diet had the strongest association of all the dietary patterns studied with higher objectively measured global cognition (mean z-score difference comparing 90th vs 10th percentile 0.053; 95% CI: 0.015–0.091).[48]

On the other hand, a 2023 randomized trial (N=604 adults with a family history of dementia) evaluated the Mediterranean–DASH Intervention for Neurodegenerative Delay (**MIND**), which is a hybrid of the Mediterranean diet and the DASH diet, modified to include foods that have been associated with a decreased risk of dementia.[49] At 3-year follow-up, no significant differences were found in global cognition scores between those on the MIND diet and those on a control diet with mild caloric restriction (increases of 0.205 standardized units in the MIND group and 0.170 standardized units in the control group (mean difference, 0.035 standardized units; 95% CI: −0.022 to 0.092; P=0.23).

Given the relatively low risk of harm and its proven benefit for cardiovascular outcomes, it may be reasonable to recommend a Mediterranean diet, which emphasizes vegetables, fruits, whole grains, and fish, while limiting foods containing trans−fats, cholesterol, added sugars, and salt.

Multimodal interventions

The evidence for the efficacy of multimodal interventions to reduce the risk of dementia is inconsistent and may depend on the resource intensity of the intervention and combination of risk factors addressed.

The 2025 **US-POINTER** trial randomized 2,111 individuals at risk for cognitive decline to a 2-year multidomain program involving 38 facilitated peer team meetings encouraging increased physical and cognitive activity, healthy diet, social engagement, and cardiovascular health monitoring vs. a self-guided program that covered the same topics.[50] At follow-up the structured intervention group had a statistically

significant, but small, enhancement in cognitive function (0.029 SD on a global cognitive composite score; 95% CI: 0.008-0.05). The 2023 **SMARRT** trial of 172 adults at high risk for dementia and randomized to either a personalized, multidomain intervention or a health education control found similar modest improvements in cognition, dementia risk factors, and quality of life after 2-years of the intervention.[51]

A 2021 Cochrane review of nine RCTs evaluating the effect of multi-domain interventions found no evidence for prevention of incident dementia.[52] The review did not include some of the major studies mentioned above (including US-POINTER) but included the following 4 major studies:

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (**FINGER**) trial involved 1,260 adults aged >60 years who were at high risk of dementia based on their age, sex, education, systolic blood pressure, total cholesterol and physical activity.[53] It compared cognition in the intervention group to controls who received general health advice. The intervention consisted of about 200 meetings (300 hours) with health professionals and trainers over two years and included individualized nutrition planning, exercise, cognitive training, and vascular risk factor monitoring. Despite the intervention's intensity, the effects were relatively small. Participants in the intervention group showed a statistically significant (but clinically uncertain) mean advantage vs. the control group in a composite measure of cognition (neuropsychological test battery total score), executive function, and processing speed, but not memory.

The Prevention of Dementia by Intensive Vascular Care (**preDIVA**) study sought to prevent dementia by reducing vascular risk factors in a six-year multi-domain, nurse-administered intervention.[54] There were 3,526 participants from general practices randomized to an intervention consisting of monitoring smoking habits, diet, physical activity, weight, and blood pressure with individually tailored lifestyle advice supported by motivational interviewing vs. usual care. Blood glucose and lipid concentrations were assessed every two years in both groups and, when indicated, medication was given as needed for hypertension, diabetes, or dyslipidemia. After 6.7 years, there was no significant difference in dementia incidence between the intervention and usual care group (HR 0.92; 95% CI: 0.71-1.19).

The Multidomain Alzheimer Preventive Trial in France (**MAPT**) randomized 1,680 older adults with memory concerns, limitations in one instrumental activity of daily living, or slow gait speed to one of four groups: an intervention consisting of cognitive training, physical activity, and nutrition plus polyunsaturated fatty acid supplementation; the multidomain intervention plus placebo; polyunsaturated fatty acids alone; or placebo.[55] After 3 years, there were no significant differences between groups in measures of cognitive decline.

The Healthy Aging Through Internet Counseling in the Elderly (**HATICE**) trial randomized 2,724 adults at high risk for cardiovascular disease to an interactive internet-based coach-supported program of self-management vs. a control group who received internet-based advice about cardiovascular statistics.[56] After 18 months of follow-up there was a very modest change in the CAIDE dementia risk score (mean score difference -0.15 points on a 15-point scale, P=0.04) and no significant difference in cognitive function as measured by the Mini-Mental State Examination (MMSE).

Other risk factors

Education

Higher levels of educational achievement appear in some studies to be linked with a lower risk of dementia, possibly because education creates and sustains neural or synaptic connections that build up a "cognitive reserve" that helps buffer the neuronal erosion/degeneration of dementia.[57] A population-based longitudinal survey of U.S. adults aged 65 years or older from 2000 (N=10,546) to 2012 (N=10,511) examining the effects of education on dementia risk found that greater years of education was associated with a lower risk of incident dementia (all comparisons are to individuals with less than 12 years of education):[58]

- 12 years of education: odds ratio (OR) 0.42; 95% CI: 0.37-0.48
- 13-15 years: OR 0.36; 95% CI: 0.30-0.44
- ≥ 16 years: OR 0.27; 95% CI: 0.21-0.35

On the other hand, a 2019 prospective cohort study of 2,899 older adults found that although higher education levels were associated with higher baseline cognitive functioning, education level was not associated with either the age of onset of dementia or the rate of cognitive decline in those diagnosed with dementia.[59]

Obesity

The relationship between obesity and dementia is complex and can be difficult to quantify because body mass index (BMI) in older adults with dementia is typically lower than age peers, with weight loss appearing to start years before clinical onset of dementia. A combination of pre-dementia apathy, loss of initiative, and reduced olfactory function could explain this association.[60]

Exactly how obesity might contribute to dementia risk remains poorly understood. Obesity in midlife and at older ages is associated with brain atrophy.[61,62] Obesity is also likely to influence cognition through its impact on vascular risk factors and pathology.[63]

An analysis of data from the U.K. Whitehall II study (N=10,308), which followed participants for at least 28 years, found that having obesity at age 50 was associated with an increased risk of dementia (HR 1.93; 95% CI: 1.35-2.75), but that having obesity at ages 60 or 70 was not significantly associated with dementia.[63] A similar pattern was found in a systematic review and meta-analysis of 13 studies, in which having obesity had a positive association on incident dementia for those below the age of 65 years (RR 1.41; 95% CI: 1.20–1.66), but not in those aged 65 and over (RR 0.83; 95% CI: 0.74–0.94).[64]

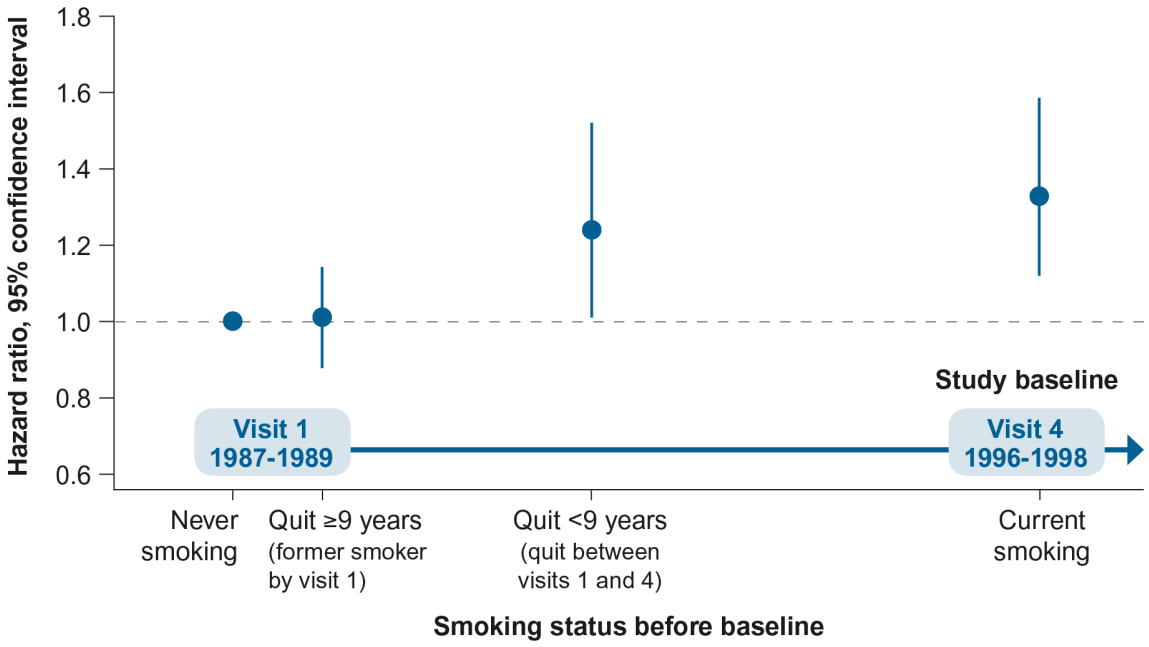
Whether reducing obesity can reduce risk of dementia remains unclear. For example, unpublished preliminary results from two clinical trials comparing the GLP-1 agonist semaglutide vs. placebo found no significant changes in rates of AD progression after 2-years of follow-up.[65] Eligible participants were men or women age 55-85 with mild cognitive impairment or mild dementia due to AD with confirmed amyloid abnormalities.[66] The primary endpoint was the difference on change from baseline in the Clinical Dementia Rating - Sum of Boxes score.

Smoking

Cigarette smoking, even in low doses, increases the risk for vascular disease and stroke, which provides a strong biological rationale for a relationship between smoking and cognitive decline. Cigarette smoke also contains neurotoxins (e.g., heavy metals), which may heighten the risk of cognitive dysfunction.[67] Observational data support an association between current smoking and dementia or cognitive decline.[68,69] The extent of this association may be underestimated given methodological limitations such as selective loss of susceptible smokers due to death or dropout from a study over time (particularly if participants are required to attend clinic visits during follow-up to have cognition measured).

A 2019 cohort study using data from the Atherosclerosis Risk in Communities study (N=13,002) found that compared to participants who never smoked, current smoking significantly increased the risk of dementia (HR 1.33; 95% CI: 1.12-1.59), as did smoking within nine years of baseline measurement of cognitive functioning (HR 1.24; 95% CI: 1.01-1.52; Figure 4).[70] Participants who quit smoking more than nine years before baseline had no significant increase in dementia risk compared to never-smokers.

Figure 4: Association between smoking status and risk of dementia[70]



Depression

Depressive symptoms can be a part of the clinical presentation of dementia, which can blur the causal relationship between the two conditions, especially as depressive cognitive disorders can mimic the cognitive profiles of neurodegenerative conditions (often referred to as 'pseudodementia'). Longitudinal cohort studies show a link between number of depressive episodes and risk of dementia, which strengthens the assertion that depression is a risk factor for dementia.[71] The mechanism is likely to be multifactorial, as depression is linked to cerebrovascular pathology, and affects stress hormones, neuronal growth factors, and hippocampal volume.[72]

An analysis of the Whitehall II cohort study (N=10,189) found no increased risk for dementia among those reporting depressive symptoms in 1985 (mean follow-up 27 years). However, those with depressive

symptoms in 2003 (mean follow-up 11 years) did have an increased risk (HR 1.72; 95% CI: 1.21-2.44).[73] A 2022 prospective cohort study in Finland with a mean follow up period of 25 years found that self-reported symptoms of psychological distress were significantly associated later on with increased risk of dementia.[74] A cohort study of 46,820 individuals with depression found that those whose depression was treated with psychotherapy or antidepressant medications had a significantly reduced risk of dementia than those who were untreated, after adjustment for potential confounding (HR 0.70; 95% CI: 0.62-0.77).[75]

Social isolation

A growing body of evidence suggests that social isolation may be a risk factor for dementia, either directly or because such isolation is associated with other dementia risk factors such as hypertension, coronary heart disease, and depression.[26] Social isolation may result in cognitive inactivity, which appears to be linked to faster cognitive decline and low mood. A 2022 study demonstrated that socially isolated individuals had a 1.26-fold increased risk of dementia (95% CI: 1.15-1.37), and lower gray matter volumes on MRI in the temporal, frontal, and hippocampal regions.[74,76]

Longitudinal studies suggest that social interaction may prevent or delay dementia but there is a lack of evidence for interventions focused on social activity that prevent cognitive decline or dementia. People who live alone, have never married, or are divorced or widowed have an increased risk of all-cause dementia.[77] Systematic reviews and meta-analyses of social activity have found some evidence after 2 to 21 years of follow up that low engagement in social activity and poor social networks were significantly associated with poor late-life cognitive function,[78] and social engagement was modestly protective.[79] In addition, prospective cohort studies found that more frequent social contact later in life was associated with a lower dementia risk.[80,81] The relatively short follow-up period in some studies precludes strong conclusions about the direction of causation (i.e., since persons with dementia may become socially withdrawn, it is possible that some of these associations are attributable to reverse causation).

Hyperlipidemia

Observational studies have associated hyperlipidemia with increased risk of AD, although the multi-factorial nature of the risk (i.e., the co-occurrence of hypertension, metabolic syndrome, smoking and diabetes) makes it difficult to draw firm conclusions about the independent role of lipids on AD risk.[82] Lipid-lowering agents (e.g., statins) were associated with cognitive impairment in some small studies, but larger trials and meta-analyses have not shown links between statins and cognitive function.[82] In fact, a meta-analysis of 34 statin trials including cognitive assessments found statins to be associated with a *decreased* risk of dementia [OR 0.80; 95% CI: 0.75-0.86) and AD specifically (21 studies, OR 0.68; 95% CI: 0.56-0.81).[83] A more recent meta-analysis did not find evidence of a protective or positive effect of statins, but also found no cognitive harms associated with statins. In this meta-analysis of 15 trials (N=139,169) lipid-lowering therapy compared with control was not associated with a significant reduction in dementia or cognitive impairment over a mean trial follow-up of 34.5 months (OR 0.96; 95% CI: 0.74-1.26).[84]

Diabetes

Observational studies have long suggested that patients with diabetes have an elevated risk of developing AD,[85,86] but the relationship has not been clear. Diabetes contributes to vascular dysfunction,

which increases stroke risk, but in autopsy studies patients with diabetes did not have more amyloid plaques or tau tangles than people without diabetes.[87]

The relationship between hypoglycemia and dementia appears to be bidirectional. Severe hypoglycemic episodes were associated with a nearly two-fold increased risk of incident dementia in a systematic review of 10 studies (RR 1.77; 95% CI: 1.35-2.33).[88] Conversely, having dementia and diabetes more than triples the risk of having a subsequent hypoglycemic event (HR 3.1; 95% CI: 1.5-6.6).[89] Potential mechanisms for this observed relationship include increased risk of medication misuse (e.g., unintentional or intentional nonadherence, self-administration mistakes) and/or dietary intake changes in persons with dementia.

Despite evidence for an association between diabetes and incident dementia, treatment of diabetes has not been demonstrated to reduce the incidence of dementia. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, for example, intensive glycemic control vs. usual care did not lead to a difference in cognitive outcomes at 40 months.[90]

Exercise and physical activity

Physical exercise may improve cognition or prevent dementia both indirectly (e.g., via effects on obesity, insulin resistance, hypertension, hypercholesterolemia, and general cardiovascular fitness) or directly (e.g., increased neurogenesis, cerebral blood flow, and levels of brain derived neurotrophic factor).[91]

Observational data have generally supported an association between higher levels of exercise or physical activity and a reduced risk for dementia. However, the data are difficult to interpret because people with dementia become less physically active as their disease progresses, and perhaps also before a diagnosis is formally established.

The 2018 HUNT study in Norway found that at least weekly midlife moderate-to-vigorous physical activity was associated with reduced dementia risk over a 25-year follow up period, though the confidence intervals were wide.[92] However, a 2017 analysis of data from the Whitehall II cohort study with a mean follow-up of 27 years found no difference in physical activity between dementia cases and dementia-free controls 20 years before diagnosis.[93] In fact, physical activity in people with dementia began to decline up to nine years before diagnosis.

By contrast, a meta-analysis of 15 prospective cohort studies following 33,816 patients without dementia for 1 to 12 years found that greater physical activity was associated with a lower incidence of cognitive decline, with high levels of exercise being the most protective (HR 0.62; 95% CI: 0.54-0.70).[94] In this study, even low-to-moderate exercise appeared beneficial (HR 0.65; 95% CI: 0.57-0.75). Another meta-analysis of 19 observational studies of relatively young adults found an increased incidence of dementia (HR 1.4; 95% CI: 1.2-1.7) in those who were physically inactive in the 10 years preceding the diagnosis.[95] However, it is also possible that the decreased physical activity in this period was due to early cognitive impairment.

Randomized trials of exercise interventions to improve cognition in healthy older adults, however, have been less successful than might have been expected in light of the associations seen in longitudinal cohort studies. Meta-analyses have reported either no overall evidence that exercise improves cognition in healthy older adults,[96] or benefits that were limited to specific cognitive domains. A 2014 meta-analysis, for example, reviewed 25 studies of aerobic exercise, resistance training, or tai chi.[97] Fifteen individual studies reported significant improvements for exercise vs. controls on measures of executive function,

memory or composite measures of cognition. However, the only significant results from the meta-analysis were for resistance training improving reasoning compared to controls (two studies, 135 participants, mean difference 3.16; 95% CI: 1.07-5.24) and tai chi improving processing speed and attention vs. no-exercise controls (two studies, 156 participants).[97]

A 24-month trial of 1,766 sedentary older adults without cognitive impairment did not find any effects on cognition between the group randomized to modest physical activity (30 min. walking, 10 min. stretching, and 10 min. lower body weights weekly) compared to talks about health education with 10 min. of stretching weekly.[98] A 2022 RCT found no significant differences in memory improvement or executive function after six months of mindfulness training, exercise, or both.[99]

Taken together, these findings raise the suspicion that cognitive impairment may cause decreased levels of exercise, rather than the other way around.

Anticholinergic medications

Anticholinergic drugs (e.g., some antihistamines, antidepressants, and medications for gastrointestinal and bladder disorders) can have short-term adverse effects, including confusion/delirium and memory loss in older people, and some evidence exists for long-term adverse effects on cognition.[100]

A nested case-control study of 58,769 patients with dementia (60% of whom had AD) and 225,574 matched controls found increased risks of dementia with rising doses of anticholinergics, from OR 1.06 (95% CI: 1.03-1.09) at the lowest doses, to OR 1.49 (95% CI: 1.44-1.54) at the highest doses.[100] The greatest risks were associated with antipsychotics and bladder antimuscarinics, and the population attributable fraction of these medications for dementia was calculated to be 10%.[26] Another prospective cohort study of 19,114 community-dwelling patients aged 65 or older found that increased anticholinergic exposure was associated with an increased risk of dementia after a follow up of 4.7 years (HR 1.4; 95% CI: 1.0-1.8).[101] However, not all these studies were able to rule out the problem of confounding by indication, or reverse causation: that is, the possibility that some drugs (such as the antipsychotics) were prescribed to treat early symptoms of a developing or existing dementia, rather than causing it.

Benzodiazepines

Many observational studies have examined the relationship of benzodiazepine use and dementia risk, with mixed results. A frequently acknowledged limitation is that reverse causation may explain the observed associations (i.e., benzodiazepines may be prescribed for prodromal symptoms of dementia such as anxiety or insomnia). A 2018 systematic review and meta-analysis of 15 studies that attempted to account for the possibility of reverse causation found that any benzodiazepine use was nonetheless associated with a significantly increased risk of dementia (OR 1.39; 95% CI: 1.21-1.59).[102]

Although no evidence suggests that deprescribing benzodiazepines lowers the risk of dementia, it may, nonetheless, be warranted for other health-related reasons. Deprescribing can involve substitution of other drugs (e.g., melatonin or trazodone for sleep), provision of psychological support, and patient education. A review of various deprescribing programs for benzodiazepines found success rates after six-12 months of between 27% and 80%.[103] A cluster randomized trial involving 30 community pharmacies and 303 long-term users of benzodiazepines compared a patient empowerment intervention with a tapering protocol vs. wait-list control.[104] After six months, 27% of patients in the intervention group had discontinued benzodiazepines vs. 5% in the control group, and 62% of those in the intervention group had initiated a conversation about reducing their use with a physician or pharmacist.[104] Using a slow taper

to discontinue benzodiazepines was a key recommendation of the 2025 clinical practice guidelines endorsed by such organizations as the American Society of Addiction Medicine. The American Geriatrics Society, and the American Academy of Family Physicians.[105]

Nutrients

A wide range of vitamins, antioxidants, and macronutrients have been examined for potential roles in either contributing to or protecting people from dementia, generally with nonsignificant results. Among the few RCTs that have been conducted, most have not demonstrated any protective effect for individual vitamins, multivitamins, fatty acids, or other supplements.[42,106] A systematic review and a Cochrane review of RCTs of supplements, minerals, and vitamins found no evidence to support their use to preserve cognitive function or prevent dementia.[107-110]

More recently, the 2023 **COSMOS-Web** study, which initially focused on the prevention of cancer and heart disease, randomized 3,562 older adults to multivitamin or placebo. To measure cognition, the investigators used annual internet-based memory assessments over three years.[111] Immediate recall improved in patients taking a multivitamin at one- and three-years follow-up. However, no significant changes were seen in other outcomes such as episodic memory, novel task recognition, or executive function. The COSMOS-Mind trial found very small cognitive effects from multivitamins in a secondary analysis of a primary trial with a variety of outcomes.[112] Some speculate that improvements in cognition that may occur with multivitamins might be the result of their treating an undiagnosed deficiency in some patients, such as vitamin B_{12}.

Despite the uncertainty about evidence for their effects on mental functioning, multivitamins are generally safe when taken as directed, and low-cost, if generic preparations are used, so it may not be unreasonable if patients choose to take them. Assessing for deficiencies where specific supplementation may address cognitive concerns, such a vitamin B_{12}, is also a reasonable strategy.

Sleep

Disruptions in sleep rhythms have been associated with biologic changes seen with developing or worsening of AD and other dementias.[113] A longitudinal study with a 2-year follow up demonstrated that patients with obstructive sleep apnea (OSA) experienced faster rates of brain amyloid burden and tau protein aggregation.[114] In addition, treatment of OSA was associated with improvements in both slow-wave sleep and CSF amyloid-beta levels.[113] Ongoing research is examining the ties between circadian rhythm disruption and dementia, but suggests a need to screen for underlying sleep disturbance in patients reporting cognitive disturbance.

Frailty

Frailty is characterized by a reduced ability to maintain homeostasis in response to stressors, with clinical features including low energy, slow gait, weakness, weight loss, and fatigue – all factors common in dementia as well. The prevalence of frailty increases from about 11% in adults aged >65 years to 25% in adults aged >85 years, and >50% in institutionalized older adults.[115,116] A meta-analysis of three studies found a significantly increased risk of dementia among frail patients as compared to “robust” patients (HR 1.33; 95% CI: 1.07-1.67).[117] A 2021 prospective cohort study found that a 10% increase in a frailty index was associated with an increased risk of dementia (HR 1.17; 95% CI: 1.07-1.18).[118]

While the mechanisms and pathophysiology underlying the increased risks of dementia in frail older people are not clear, both frailty and dementia are heterogeneous entities that share multiple risk factors for their development, including diabetes, myocardial infarction, hypertension, congestive heart failure, cerebrovascular disease, and chronic inflammation.

A cross-sectional analysis of data from the Rush Memory and Aging Project (N=456) found that patients with low levels of frailty can tolerate a higher level of AD symptoms and, conversely, when frailty is high even a few AD symptoms are more likely to result in a diagnosis.[119]

BOTTOM LINE: Approximately 45% of dementia is attributable to a combination of potentially modifiable risk factors, but no definitive ways to prevent dementia have been found. Blood pressure control, eating a Mediterranean or DASH diet, getting routine immunizations for older adults (particularly herpes zoster), and addressing hearing loss may slow cognitive decline. Prevention efforts aimed at other risk factors remain unproven, though they may benefit overall health.

Evaluation of cognitive impairment and dementia

Screening

The latest guidance from the U.S. Preventive Services Task Force (USPSTF) regarding screening for cognitive impairment in older adults concluded that "the current evidence is insufficient to assess the balance of benefits and harms for screening" in unselected community-dwelling older adults *without* signs or symptoms of cognitive impairment.[120] Only a single randomized clinical trial (n=4,005, 1-year follow-up) has assessed whether screening for cognitive impairment by primary care providers affects patient outcomes, and it failed to demonstrate any benefit or harm from general screening.[121]

It is important to recognize that this USPSTF recommendation does not apply to conducting an assessment of signs and symptoms reported or recognized by the patient, family, or clinician for diagnostic purposes,[120] which may include the following situations:

- patients with subjective cognitive concerns, conveyed either by the patient or a knowledgeable informant
- patients with mood or anxiety concerns (particularly of new onset), conveyed either by the patient or a knowledgeable informant
- selected patients at risk for adverse safety outcomes or manifesting subtle objective impairments (e.g., living alone, poor medication adherence, changes in personal hygiene, working in professions in which cognitive dysfunction places them or others at risk)

Medicare covers testing and screening for cognitive impairment as a part of annual wellness visits (AWVs), though evidence is mixed on whether screening with AWVs increases diagnoses of dementia.[122-124] One study found that though AWV cognitive impairment screening did not increase dementia diagnoses, it increased some measures of cognitive care, including laboratory testing.[123]

Diagnosis

A focused differential diagnosis of dementia or MCI is appropriate for older people with an insidious onset and gradual progression of memory loss as the main presenting symptoms. Features such as early age of onset, rapid progression, atypical (non−memory related) cognitive deficits, and unusual associated neurological or general medical symptoms should prompt referral to a specialist for consideration of atypical causes.

A diagnosis of dementia requires: (1) a significant decline in cognitive function from a previous level of performance in one or more cognitive domains that interferes with independence in everyday activities and (2) evidence of cognitive dysfunction on a mental status examination or formal neuropsychological testing.[125] Selected labs and studies are recommended to establish a clinical diagnosis (see below) to assess potentially reversible or modifiable factors.

In 2024 the Alzheimer's Association Workgroup proposed a purely biologic definition of AD, arguing that it is now possible to diagnose "preclinical AD" even in asymptomatic individuals using positive results from biomarker tests such as an amyloid PET scan, or cerebrospinal fluid or blood-based biomarkers.[126] This contention has been disputed by others, such as the International Working Group, who argue that AD should remain a clinical/pathological entity requiring objective cognitive impairment, because recent literature shows that most biomarker-positive cognitively normal individuals will not become symptomatic in "a proximate timeline."[127] The group notes that giving a diagnosis of AD to cognitively normal people based on only one biomarker result would be "problematic"; they recommend that the term "presymptomatic AD" be used for those with a specific pattern of biomarkers, indicating that they are at risk for symptoms in the future.

History

The goals of a history pertaining to cognitive impairment include: (1) determining the nature and time course of the cognitive dysfunction; (2) reviewing a patient's usual activities, functional status with activities of daily living and instrumental activities of daily living, and changes that have arisen due to cognitive dysfunction; (3) conducting a focused review of other pertinent information from the medical history, social history, family history, and review of systems. Obtaining informant input is critical for the history given the possibility that some people with cognitive impairment may not be able to report aspects of history reliably (in fact, a lack of awareness/insight into one's illness/deficits may be a feature of dementia for some people). The overall objective is to think broadly about reversible causes of cognitive impairment (e.g., B_{12} deficiency, sleep disorders, hormone dysregulation) while simultaneously considering a neurodegenerative cause for the condition.

The medical history should particularly assess:

- functional status with activities of daily living (e.g., dressing, eating) and instrumental activities of daily living (e.g., managing medications, finances), which is critical for differentiating MCI from dementia as well as developing treatment plans
- detailed review of medications with potential to affect cognition, including all prescriptions (including from other health care professionals), as well as over-the-counter products and herbal remedies or dietary supplements
- non-prescribed substance and alcohol intake
- family history of cognitive impairment, dementia, neurological, or psychiatric conditions
- bowel/bladder incontinence

- mood, anxiety, sleep, and pain
- history of head trauma, encephalitis, meningitis, seizures, or other neurological or psychiatric illness
- educational and occupational history

Medications that have been associated with cognitive impairment should be reviewed to determine if alternative treatment options for relevant conditions are feasible. For many of these medications, the effects are similar across the class, with the exception of the SSRI paroxetine which has stronger anticholinergic side effects than other SSRIs. Table 2 summarizes some common medications that may affect cognition.

Table 2: Medications that may impair cognition[128]

Medication class	Example medications*
Anticholinergics	
Antidepressants	amitriptyline doxepin (> 6mg/day) nortriptyline paroxetine
Antiemetics	prochlorperazine promethazine
Antihistamines	chlorpheniramine diphenhydramine hydroxyzine promethazine
Antimuscarinics	oxybutynin solifenacin trospium
Skeletal muscle relaxants	cyclobenzaprine
SSRI	paroxetine**
Antipsychotics (excluding as needed use)	aripiprazole olanzapine quetiapine risperidone
Benzodiazepines	clonazepam diazepam lorazepam temazepam
Nonbenzodiazepine receptor agonist hypnotics	eszopiclone zaleplon zolpidem

*This list is not complete but reflects examples of medications of concern within a class. ** Paroxetine is unique among SSRIs for its anticholinergic side effects.

Eliciting examples of a patient's cognitive functioning from both patients and informants can help determine which domain(s) of cognition are affected. (Patients who lack reliable informants may require extra detective work, e.g., calling friends or asking the patient to bring in trusted neighbors.)

Frequent repetition of questions and difficulty remembering recent events, for example, suggest impairment of episodic memory. Difficulties retrieving words, speaking fluently, or understanding spoken or written material suggest impairment of language. Problems finding routes, locating objects in plain view, or putting on clothes correctly reflect impairments in higher order visual/spatial functions. Inability to complete tasks requiring multiple steps, to maintain focus on a single task, or to hold information "in mind" for short periods of time suggest impairments in attention and executive functions. Early on, AD typically causes impairment of episodic memory out of proportion to impairments in other cognitive domains.

Table 3: Differentiating dementia from normal cognitive aging

Warning sign	Features	What's normal?
1. Memory loss that affects job skills or other usual tasks	Forgetting recently learned information is one of the earliest signs of dementia. A person with dementia becomes forgetful more often and is unable to recall information.	*Occasionally forgetting names or appointments*
2. Difficulty performing ADLs and IADLs	Finding it hard to plan or complete everyday tasks. Patients may lose track of the steps to prepare a meal, place a telephone call, or play a game	*Occasionally forgetting why you came into a room or what you planned to say*
3. Problems with language	Forgetting simple words or substituting unusual words, making speech or writing hard to understand. For example, they may be unable to name a watch, for example, and instead ask for "that thing for time."	*Sometimes having trouble finding the right word, particularly if the word is less frequently used*
4. Disorientation to time and place	Becoming lost in their own neighborhood, forgetting where they are or how they got there, and not knowing how to get back home.	*Forgetting the day of the week or why you went into a room in your house*
5. Poor or decreased judgment	Dressing inappropriately, such as wearing several layers on a warm day or little clothing in the cold. Showing poor judgment about money, such as giving away large sums to telemarketers.	*Making a questionable or debatable decision from time to time*
6. Problems with abstract thinking	Having unusual difficulty performing complex mental tasks, such as forgetting what numbers are and how they should be used.	*Finding it challenging to balance a checkbook*
7. Misplacing things	Putting things in unusual places: a toothbrush in the freezer, or keys in the sugar bowl.	*Misplacing keys or a wallet occasionally*
8. Changes in mood	Having rapid mood swings – from calm to tears to anger – for no apparent reason.	*Occasionally feeling sad or moody*
9. Changes in behavior	Manifesting unexpected agitation, aggression, wandering, or sexual disinhibition.	*Occasionally losing your temper or feeling frustrated*
10. Changes in personality	Rapidly changing personality, in which the patient becomes extremely confused, suspicious, fearful, or dependent on a family member.	*People's personalities do not usually change dramatically or suddenly with age*
11. Loss of initiative	Becoming passive and apathetic, sitting in front of the TV for hours, sleeping more than usual, or not wanting to do usual activities.	*Sometimes feeling weary of work or social obligations*

Warning sign	Features	What's normal?
12. Psychosis	Having hallucinations (audio or visual) and/or delusions (often paranoid in nature).	*Hallucinations and delusions are never normal*

* ADL: activities of daily living (e.g., bathing, eating); IADL: instrumental activities of daily living (e.g., paying bills, cooking meals, managing medications)

It is also important to differentiate dementia from delirium, which can cause similar symptoms but generally has an abrupt onset with time-limited symptoms (Table 4).

Table 4: Differentiating delirium from dementia[19]

	Delirium	Dementia
Onset	abrupt, although initial loss of mental clarity can be subtle	insidious and progressive
Duration	hours to days (although it can be prolonged in some cases)	months to years
Attention	reduced ability to focus, sustain, or shift attention is a hallmark feature that occurs early in presentation	normal except in severe dementia
Consciousness (i.e., awareness of the environment)	fluctuating (thus assessment at multiple time points is necessary); reduced level of consciousness and impaired orientation.	generally intact
Speech	incoherent and disorganized; distractible in conversation	ordered, but development of anomia or aphasia is possible
Cause	underlying medical condition, substance intoxication, or side effect of drugs	underlying neurological process (e.g., amyloid plaque accumulation in Alzheimer's disease)
Other features	hyperactive, hypoactive, and mixed forms, as determined by the type of psychomotor disturbance, are possible; disruption in sleep duration and architecture; perceptual disturbances	symptoms vary depending on underlying pathology (e.g., fluctuations in cognition are a feature of Lewy body dementia)

Reviewing a patient's usual activities (e.g., driving, managing personal finances/paying bills, completing chores, engaging in hobbies, medication compliance, grooming/bathing) provides an opportunity to assess for additional symptoms and complications associated with cognitive impairment, including potential safety issues.

Detailed cognitive examination

If cognitive impairment is suspected, it is important to use a validated instrument for evaluation, because routine history and physical examinations are not always sensitive for detecting impairment. Patients and caregivers are likely to benefit from having a clear diagnosis as well as from interventions aimed at safety, optimizing cognition, planning for the future, and enhancing overall well-being.

Initial evaluation of cognitive impairment in primary care can be quick. Examples of screening instruments that take five minutes or less to administer include: the Clock Drawing Test, the Mini−Cog assessment, the Memory Impairment Screen, the Mental Status Questionnaire or Short Portable Mental Status Questionnaire, the Verbal Fluency test, the AD8 Dementia Screening Interview, and Clock-in-the-Box. These instruments have variable, but acceptable, sensitivity for the detection of cognitive impairment.[129] A 2021 Cochrane review, for example, found that the accuracy of baseline Mini-Mental State Examination (MMSE) scores ranged from sensitivities of 23% to 76% and specificities from 40% to 94%.[130] A 2020 systematic review and meta-analysis of 57 observational studies evaluating the accuracy of brief cognitive tests found that many were highly sensitive and specific for distinguishing Alzheimer-type dementia from normal cognition.[131] For example, for distinguishing AD from normal cognition:

- The Clock Drawing Test had median sensitivity of 0.79 and specificity of 0.88 in an analysis of eight studies.
- The Mini-Mental State Examination had sensitivity 0.88 and specificity of 0.94 in an analysis of seven studies.
- The Montreal Cognitive Assessment had sensitivity of 0.94 and specificity of 0.94 in two studies. Accuracy was lower for all tests for distinguishing AD from MCI.

Using both a cognitive measure and a functional questionnaire may increase yield in screening and also reduce cultural and educational bias as opposed to using cognitive measures alone.[132] The Mini−Cog and the AD8 are cognitive and functional instruments, respectively, that have been reasonably well−validated.

The **Mini−Cog Test** uses a simple scored 3−item word recall test in combination with a clock drawing test. The patient is first asked to repeat and remember three unrelated words, allowing a maximum of three trials to repeat the words correctly. The patient is next asked to draw the face of a clock, and after all the numbers have been placed to draw the hands to read “10 minutes after 11 o’clock (11:10).” Finally, the patient is asked to recall the three words from earlier. The test is scored by adding the number of words recalled after the delay (0 to 3) and either 0 points for an incorrect clock or 2 points for a correct clock. Using a cutoff of 3 or greater to indicate “non−demented” and 2 or less to indicate “demented,” the Mini−Cog has a sensitivity of 76%−100% and specificity of 54%−85% for detecting signs of dementia, when validated against clinical diagnostic criteria as a gold standard.[129]

The **AD8 Dementia Screening Interview** consists of eight yes/no questions pertaining to a patient’s memory, thinking, and functioning in usual activities, answered by either the patient or an informant who knows the patient well. Two or more “yes” answers suggest the presence of dementia with a sensitivity of 96.5% and specificity of 83.4%, again using clinical diagnostic criteria as a gold standard.[133] A 2019 Cochrane review found similar values, including a sensitivity of 92% and a specificity of 64%.[134]

The **MMSE** is a 30-point questionnaire assessing orientation to time and place, attention and recall, and language, among other areas. A 2020 systematic review including 32 studies of MMSE found a pooled sensitivity and specificity of 89% and 89% to detect dementia, respectively.[129] The MMSE score may be affected by age, education, and language. Given the comparable sensitivities of the Mini−Cog and AD8 vs. the MMSE, the greater amount of time required to administer the MMSE and the fact that the MMSE is not in the public domain, the Mini−Cog and AD8 may be more efficient for selecting patients requiring a more detailed diagnostic evaluation.

The Montreal Cognitive Assessment (MoCA) includes 18 questions that assess orientation, memory, language, attention, and executive function.[135] In many cases MoCA provides sufficient information to aid in generating a differential diagnosis and can be administered in only about 10 minutes. Total MoCA

score can range from 0-30 (higher score indicating better functioning) with scores <26 points suggesting MCI or dementia. The MoCA is more sensitive for detecting MCI than the MMSE (MoCA MCI sensitivity 89%, specificity 75% vs. MMSE MCI sensitivity 62% and specificity 87%).[135] Clinicians need to complete an online training and certification program before accessing and using MoCA.[136]

In practice, an assessment of cognitive domains (e.g., using the MMSE or MoCA) can inform the profile of impairment suggested by the history and provide an additional measure of severity. As described above, the MMSE is not in the public domain and is susceptible to bias depending on patient characteristics. The MoCA also has other potential advantages over the MMSE in that it is more sensitive for detecting executive dysfunction, uses a more robust 5 item (vs. 3 item) word list for memory testing, assesses whether the patient benefits from cues or multiple choice for words not recalled after a delay, and provides subtests organized by cognitive domains.[137] (Note that education plays a role in scoring for MoCA: if the subject has 12 years of education or fewer a point is added to his or her total score.)

Concerns have been raised, however, that the MoCA performance characteristics may vary depending on the demographic characteristics of the patient being tested.[138-140] For example, one study assessed cognitive function in 231 English- or Spanish-speaking patients using both a language-appropriate MoCA and then a neuropsychologist review as a gold standard. The study found that for the MoCA to have a similar sensitivity and specificity for detecting cognitive impairment required a lower MoCA cutoff for non-English speakers (<16.5 versus <18.5 for English speakers).[141] This finding does not invalidate the use of the MoCA, but it highlights the need to consider further workup, such as referral for formal neuropsychological testing, in certain patients. Specifically, additional workup should be considered when there is discordance between patient history and cognitive screening and/or when there is concern that a screening tool may not generalize well to a given patient.

Table 5: Dementia screening and diagnostic tool sensitivity and specificity[129,133-135,142]

Dementia tool*	Sensitivity (%)	Specificity (%)
Mini−Mental State Exam	81	89
MoCA	91	81
Mini−Cog	91	54-86
AD8	96	64-83
Neuropsychological testing	80-98	44-98

*Compared to clinical diagnosis

AD and related dementias classically produce memory impairment at all levels – acquisition, retrieval, and storage. Referral for formal neuropsychological testing can be particularly useful for evaluating atypical cases, for detecting subtle impairments at an early stage, and when time does not permit a detailed cognitive examination in the office. Formal testing, however, is not necessary for most patients in order to establish a diagnosis of dementia. Neuropsychological testing involves evaluating multiple cognitive domains: attention, orientation, executive function, memory, language, calculations, mental flexibility, and conceptualization; it has a sensitivity for detecting dementia of 80-98% and specificity of 44-98%.[142,143] Neuropsychological testing may help identify patterns suggesting a particular cause of dementia, and quantify clinical worsening at a more granular level than the screening assessments above – but it should only be undertaken if the results will change management.

Physical and laboratory evaluation

A physical exam and laboratory workup can help uncover potentially modifiable factors that may cause or contribute to cognitive dysfunction. Components include:

- physical
  - assessment for parkinsonism (tremor, rigidity, bradykinesia, postural instability)
  - assessment of focal neurological signs that might suggest stroke or tumor
  - gait abnormalities
  - assessment for motor neuron disease (fasciculations, hyperreflexia, increased muscle tone, muscle atrophy)
- laboratory
  - comprehensive metabolic profile
  - complete blood count and differential
  - thyroid stimulating hormone (TSH)
  - vitamin B_{12} level
  - syphilis
  - urinalysis (if urinary symptoms present)

Staging and prognosis tools

It can be useful to assess the stage of AD progression based on functional status in order to provide interventions appropriate for the patient's need. The Functional Assessment Staging Test (FAST) is a widely-validated staging tool for this purpose (available at: mccare.com/pdf/fast.pdf). FAST scores range from 1 for people with no function or cognitive impairment to 7 for people who are totally dependent on external care, with subdivisions for different degrees of dependency. Another staging tool is the Weintraub Activities of Daily Living Questionnaire, which is a 28-item tool completed by a primary caregiver to assess impairment in the areas of self-care, household care, work/recreation, shopping/money, travel, and communication.[144]

Because the clinical course of individuals with dementia is highly variable (median survival from age at diagnosis ranges from 3.3 to 11.7 years), it can be helpful to use a prognosis or mortality prediction model.[145] The ePrognosis tool developed by the University of California San Francisco (available at: eprognosis.ucsf.edu) allows assessments for individuals tailored to their current location (e.g., in a home or long-term care facility). Outcomes include mortality (over 1-10 years) as well as prediction of need for nursing home-level care.

Neuroimaging

Neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) may reveal the presence or extent of vascular disease, focal patterns of atrophy suggestive of AD or other conditions, presence or absence of hydrocephalus, and evidence regarding other conditions potentially associated with dementia such as cerebral amyloid angiopathy. Rarely, imaging may reveal a modifiable condition not detected by neurological examination such as a subdural hematoma or a brain tumor.

The American Academy of Neurology, the Alzheimer's Association, and the Canadian Consensus Conference recommend in their guidelines at least a one-time head CT or MRI as part of an initial evaluation for dementia, particularly among those with focal signs.[146-148] MRI is usually preferred over CT imaging because of its greater sensitivity to vascular lesions and atrophy patterns.[146] Imaging is

particularly important in those suspected to have a reversible cause of dementia that can be diagnosed with imaging studies, such as normal pressure hydrocephalus (NPH), subdural hematoma, or a malignancy.[147]

More specialized kinds of imaging (e.g., PET scans) are typically ordered and performed by specialists after referral from a primary care clinician. Referral to a memory specialist or neurologist may be appropriate in the following situations:

- atypical findings or diagnostic uncertainty
- early-onset (before age 65) or rapidly progressive changes
- atypical cognitive abnormalities, sensorimotor dysfunction, severe mood/behavioral disturbance, fluctuating course
- patient is a potential candidate for and is interested in anti-amyloid monoclonal antibody therapy

Advanced diagnostic assessments

Imaging for amyloid

Functional brain imaging with 18-F fluorodeoxyglucose positron emission tomography (FDG-PET) or single-photon emission computed tomography (SPECT) reveals distinct regions of hypometabolism (PET) and hypoperfusion (SPECT) in patients with suspected AD. FDG-PET may be most useful in distinguishing AD from FTD (frontotemporal dementia) in patients with atypical presentations, as well as discriminating from non-neurodegenerative conditions, such as depression.[149]

Amyloid PET tracers that measure brain amyloid lesion burden may help differentiate AD from other causes of dementia.[150] A negative amyloid PET scan decreases the likelihood that a patient with dementia has AD, but a positive scan is not conclusive for diagnosis and does not rule out coexisting pathology.

A 2020 systematic review and meta-analysis of 15 brain imaging studies found the following median sensitivities and specificities for distinguishing neuropathologically-defined AD from non-AD in patients with dementia (Table 6).

Table 6: Sensitivity and specificity of brain imaging studies for identifying neuropathologically defined AD vs non-AD[151,152]

Imaging study	Sensitivity	Specificity
Amyloid PET	0.91	0.92
FDG-PET	0.89	0.74
SPECT	0.64	0.83
MRI	0.91	0.89
TAU-PET	0.95	0.81

A 2025 consensus opinion from the Society of Nuclear Medicine and the Alzheimer's Association concluded that amyloid/tau PET scans can be considered when AD etiology remains uncertain even after comprehensive cognitive evaluations; when the knowledge of the presence or absence of amyloid/tau

pathology is expected to alter management, or to determine eligibility for treatment with anti-amyloid therapies or monitor the response to anti-amyloid therapy.[149]

A multi-center study of 11,409 Medicare beneficiaries with MCI (N=6,905) or dementia (N=4,504) evaluated changes in management 90 days after amyloid PET scanning.[153] The diagnosis changed from Alzheimer's disease to non-Alzheimer's disease in 25.1% of patients and from non-Alzheimer's disease to Alzheimer's disease in 10.5% of patients. The use of cholinesterase inhibitors or memantine rose significantly after positive PET scans in patients with MCI or dementia, and declined marginally in patients with negative PET scans.

Tau PET imaging tracers could be potentially useful as markers of the tauopathy of Alzheimer's disease. Several studies have demonstrated that tau tracers better track disease progression and better associate with patterns of atrophy and clinical features compared to amyloid PET.[154,155] One tracer, flortaucipir F-18, has been FDA approved for determining the burden of neurofibrillary tangles in patients being evaluated for AD. A 2021 study found that tau PET tracers, including F-18, demonstrated strong prognostic utility of cognitive change over time and outperformed MRI and amyloid PET markers.[156] Insurance coverage for this approach is currently very limited.

Genetic testing

Genetic testing for AD has not been routinely recommended because results are neither sensitive nor specific, although ApoE ε4 testing is now recommended for patients considering anti-amyloid therapy.[157,158] The **CLARITY-AD** randomized trial found that patients with mutations in ApoE ε4, especially homozygotes, appeared to benefit less from lecanemab and were also more likely to have side effects. This may widen use of ApoE ε4 testing to inform the decision about whether to refer patients for consideration of this treatment; and appropriate use criteria now recommend assessing ApoE ε4 status as part of consideration for anti-amyloid therapies.

Apart from evaluation for anti-amyloid treatment, referral to a genetic counselor for consideration of testing for gene mutations associated with familial AD has thus far been recommended only for patients with early−onset AD and/or a family history of early-onset dementia or those with a family history suggesting an autosomal dominant mode of transmission. Fewer than 1% of AD cases are due to familial autosomal dominant gene mutations, such as amyloid precursor protein (APP), presenilin 1 (PSEN 1), and presenilin 2 (PSEN 2), which show 95-100% penetrance.[157] However, ApoE ε4 has three alleles that influence susceptibility for AD, with effects that vary with the population studied as well as the presence or absence of other risk factors for AD. Tests for ApoE ε4 are readily available to patients through clinical labs and companies like 23andMe. However, because having an ApoE ε4 allele is neither necessary nor sufficient to cause AD, numerous consensus statements and articles have recommended against using ApoE ε4 genotyping for predicting AD risk.[157]

Biomarker tests

Cerebrospinal fluid markers

The use of cerebrospinal fluid (CSF) markers for predicting conversion from MCI to dementia has been studied. Common markers include:

- increased levels of phosphorylated tau protein and total tau

- lower levels of amyloid beta 42 (Aß42) peptide, a low ratio of Aß42 to Aß40 levels, and a low ratio of Aß42 to tau levels

Other CSF studies can help assess atypical causes of dementia, including assessment for infectious, inflammatory, or neoplastic conditions. These can include specific tests for infectious pathogens, as well as oligoclonal bands, CSF autoantibodies, cytology and flow cytometry, as well as 14-3-3 protein and real-time quaking-induced conversion (RT-QuIC) assay to assess for Creutzfeld-Jakob disease.

Specific CSF biomarkers of AD pathology have been evaluated in a variety of studies.[159-161] Elevated levels of phosphorylated tau are thought to be associated with increased neurofibrillary tangle burden, and decreased Aß42 is felt to reflect the accelerated deposition of amyloid protein in brain tissues.

CSF biomarkers can be used to augment, but not replace, a complete evaluation for dementia. As these tests tend to have a higher sensitivity for AD pathology, negative CSF biomarkers decrease the likelihood that AD is the driving cause of a dementia, though positive biomarkers neither rule out a reversible cause nor confirm that a patient's cognitive decline is due to AD.

Blood-based biomarkers

Blood-based biomarkers have emerged as an alternative to CSF procedures for detecting AD pathology, and they are being marketed directly to consumers. Recent studies have suggested that tau plasma biomarkers, including P-tau217, may predict longitudinal cognitive decline in patients with preclinical AD.[162,163]

In May 2025, the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio test was approved to identify the presence of amyloid in adults with cognitive symptoms in specialty care as an aid to the diagnosis of AD. Results announced at the 18th Clinical Trials On Alzheimer's Disease conference in December, 2025, however, found significant drops in the accuracy of the Lumipulse p-tau217/B-amyloid I-42 plasma ratio test when values in the initial FDA approval announcement were compared to real-world results from the Mayo Clinic (Table 7).[164]

Table 7. Comparison of test statistics, FDA announcement of Lumipulse blood test vs. real-world use[164]

Test Characteristic*	FDA announcement	Real-world use
Sensitivity	95%	100%
Specificity	95%	**23%**
True positives	285	300
False positives	35	**539**
True negatives	665	161
False negatives	15	0
Positive predictive value	89%	**36%**

* assume AD pathology prevalence of 30%; performance differences highlighted in red.

In October 2025, the Elecsys pTau 181 test was approved to rule out the presence of amyloid in adults with cognitive symptoms in primary care. Instead of providing diagnostic certainty, this test may help say AD is less likely (i.e., used as a "rule out" test). As such, understanding the test characteristics of a given blood-based biomarker test is critically important. For example, a positive pTau 181 test would require further testing with a PET scan or CSF test to confirm whether amyloid is present. As many as 4 in 5 patients with a positive test may not have amyloid on further testing.[165]

Although only these two tests are FDA approved to date, a host of other biomarkers are available and being marketed by laboratory companies. A 2025 systematic review evaluated 31 different blood-based biomarkers and found marked variation in diagnostic accuracy compared to amyloid PET, CSF biomarkers, or neuropathology.[166] Single cutpoint analyses showed pooled sensitivity ranging from 49% to 91% and specificity ranging from 62% to 97%, with the certainty of evidence across tests ranging from moderate to very low. Most included studies had a high risk of bias, particularly related to patient selection, variations in the type of tests evaluated, and reference standards used. Blood-based biomarkers may be vulnerable to generating false positive results due to common conditions including kidney dysfunction, inflammation, and/or obesity, as well as the use of certain medications (e.g., sacubitril/valsartan).[126,167]

Caution is warranted in the use of these tests, because no broadly-accepted and evidence-based guidelines yet exist for implementing such tests in primary care. Many questions remain unanswered about such issues as exact cut offs for diagnosis, real-world lab techniques, and generalizability and performance in representative populations. In addition, one study has found markedly reduced accuracy in Black vs. white patients, for reasons that remain unclear.[168]

These tests require specialist or laboratory expertise to correctly interpret and evaluate and should not be used in asymptomatic patients or patients without objective cognitive impairment, because some cognitively unimpaired patients with positive blood-based biomarker results may never progress to MCI or dementia.

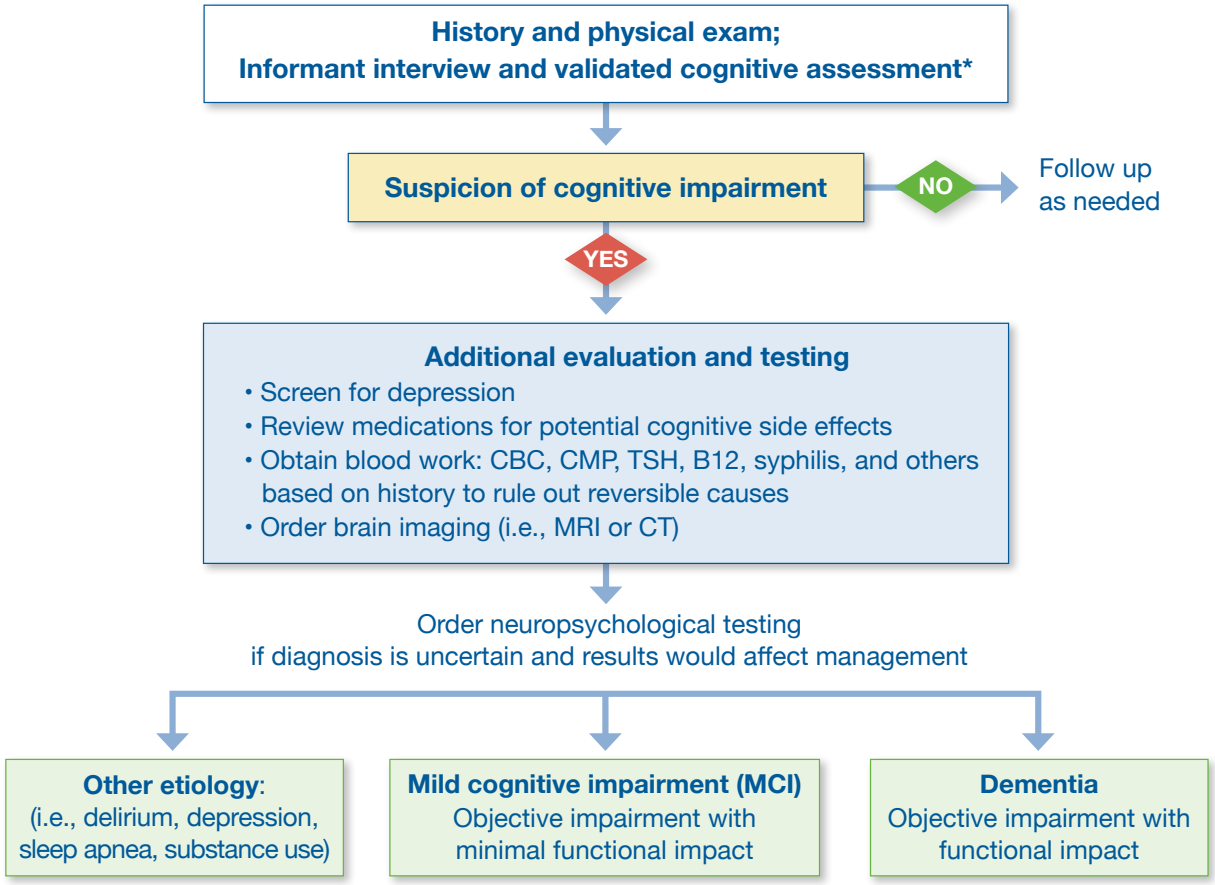
Although blood-based biomarkers signal a likelihood that an individual has amyloid pathology in their brain, they do not:

- distinguish normal aging from MCI or dementia
- rule out other potential causes of cognitive symptoms (e.g., in a person who has a positive amyloid biomarker indicating presence of amyloid in their brain but whose cognitive impairment is actually being driven by undiagnosed and untreated depression)
- establish severity or stage of cognitive impairment
- capture functional impairments that make cognitive change consequential
- differentiate between AD and other co-occurring pathologies
- accurately predict the risk of developing dementia in diverse older adults

A primary care approach to cognitive assessment

Figure 5 (next page) illustrates a high-yield way to approach patients who present in a primary care setting with concerns of cognitive impairment or difficulties.

Figure 5. Algorithm for approach to patients with cognitive concerns[158]



*Validated assessment tools include the Mini-Cog, Montreal Cognitive Assessment (MoCA), Ascertain Dementia 8 (AD8), or Mini-Mental State Examination (MMSE).

BOTTOM LINE: Patients with concerns about cognitive impairment should undergo a careful history, cognitive assessment, and evaluation for reversible causes. A one-time head CT or (preferably) MRI is recommended as part of an initial evaluation for dementia, particularly among those with focal neurological signs. Imaging is particularly important in those suspected to have a reversible cause of dementia that could be diagnosed with imaging studies. Additional testing (e.g., blood-based biomarkers, CSF testing, or PET scan) may be needed depending on the management strategy the patient and family choose, but are useful only in select situations.

Non-pharmacological strategies in dementia management

Identifying and treating non−neurological conditions that can negatively affect cognition is an important first step towards optimizing cognitive status. General medical illnesses, medications, and psychiatric

illnesses can affect frontal−associated brain networks important for attention and executive functions. For example, since depression can masquerade as dementia, and dementia can appear as depression, teasing out the causal relationship (e.g., by treatment with an antidepressant) is an important component of dementia care.

Treating issues that do not immediately appear to be tied to dementia may support cognition and provide patients with more reserve with which to compensate for the effects of the underlying cause of their MCI or dementia.

General lifestyle interventions

Lifestyle changes that can provide psychological, physical, and (possibly) cognitive benefits include regular exercise, stimulating cognitive activities, engaging in social activities, and eating a healthy diet. In making lifestyle recommendations to patients and caregivers, consider that apathy and anxiety about reduced functionality are common and may lead to resistance to such changes. Goals should be realistic, adaptable, and pleasurable (or at least not negative) for the patient. Using structured environments, such as scheduled group activities, may improve adherence and provide the additional benefit of social interaction. Establishing a regular routine including a consistent schedule for eating, taking medications, exercising, sleep, chores, hobbies, social activities, and other pleasurable activities can reduce the complexity and effort supporting desired behaviors.[50]

Exercise

Physical exercise is associated with a range of benefits in older people, including improving balance and reducing falls,[169] improving mood,[170] and improving function.[171] However, to date, evidence that exercise-based interventions can slow or reverse cognitive decline has been mixed, at best.

In a review of 14 studies evaluating exercise programs and cognitive outcomes in people with MCI, 92% of cognitive outcomes reported were non-significant, and only 42% of effect sizes were classified as potentially clinically relevant (effect size >0.20).[172] A systematic review of 41 studies found no improvements in memory-related outcomes with exercise.[173] In one high-quality study, there was no effect of a year-long moderate aerobic exercise group compared with an active control group that did relaxation and exercises to improve balance and flexibility.[174]

Following the publication of the review, a trial of 100 adults with MCI, randomized to resistance training or cognitive training, reported that resistance training very modestly improved the primary cognitive outcome (change on the 70−point Alzheimer's Disease Assessment Scale−cognitive [ADAS-Cog)] (effect size -0.33 points; 95% CI: -0.73 to -0.06 points) at six months.[175]

The Finnish **FINALEX trial** randomized 210 home-dwelling AD patients being cared for by a spouse to a program of home exercise (one hour, twice weekly for 12 months), a group exercise program (one hour, twice weekly for 12 months), or a control group.[176] At follow-up, participants in both of the exercise groups had significantly fewer falls than the control group and improved measures of functional independence, but there was no significant difference across the groups in the cognitive assessments included as part of the Functional Independence Measure. Similar results were found in the Dementia and Physical Activity (**DAPA**) trial of moderate- to high-intensity exercise training.[177] In this trial of 494 people with dementia, with one-year follow-up, exercise improved six-minute walking distance, but was not associated with any significant changes in cognitive function.

Exercise may improve physical functioning in patients with dementia and reduce problems related to agitation, wandering, and insomnia, although randomized trials are small (Ns=20-40), of low quality, and with substantial heterogeneity between studies.[97,178-180]

Addressing hearing loss

Approximately two-thirds of adults over 70 years old have some degree of hearing loss, which is independently associated with dementia, though less than 20% receive treatment with hearing aids.[181] Whether the use of hearing aids or other amplification devices can reverse or stem cognitive decline in later years is uncertain. A review of six studies (most of low-to-moderate quality) of hearing interventions with cognitive outcomes assessed over longer than three years found that three studies reported an association of hearing aid use with slowing of cognitive decline or reduction in incident cognitive impairment, while three studies reported no such association.[182] A small study evaluated 20 patients with dementia and their caregivers one month after giving the patients a hearing amplification device. Participants with high symptom burden (e.g., comorbid depression, agitation, anxiety, apathy) at baseline showed improvement in depression and neuropsychiatric outcomes.[183] The intervention had no effect on measures of caregiver burden. However, caregivers described improved engagement with their loved ones, such as laughing more, telling more stories, asking more questions, and having more patience.[183]

Enhancing personal safety

Preserving the safety of patients with dementia can mean reducing their independence, and this tension should be recognized as the disease/condition progresses. Finding the right balance between safety and independence can be challenging. Driving is perhaps the most common example of this issue and can be especially fraught.[184]

The ability to drive represents both real and metaphorical freedom that many are unwilling to give up. But the risks posed by driving often require preventive actions. In a study following 50 patients with AD vs. 50 age-matched controls without dementia, the proportion of car crashes was almost five times higher in those with dementia over five years (47% vs. 10%).[185]

Clinicians can play a valuable role in decisions about “giving up the keys” because they are trusted and generally perceived as neutral. Discussions about driving should be part of advance care planning (ACP), and the topic can be raised repeatedly over time, with an awareness of how emotionally charged the topic can be. Clinicians can focus attention on changes in driving ability related to medications or illness, rather than on the age of the person. Whenever possible, attempt to engage and empower the patient to make informed decisions, rather than forcing a decision on them. Explore all options, including having a driving evaluation or looking for alternatives to driving (there may be a range of services beyond public transportation).

A review by the American Academy of Neurology found high-quality evidence that the Clinical Dementia Rating (CDR), which is a global measure of dementia severity, is useful for identifying patients at increased risk for unsafe driving.[186] Individuals with CDR 0.5-1 fall into a range in which evaluation for risk factors associated with risky driving is recommended. Such risk factors include caregiver report of marginal or unsafe skills (high level of evidence); history of citations, history of crashes, driving <60mi./week, aggression/impulsivity, and score on the MMSE less than 24. Additional factors that may increase risk include use of alcohol, medications with sedative effects, sleep disorders, visual or hearing impairment, and motor impairments.

More information about driving and dementia can be found at the Alzheimer's Association (qrco.de/Alz_driving) and AAA (qrco.de/AAA_driver_safety). Some states require clinicians to report patients with all medical conditions that could impair driving ability to the Department of Motor Vehicles. Clinicians should be aware of their state's reporting laws.

Other potentially unsafe situations or activities include cooking without supervision, operating hazardous power tools or appliances, and keeping firearms or other weapons at home. Families and caregivers should be counseled about removing access to potentially dangerous objects at home, and monitoring kitchen activities as needed. Patients with dementia who have a propensity to wander, but who do not require around−the−clock supervision for other indications, may benefit from wearing an identification bracelet or an electronic monitor, and/or by measures to prevent them from leaving the house unsupervised. Self−administration of medications should be monitored for errors, and assistance provided when necessary. Pill boxes with designated compartments for different days and times can help reduce confusion about what medications should be taken when. To avoid a false sense of security with pill boxes, it is important to continually assess the ability of a person with dementia to self-manage their medications, as some patients with dementia will progress to a stage in which the pillbox itself is confusing.

Social interactions

Only very limited evidence exists about the effect of social activity interventions on cognition. One trial randomized 149 older adults to a social activity intervention vs. usual care and found that subjects with impaired executive function at baseline showed improvements of 44% and 51% in measures of executive function and memory, respectively, at follow-up of between 4-8 months, as compared to controls.[187] Another pilot RCT compared cognitive training, a health promotion course, and a book club as interventions for older adults with subjective memory problems (but not dementia) and found no between-group differences in cognitive outcomes.[188] An additional observational study of 462,619 patients found that social isolation was associated with a 1.26-fold increased risk of dementia (95% CI: 1.15-1.37), as well as with decreased gray matter volumes seen on structural MRI in a subset of 32,263 patients.[76]

Treating sleep apnea

Untreated obstructive sleep apnea (OSA) can induce or worsen inattention, memory, and cognitive deficits, which can manifest as impaired executive function and an increased risk of errors and accidents.[189] A meta-analysis of 11 RCTs (N=923) evaluating cognitive testing of patients with OSA before and after treatment found a significant post-treatment improvement for the Trail Making Test part B (SMD 0.93; 95% CI: -1.60 to -0.25) but no effects on other neuropsychological assessments.[189]

Cognitive interventions

A range of interventions to preserve or improve cognitive functioning in patients with MCI or dementia have been tested in trials and studies, with generally weak results.[190,191] A review of 15 RCTs of cognitive stimulation in patients with mild-to-moderate dementia found only minimal effects.[192] A Cochrane review of cognitive training exercises for dementia and MCI in Parkinson's disease found no evidence of cognitive improvement.[193] Nonetheless, despite limited evidence for efficacy, more and more people are using cognitive interventions in the hope that they might optimize and extend cognitive and functional skills.[194]

Three major types of cognitive interventions are:[195]

- **cognitive stimulation:** engagement with activities and materials involving cognitive processing, usually in a social context, with an emphasis on enjoyable activities.
- **cognitive training:** individual or group training exercises geared to specific cognitive functions, which may include practice and repetition, and computer−assisted learning.
- **cognitive rehabilitation:** working on personal goals, often using external cognitive aids and/or learning strategies.

Some evidence supports the use of cognitive stimulation for people with mild to moderate dementia who are treated with cholinesterase inhibitors. Improvements in quality of life have been demonstrated, in addition to modest improvements in cognitive function, and such interventions are likely to be cost effective. One study evaluated the effect of six months of cognitive stimulation (reality orientation therapy) in addition to donepezil (Aricept, generics) compared to donepezil alone in patients with mild to moderate AD. All participants had been treated with donepezil for at least three months.[196] There was a small, statistically significant benefit of combined therapy compared to donepezil alone, with a net difference between the two groups of 2.9 points on the 70-point ADAS–Cog (P=0.01). This difference is likely not clinically significant.

BOTTOM LINE: Despite limited evidence for their efficacy, non−pharmacological interventions such as exercise and cognitive training are increasingly used in an attempt to preserve physical function and quality of life for people with MCI and dementia.

Pharmacological interventions

The medications available to treat dementia are of limited efficacy. Drugs in three therapeutic classes have received full FDA approval to treat dementia−related cognitive dysfunction: cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine), the N−methyl−D−aspartate (NMDA) receptor antagonist memantine, and anti-amyloid medications (e.g., donanemab, lecanemab) for Alzheimer's disease. (A third anti-amyloid therapy, aducanumab, was pulled from the market in 2024.)

When interpreting the evidence related to drugs approved for dementia, it is critical to keep in mind that these medications have been approved on the basis of changes in a variety of primary outcome measures. These have varied from purely cognitive tests (e.g., MMSE) to more global measures of dementia severity the incorporate elements of cognition and function (e.g., CDR-SB). Table 8 summarizes the tests most commonly used in clinical trials of dementia drugs and the minimal score changes considered clinically important (i.e., likely to be perceived by a patient to be beneficial and meaningful enough to justify a change in management).

Table 8: Common tests and minimal clinically important scores

	Scale	Range	Direction	Minimal clinically important difference (MCID)
Cognition	MMSE	0-30	Higher is better	≥3
	ADAS-Cog	0-70	Lower is better	≥4
	SIB	0-100	Higher is better	≥7
Global	CIBIC-plus	1-7	Lower is better	≥1
	CDR-SB	1-18	Lower is better	0.5-2
	iADRS	0-144	Higher is better	≥5
Behavior	NPI	0-144	Lower is better	≥4

MMSE: mini-mental state examination; ADAS-Cog: Alzheimer's disease assessment scale-cognitive subscale; SIB: Severe impairment battery; CIBIC-plus: Clinician's Interview-based impression of change plus caregiver input; CDR-SB: Clinical dementia rating – sum of boxes; iADRS: integrated Alzheimer Disease Rating Scale; NPI: neuropsychiatric inventory

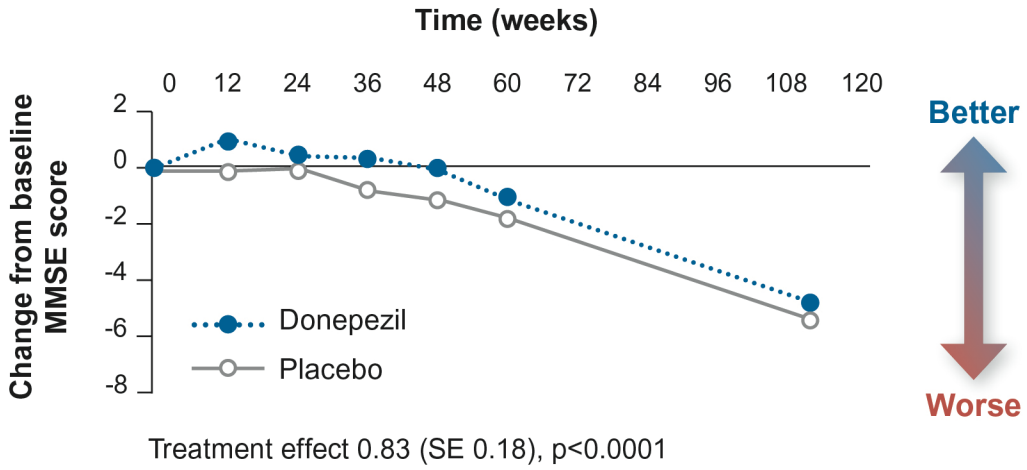
Cholinesterase inhibitors

The cholinesterase inhibitors donepezil (Aricept, generics), galantamine (Razadyne, generics), and rivastigmine (Exelon, generics) increase activity of the neurotransmitter acetylcholine in the central nervous system by inhibiting cholinesterase at the synaptic cleft. Acetylcholine is important for memory and attention, and AD is associated with degeneration of cell populations in the basal forebrain that provide cholinergic projections to widespread areas of the cerebral cortex.[197] However, attempts to address this underlying pathophysiology have not translated into clear clinical benefits.

Efficacy in dementia

Most trials of cholinesterase inhibitors have been short-term (six months or less) and in community−dwelling patients with mild-to-moderate AD, though memantine has been studied in patients with greater impairment. Overall, these trials have found statistically significant but clinically marginal effects on cognitive function and global functional status.[198] The benefit, when it occurs, is manifested by a small reduction in the rate of cognitive decline, rather than a reversal of cognitive decline. No evidence shows increasing benefits with longer duration of therapy. One of the few long-term studies was the AD2000 study of 565 community-dwelling patients with mild-to-moderate AD who were followed for 3 years. The trial showed a small effect on the rate of decline of cognitive function and functional status "below minimally relevant thresholds" at 2 years (see Figure 6) but no difference in nursing home admission or progression of disability at 3 years.[199]

Figure 6: Modest improvements of MMSE score (MCID ≥ 3) disappears within 12 months[199]



Treatment effect 0.83 (SE 0.18), p<0.0001

Most evidence of cholinesterase inhibitors in AD is summarized in a 2006 Cochrane review, which found only modest results of questionable clinical significance:[200]

- mean difference in ADAS-Cog: -2.37 points (range: 0-70, clinically important difference ≥4 point reduction)
- mean difference in MMSE: 1.37 points (range: 0-30, clinically important difference ≥3 point improvement)
- mean difference in ADL: 2.40 points (range: 0-100)

Donepezil was shown to modestly improve functional skills as assessed by the Clinical Dementia Rating Scale (CDR-SB) in a 1999 clinical trial comparing donepezil to placebo, with greater improvement in the 10 mg. group compared to the 5 mg. group (mean drug-placebo differences 0.3 and 0.4 points, respectively).[201] A 2018 Cochrane review evaluated 28 studies of donepezil (5 mg/day or 10 mg/day) in people with mild, moderate, or severe dementia.[198] Most studies were of 6 month duration or less. After 26 weeks of treatment, donepezil was associated with better outcomes for cognitive function measured with the ADAS-Cog (mean difference -2.67 points; 95% CI: -3.31 to -2.02), the MMSE (MD 1.05 points; 95% CI: 0.73 to 1.37) and the Severe Impairment Battery (MD 5.92 points; 95% CI: 4.53 to 7.31 points). No differences were observed between donepezil and placebo for behavioral symptoms measured by the Neuropsychiatric Inventory or by the Behavioral Pathology in Alzheimer's Disease scale. As already noted, all of these outcomes were not clinically different from placebo.

A 2020 systematic review and meta-analysis of 55 studies found mostly low-strength evidence suggesting that compared with placebo, cholinesterase inhibitors produced small average improvements in cognition (standardized mean difference [SMD], 0.30 [range: 0.24 to 0.52]), no difference to small improvements in function (median SMD, 0.19 [range: −0.10 to 0.22]), no difference in the likelihood of at least moderate improvement in global clinical impression (median absolute risk difference, 4% [range: 2% to 4%]), and increased withdrawals due to adverse events.[202]

A few studies in community-dwelling patients or nursing home residents with severe AD showed some modest benefit in cognitive function and functional status.[203-207] However, the practical value of such modest benefits may be limited in these patients and should be weighed against the risk of side effects.

Response to treatment can vary substantially. Up to half of patients receiving cholinesterase inhibitors show no discernible benefit and only a small minority of patients, estimated as 1 in 5, derive a strong benefit (e.g., 7 or more points on the ADAS−Cog or 3 or more points on MMSE, equivalent to stemming a year or more of natural cognitive decline).[208,209,]

Escalating the donepezil dose to 23 mg per day does not affect cognitive decline. A randomized double-blind study (N=1,467) examined the effect of increasing the dose of donepezil from 10 to 23 mg/day in patients with moderate to severe AD.[210] The results showed a statistically significant but clinically modest impact on the Severe Impairment Battery (SIB) cognitive function score after 24 weeks (SIB score greater with donepezil 23 mg/day than with donepezil 10 mg/day: +2.6 points vs. +0.4 points; P<0.001).[210] A Cochrane meta-analysis of two trials comparing donepezil 10 mg/day vs. 23 mg/day found no differences in efficacy outcomes, but fewer participants on 10 mg/day experienced adverse events or withdrew from treatment.[198]

In the few studies comparing cholinesterase inhibitors head−to−head there is no suggestion of superior efficacy for any one over the others.[200]

Cholinesterase inhibitors have been studied in patients with other types of dementia, with results as modest or equivocal as those seen in studies in patients with AD:

- Lewy Body dementia: some evidence to support use of donepezil[211,212]
- Parkinson's disease dementia: limited clinical improvement from rivastigmine[213] (rivastigmine has a specific approval for PDD[214])
- Vascular dementia: possible improvement in cognition,[215,216] although the change is unlikely to be clinically important[217]
- Frontotemporal dementia: no convincing evidence of benefit[218]

It can be difficult to determine whether a patient who initially responds to treatment is continuing to benefit as time passes and cognition worsens, because one cannot know what the patient's course would have been in the absence of treatment.

Cholinesterase inhibitors in MCI

A 2012 Cochrane Review of nine studies of cholinesterase inhibitors in patients with MCI found no significant differences in cognitive test scores, no differences in Activities of Daily Living (ADL), and only weak evidence for a slowing in the progression to dementia over a 3-year period.[219] Two 2013 systematic reviews further concluded that cholinesterase inhibitors were ineffective in preventing dementia and did not improve cognition or function in patients with MCI.[173,220]

Safety

Medications with anticholinergic activity may reduce the efficacy of the cholinesterase inhibitors and can also cause delirium in patients receiving such treatment.[221] These drugs include antihistamines, tricyclic antidepressants, antipsychotics, and drugs used for urinary incontinence, such as oxybutynin, tolterodine, and solifenacin. These medications can reduce or negate any beneficial effect on cognition by cholinesterase inhibitors.[222]

The most common adverse effects of cholinesterase inhibitors are gastrointestinal, and include anorexia, nausea, vomiting, and diarrhea.[223] These drugs can also cause dizziness, hypertension, syncope,

bradycardia, QT interval prolongation, muscle cramps, arrhythmia, angina pectoris and heart block.[222] Meta−analyses suggest that the frequency of dizziness with cholinesterase inhibitors is 10% (8% with donepezil, 10% with galantamine, and 22% with oral rivastigmine).[224] Compared with placebo, cholinesterase inhibitors are associated with 53% increase in the risk of syncope, but not with falls, fractures, or accidental injury.[225] In clinical trials, 29% of patients stopped therapy due to adverse effects.[226] Donepezil may cause fewer adverse effects than oral rivastigmine.[200] A 2017 pragmatic trial in which patients were randomly assigned to donepezil, galantamine, or rivastigmine found that at 18 weeks, rates of discontinuation for any reason were similar for the three drugs (39%, 53%, and 59%, respectively).[227]

Doses of cholinesterase inhibitors should be started low, and slowly up-titrated to minimize adverse effects.[208] Transdermal administration of rivastigmine appears to improve GI tolerability compared to oral rivastigmine.

Dosing

Table 9 shows recommended dosing of the cholinesterase inhibitors. Standard maintenance doses are 10-23 mg/day for donepezil, 16−24 mg/day for galantamine, and 9.5 mg/day for transdermal rivastigmine. Because different doses of the same drug have rarely been studied head−to−head, it is not clear whether doses lower than these standard maintenance doses have similar efficacy. Patients with severe AD may achieve incremental cognitive benefits from donepezil doses higher than 10 mg/day but are also more likely to experience side effects.[210]

Table 9: Dosing of cholinesterase inhibitors[14]

Drug	Starting dose	Titration	Target dose
donepezil (Aricept) - oral	5 mg once daily	Increase to 10 mg once daily after 4−6 weeks according to response. After 3 months at 10 mg, increasing in increments of 5 mg to maximum dose of 23 mg/day can be considered in selected patients who show marked improvement on lower doses.	10 mg/day Maximum dose: 23 mg
galantamine (Razadyne)	4 mg orally (immediate−release) twice daily, 8 mg/d 8 mg orally (extended−release) once daily	Increase by 8 mg/day every 4 weeks according to response, to a maximum 24 mg/day in two divided doses Increase by 8 mg/day every 4 weeks, maximum 24 mg/day	16-24 mg/day Maximum dose: 24 mg
rivastigmine (Exelon)−oral rivastigmine (Exelon) − transdermal	1.5 mg orally twice daily 4.6 mg/24 hour patch once daily	Increase by 3 mg/day every 2 weeks according to response, maximum 12 mg/day in two divided doses Increase to 9.5 mg/24 hour patch once daily after 4 weeks according to response; starting dose varies if switching from oral to transdermal therapy. 13.3 mg/24 hour patch may be considered in selected patients with marked improvement on lower doses.	Maximum dose 12 mg/day 9.5-13.3 mg/day

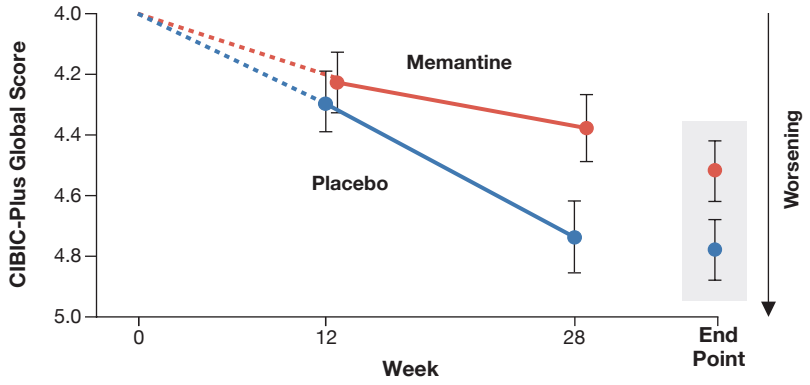
NMDA antagonist (memantine)

Memantine (Namenda) is a non−competitive NMDA receptor antagonist. By inhibiting the NMDA receptor, memantine is thought to reduce glutamate−mediated excitotoxicity and thus potentially improve the functioning of neurons.[228]

Efficacy

Clinical trials suggest a slight reduction in the rate of cognitive deterioration with memantine in patients with moderate to severe AD dementia, but not mild AD dementia (Figure 7).[229-231] Most studies are short-term and were conducted in patients with moderate to severe AD. A few studies in patients with mild AD did not show consistent benefits.[231,232,] Evidence from two trials with approximately 750 participants suggests a small clinical effect for memantine in patients with mild-to-moderate vascular dementia (mean difference of 2.15 points on ADAS-Cog; 95% CI: 1.05-3.25 points), but there is limited or very low-quality evidence for a benefit in other types of non-Alzheimer's dementia.[231]

Figure 7: Modest treatment effect of memantine in moderate-severe AD[229]



Safety

Memantine has been well−tolerated in clinical trials.[233] Most studies found the overall incidence of adverse effects and dropouts due to adverse effects to be similar to that of placebo.[233] The most common adverse effects are agitation, urinary incontinence, urinary tract infection, insomnia, and diarrhea.[229] A meta-analysis showed that memantine was not associated with increased risk of falls, syncope, fractures, or accidental injury compared with placebo.[225] In general, memantine is better tolerated than cholinesterase inhibitors (Table 10), and may be trialed before a cholinesterase inhibitor if patients have significant bradycardia or GI disease.[14]

Table 10: Comparison of adverse effects for cholinesterase inhibitors vs. memantine[14]

	Cholinesterase inhibitors	Memantine
Adverse effects	• nausea/vomiting • loss of appetite • increased frequency of bowel movements • vivid dreams • insomnia • local skin irritation (rivastigmine patch only)	• dizziness • headache • constipation • hallucination
Conditions in which to use caution	• peptic ulcer disease • chronic obstructive pulmonary disease and/or asthma • seizure disorder • urinary tract obstruction	• recent myocardial infarction • congestive heart failure • uncontrolled hypertension seizure disorder • severe hepatic impairment
Contraindications	• bradycardia	

Dosing

The standard dose of memantine is 20 mg/day (immediate release formulation), and dosages of immediate release memantine above 20 mg/day have not been studied. An extended-release formulation is available in daily doses of up to 28 mg/day.

Table 11: Dosing of memantine[14]

Drug	Starting dose	Titration	Target dose
memantine (Namenda)	5 mg once daily	Increase by 5 mg/day every week to a target dose of 10 mg twice daily; give in two divided doses if dose >5 mg per day	20 mg/day, 10 mg/day if renal insufficiency
	7 mg once daily (extended−release)	Increase by 7 mg/day every week to a target dose of 21−28 mg/daily	28 mg/day, 14 mg/day if renal insufficiency

Discontinuing cholinesterase inhibitors and memantine

There is limited evidence to suggest that withdrawal of cholinesterase inhibitors in AD may result in worse cognition, neuropsychiatric status, and functional status.[234] A post-hoc analysis of the DOMINO trial[207] found that withdrawal of donepezil in patients with moderate to severe AD increased the risk of nursing home placement after 12 months of treatment, but made no difference at 3 years of follow up.[235] Discontinuation of memantine may also lead to worsening cognition, though a 2021 Cochrane systematic review found only one trial that evaluated the effects of withdrawing memantine.[234] The trial only evaluated the effect of withdrawing memantine and cholinesterase inhibitors together and did not report the effects of withdrawing memantine only.

In light of the weak evidence base, clinical judgment combined with caregiver and family preferences must be used to determine how long patients should be treated with these agents.[236] In addition, when

discontinuing donepezil or memantine, a taper of a 50% dose reduction or stepwise reduction every 4 weeks to the lowest dose prior to discontinuation should be employed.

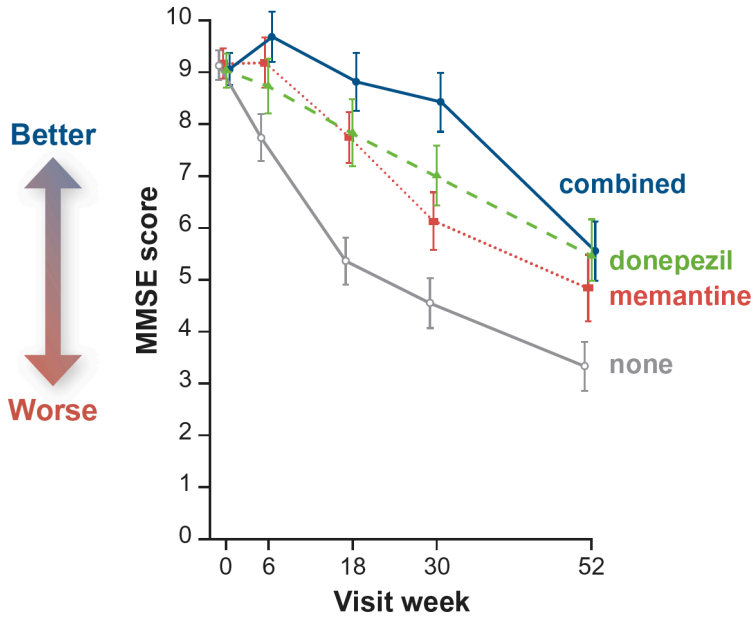
Clinical guidelines identify a number of possible "triggers" for discontinuation:[237]

- cognition/function significantly worsened over past 6 months
- no benefit seen during treatment (i.e., no improvement, stabilization, or decreased rate of decline)
- severe/end-stage dementia (dependence in most activities of daily living)
- uncomfortable or intolerable side effects
- patient/family decision
- refusal/inability to take meds

Dual therapy with memantine and a cholinesterase inhibitor

The effect of adding memantine to a cholinesterase inhibitor in patients with moderate to severe AD had been hoped to provide a small advantage over each drug alone, but benefits become less significant over time and the difference relative to placebo may not be clinically relevant (Figure 8).[238-240] A 52-week study in 295 community-dwelling patients with moderate to severe AD dementia found no additional benefit from combination therapy at the study endpoint, and patients demonstrated similar benefits from donepezil or memantine.[207]

Figure 8: Addition of memantine to donepezil in patients with moderate-severe AD[239]



A 2020 systematic review and meta-analysis of 55 studies found that in adults with moderate-to-severe AD, adding memantine to a cholinesterase inhibitor inconsistently improved cognition and improved global clinical impression, but did not improve function.[202]

Table 12: Dosing of the combination of memantine and donepezil

Drug	Starting dose	Titration
memantine/ donepezil (Namzaric)[241]	Patients stable on donepezil 10 mg: 7 mg/10 mg once daily in the evening	Increase the memantine component by 7 mg/day, no more frequently than weekly to a target dose of 28 mg/10 mg once daily
	Patients stable on donepezil 10 mg and memantine 10 mg twice daily or 28 mg daily: 28 mg/10 mg once daily in the evening	No titration required; patients initiated on maximum dose.

Note: although the combination product is available, prescribing individual generic components is significantly more cost effective.

Overall, cholinesterase inhibitors and NMDA receptor agonists have minimal efficacy and often cause side effects. Given their modest and transient benefits, the French Pharmacoeconomic Committee no longer recommends the use of these drugs,[242] while other groups (e.g., the British National Health Service's NICE) recommend they be prescribed only by neurologists or clinicians with specific expertise in dementia.[243] However, it may be reasonable for primary-care clinicians to offer a trial of these medications after carefully considering the potential benefits vs. risks in the context of the patient's goals, with a plan for monitoring both response and side effects, and for consideration of discontinuation if no ongoing benefit is evident.

BOTTOM LINE: Cholinesterase inhibitors provide modest, statistically significant improvements in cognition for those with mild-severe AD, but the clinical significance is uncertain because the effects seen in trials are smaller than minimal clinically important differences on most scales. Side effects such as nausea, vomiting, and diarrhea are relatively common. A time-limited trial may be reasonable based on clinician, patient, and caregiver preferences.

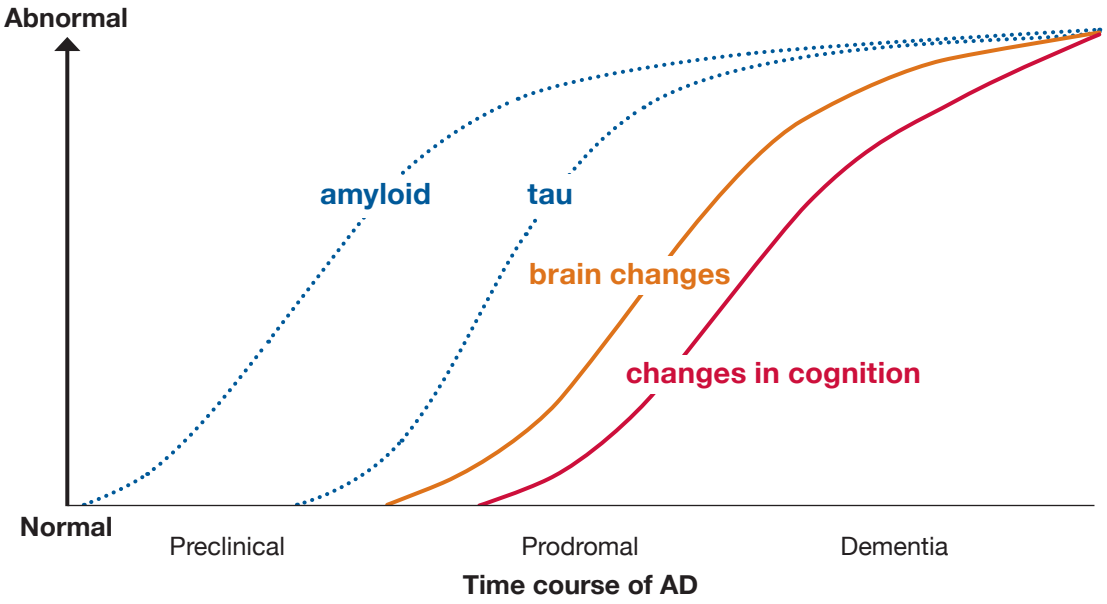
Memantine, or the combination of memantine and a cholinesterase inhibitor, provides benefits of questionable clinical significance for those with moderate-severe AD. Side effects of memantine tend to be less severe than with cholinesterase inhibitors. Titrate to recommended dose and reassess at 3-6 months to determine if risk-benefit relationship warrants continued treatment.

Monoclonal antibodies

The amyloid hypothesis

Many patients who die with AD are found on autopsy to have deposits of amyloid in their brains, which led to the theory that buildup of amyloid causes cognitive deterioration. Many cognitively intact patients, however, also have amyloid deposits, and not all people with AD have such deposits. Figure 9 illustrates an idealized model of the time courses of different characteristics of AD. The biomarkers for AD, amyloid and tau, are thought to occur before neurodegenerative changes, and such timing drives the hypothesis that anti-amyloid treatment should occur sooner than later in disease progression to prevent the physiological changes occur before their effects are seen on cognition.

Figure 9. Hypothesized time course of pathological changes along the AD continuum[244]



Lowering amyloid alone may not be sufficient. Several drugs designed to reduce brain amyloid have failed to show improvements in cognition (e.g., solanezumab, crenezumab, gantenerumab) and never made it to market.[245] Studies of existing anti-amyloid medications have shown statistically significant, but nonetheless minimal clinically detectable results on cognition, while at the same time having significant associated adverse effects.[246] In addition, most patients do not have "pure" AD; mixed dementia is more common.[247] Controversy thus exists about the accuracy and utility of the amyloid hypothesis and the efficacy of agents targeting amyloid as treatments for AD.[248]

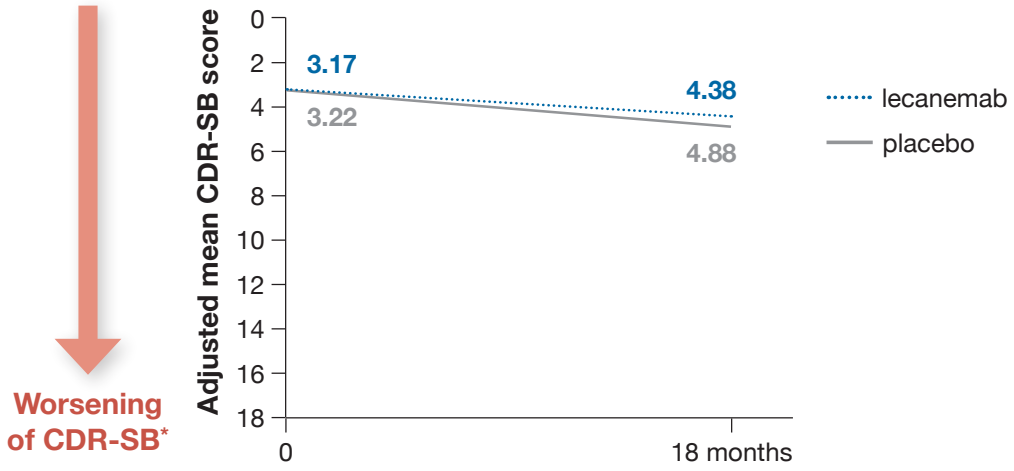
Lecanemab

Lecanemab (Leqembi, Leqembi Iqlik) is an antibody that targets soluble amyloid-beta protofibrils. It can be administered either as an IV infusion in-clinic or with a subcutaneous autoinjector (Leqembi iqlik) that can be used by patients at home; the subcutaneous autoinjector is indicated for maintenance dosing after 18 months of IV treatment.[249]

The 2023 phase III randomized trial **CLARITY-AD** assessed the safety and efficacy of lecanemab.[250] It included patients aged 50-95 diagnosed with either MCI or mild AD. Amyloid positivity was determined by PET or CSF studies. Patients were administered either lecanemab or placebo intravenously every two weeks for 18 months. The primary clinical endpoint was change in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) score. On this 18-point scale (which is a six-domain scoring system assessed by a trained clinician), at 18 months the decline of cognitive performance in patients receiving lecanemab was 0.45 points less than that seen in those given placebo (Figure 10), which was interpreted as a relative 27% reduction in the rate of decline. On the ADAS-Cog-14 scale (MCID ≥4), patients receiving lecanemab performed 1.44 points better than those who received placebo at 18 months. Importantly, the

drug did not produce an improvement in cognitive functioning; rather, it resulted in a slight slowing of the rate of decline. Lecanemab did, however, significantly reduce amyloid levels compared to placebo.

Figure 10: Change in CDR-SB at 18 months with lecanemab vs. placebo[250]



*Clinical dementia rating—sum of boxes scale

The clinical significance of a 0.45 reduction in the CDR-SB scale is unclear. Prior studies have indicated that across all stages of AD, on average, a 1 to 2 point decrease in CDR-SB reflects a clinically meaningful change.[251] Patients in earlier stages of AD, including MCI, had lower clinically meaningful thresholds. Other studies have defined a difference of at least 0.5 to define a clinically meaningful change.[252]

Safety

In the CLARITY-AD trial, lecanemab was also associated with a substantially higher rate of adverse events compared to placebo (Table 13). More than 25% of lecanemab patients had infusion-related reactions, 13% had amyloid-related imaging abnormalities (ARIA) with brain effusions and/or edema, and 14% had ARIA with microhemorrhage and hemosiderosis. Subjects who were ApoE ε4 homozygotes were more likely to experience symptomatic ARIA and less likely to benefit from lecanemab; a smaller effect was seen in heterozygotes. Overall, most (78%) ARIA events were asymptomatic at time of detection. However, the remainder of participants developed symptomatic ARIA, with symptoms ranging from mild (e.g., headache, confusion, vomiting, visual/gait changes) to serious (e.g., seizures, encephalopathy, stupor, stroke-like deficits, often involving hospitalization). Three catastrophic cerebral hemorrhages were reported later in patients given lecanemab, raising concerns about the concurrent use of tPA or anticoagulants, and whether the use of anticoagulants should be a contraindication for lecanemab initiation.[253]

The current FDA label does not list cerebral hemorrhage as a contraindication[249] although appropriate use criteria for lecanemab suggest withholding therapy for patients on anticoagulants.[254] Monitoring and management of ARIA is an ongoing area of investigation.

Table 13. Adverse events reported in CLARITY-AD trial[255]

Adverse event	Lecanemab (n=898)	Placebo (n=897)
Any adverse event	89%	82%
Related to intervention	45%	22%
Serious adverse event	14%	11%
Specific adverse reactions		
Infusion related reactions (e.g., flu-like symptoms, nausea, vomiting; can often be managed with premedication)	26%	7%
Headache	11%	8%
Amyloid-related imaging abnormalities (ARIA)		
Cerebral edema or effusions	13%	2%
Cerebral hemorrhage	17%	9%

Administration of lecanemab for the first 18 months of treatment is also logistically burdensome requiring intravenous infusions every two weeks, a PET scan or lumbar puncture to assess brain amyloid levels prior to lecanemab initiation, and regular screening MRIs to detect cerebral edema or hemorrhage. The current list price of $26,500 per year for lecanemab does not include the costs of pre-treatment assessment, the biweekly IV infusions, or the required follow-up MRI testing. Patients with AD beyond the mild stage are not eligible for lecanemab, as they were not studied in its pivotal trial and there is no evidence of benefit in this group.

Donanemab

Donanemab (Kisunla) was evaluated in the TRAILBLAZER ALZ-2 trial that randomized 1,736 patients ages 60-85 with early symptomatic AD and positive amyloid and tau pathology to Donanemab IV every 4 weeks for 72 weeks (or treatment completion criteria at 24 or 52 weeks based on amyloid clearance by PET scan) vs. placebo.[256] The primary outcome was change in the integrated Alzheimer Disease Rating Scale (iADRS), which ranges from 0 to 144 with lower scores indicating greater impairment, and a clinically meaningful difference considered to be a change of 5 points.[257] Outcomes were assessed in low/medium, and high tau pathology groups, as well as an analysis combining these two groups.

Efficacy

The mean change in iADRS score in the low/medium tau population at 76 weeks was -6.02 points (95% CI: -7.01 to -5.03 points) in the donanemab group and -9.27 points (95% CI: -10.23 to -8.31) in the placebo group (difference 3.25 points). The mean iADRS score in the combined population was -10.2 points (95% CI: -11.22 to -9.16 points) with donanemab and -13.1 points (95% CI: -14.10 to -12.13 points) with placebo (difference 2.9 points) (Figure 13). The differences for both groups were, thus, statistically significant, but did not meet the criteria for clinically meaningful results. The results of assessments using the CDR-SB were similarly minimal. The mean change in CDR-SB score at 76 weeks was 1.20 points (95% CI: 1.00-1.41) with donanemab and 1.88 points (95% CI: 1.68-2.08) with placebo (difference, -0.67 points; $P < .001$) in the low/medium tau population. The mean CDR-SB score change was 1.72 points

(95% CI: 1.53-1.91) with donanemab and 2.42 points (95% CI: 2.24-2.60) with placebo (difference, -0.7 points; P < .001) in the combined population.

Safety and logistics

Adverse effects reported for donanemab were broadly similar to those reported for lecanemab, although rates of ARIA were greater for donanemab (Table 14).

Table 14. Adverse events reported in TRAILBLAZER ALZ-2[256]

Adverse event	Donanemab (n=898)	Placebo (n=897)
Any adverse event	89%	82%
Death considered due to treatment	0.4%	0.1%
Serious adverse event	17%	16%
Specific adverse reactions		
Infusion related reactions	9%	0.5%
Headache	14%	10%
Amyloid-related imaging abnormalities (ARIA)		
Cerebral edema or effusions	24%	2%
Cerebral hemorrhage	20%	7%

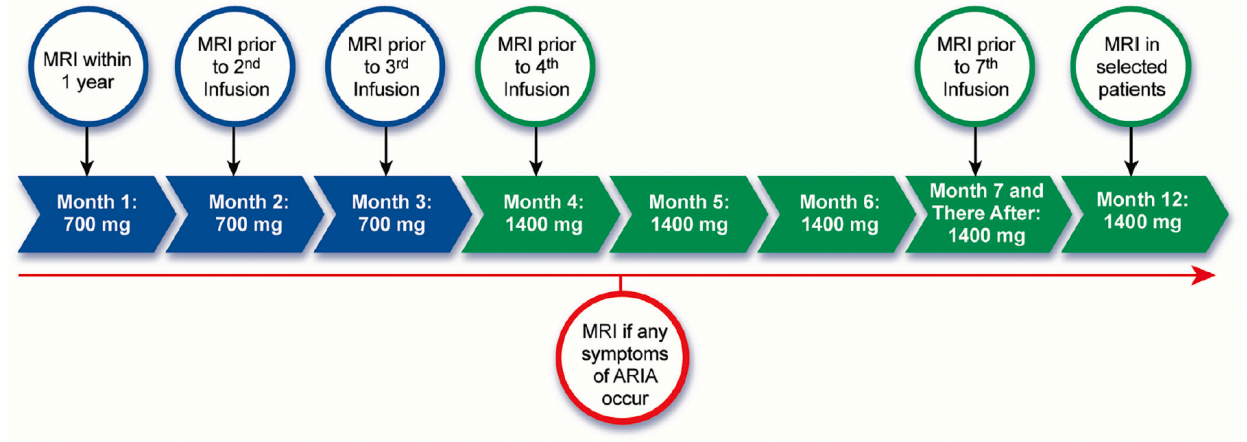
When ARIA events occurred, they were asymptomatic (i.e., only detected by screening MRI) in 75% and symptomatic in 25% of donanemab-treated patients. Importantly, for 1.6% of participants in the donanemab treatment group, ARIA led to serious outcomes, including hospitalization and requiring supportive care and intervention with corticosteroids. Three deaths in the donanemab treatment group occurred subsequent to development of ARIA and were deemed related to treatment, compared to only 1 death in the placebo group.

Other factors to consider about using donanemab:

- antibody targets insoluble, mature amyloid-beta plaques
- given every 4 weeks for 18 months or until clearance of plaques by PET scan (assessed at 24 or 52 weeks)
- delivered via infusion
- current cost is approximately $48,000 for 18-month course

An additional logistical consideration is the need for monitoring MRI scans during therapy with donanemab—at least six in the first year, possibly more if symptoms of ARIA occur (Figure 11).

Figure 11. Dose titration and MRI monitoring schedule for donanemab[258]



Summary for anti-amyloid therapies

These medications have unclear benefit with heightened risk of significant side effects and very little real-world evidence (as of this writing). Few patients may actually be eligible for these therapies. One study of patients seen in a specialized memory clinic found that only 6% of those referred to the center were eligible for therapy after applying appropriate use criteria (e.g., excluding ApoE ε4 homozygotes or those on anticoagulants).[259] In addition, anti-amyloid therapies have failed to show preservation of brain volume. In fact, meta-analyses of results for lecanemab and donanemab show accelerated loss of whole-brain and hippocampal volume and increased ventricular size among those on therapy. In the CLARITY AD trial, brain volume declined 26% faster among patients on lecanemab vs. placebo, and 33% faster among patients on donanemab in the TRAILBLAZER ALZ-2 trial.[260]

In a meta-analysis of 19 studies (N=9,429) involving patients with AD treated with anti-β-amyloid (Aβ) immunotherapy, 80.4% of patients were found to have asymptomatic ARIA, and most symptoms were resolved with dose adjustment or drug cessation.[261] Importantly, however, the long-term cognitive or functional effects of asymptomatic ARIA detected on screening MRI remain incompletely characterized.[262] Additionally, a systematic review of the literature highlighted lack of transparency in many clinical trials regarding ARIA (e.g., incomplete reporting regarding prevalence of symptomatic vs asymptomatic ARIA).[262]

Extant literature supports the contention that severe symptomatic ARIA is a rare but serious adverse effect of anti-amyloid therapy. For example, in one systematic review of 36 trial-reported cases of severe symptomatic ARIA, long-term follow-up revealed that 15 patients recovered completely, 10 had persistent cognitive deficits, and 10 died.[263]

For eligible patients who want to pursue anti-amyloid therapy the following appropriate use recommendations apply:[254,258]

- pre-treatment evaluation
  - exclude non-AD primary causes of cognitive impairment
  - brain MRI to exclude cerebral microbleeds and other factors (e.g., a non-AD cause for progressive cognitive impairment, brain tumors)
  - confirm amyloid pathology (PET or CSF, not blood biomarker)
  - APOE e4 testing to inform risk discussion

- do not prescribe for patients requiring anticoagulants (e.g., warfarin, DOACs, heparin) or who receive thrombolytics
- patients and care partners must understand potential benefits/harms and monitoring requirements for treatment (e.g., logistics of infusions and need for frequent MRI monitoring)

BOTTOM LINE: monoclonal antibody medications reduce amyloid levels but offer only small and uncertain clinical benefits while incurring significant logistical burdens and important risks for adverse events.

Weighing the decision to use medications

Given the unclear benefit of medication treatment and the risks of side effects, a clinician, patient, and family may decide not to initiate medications immediately or at all. Anti-amyloid medications appear to have a smaller window of use (currently in MCI due to AD and mild AD), but cholinesterase inhibitors and memantine remain options throughout much of the course of dementia (Figure 12). Patients and clinicians should continually re-evaluate the perceived risks and benefits of ongoing therapies, with an eye to limiting non-beneficial courses of treatment or those associated with significant side effects.

Figure 12. Dementia stage and timing of medication use

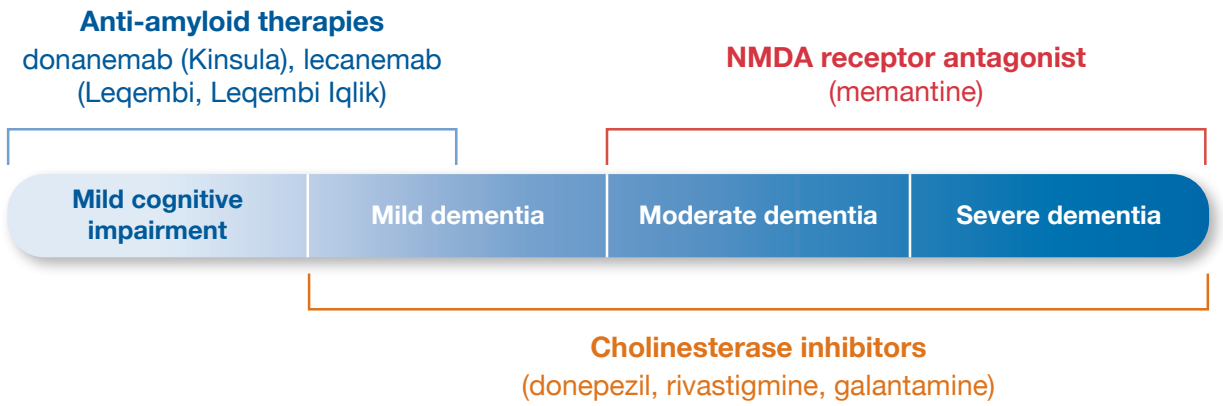


Figure 13: Change in CDR-SB relative to placebo in RCTs[255,256,264]

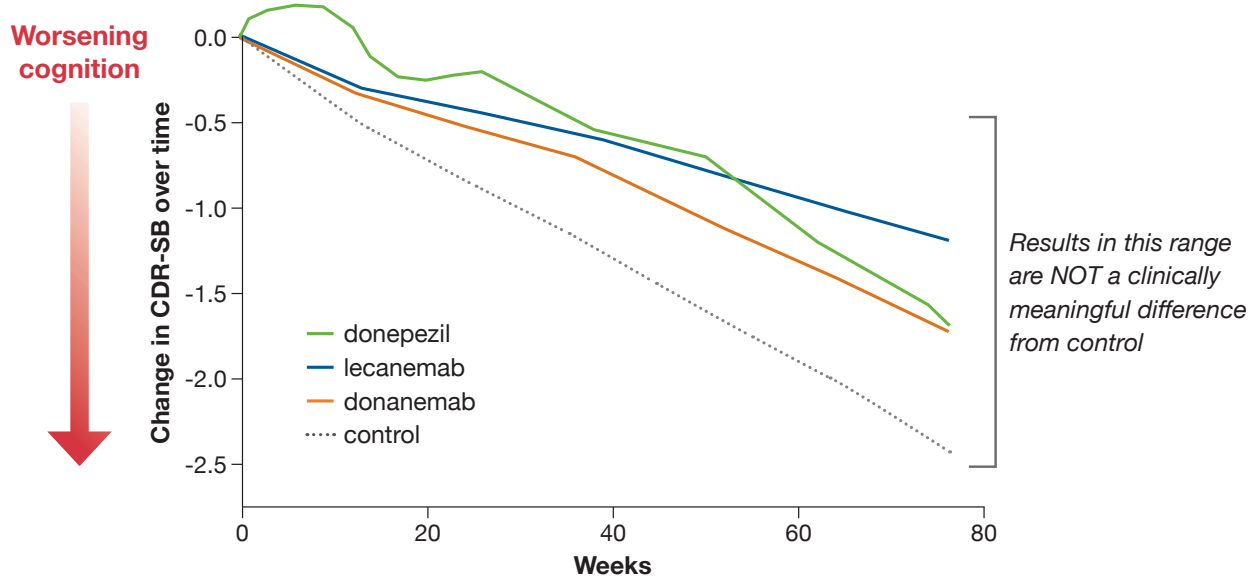
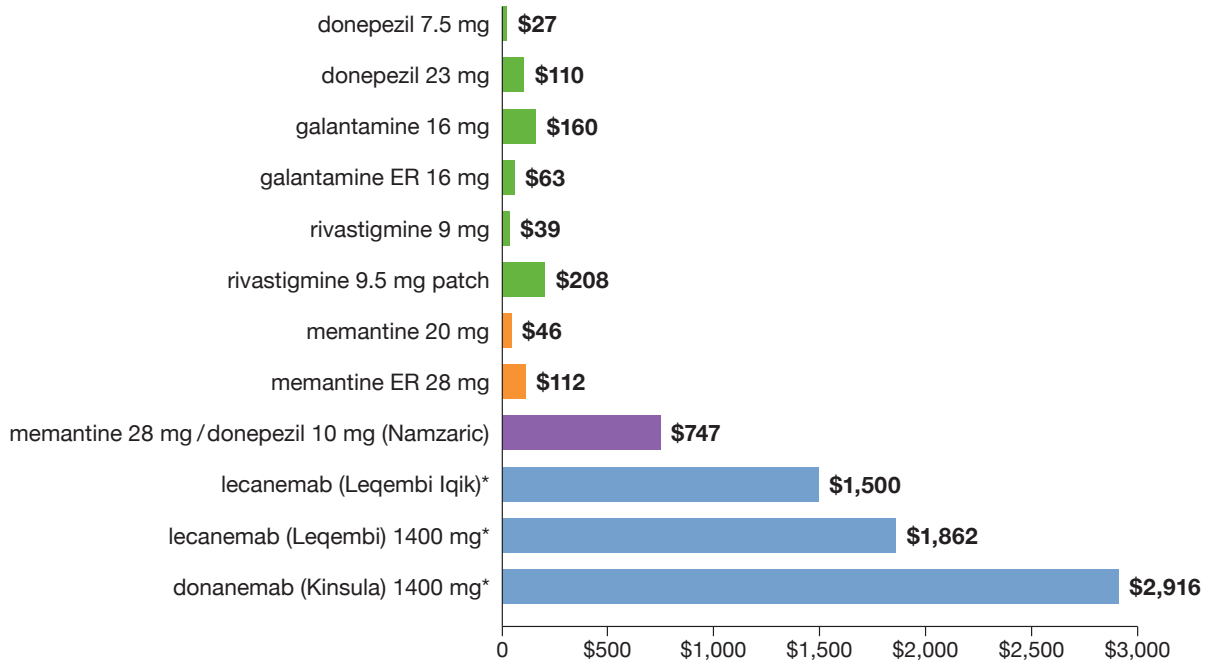


Figure 13 is a composite depiction of the results of placebo-controlled, randomized trials of donepezil, lecanemab, and donanemab to approximate the magnitude of benefit seen with these treatments across multiple studies. Of note, these interventions have not been studied in head-to-head trials, making precise head-to-head comparisons difficult. Each study enrolled different study populations with varying degrees of baseline dementia severity. Specifically, in the CLARITY-AD study of lecanemab, the baseline CDR-SB was 3.2; in the TRAILBLAZER ALZ-2 study of donanemab, the baseline CDR-SB was 4.0; and in the long-term study of donepezil by Rogers et al., the baseline CDR-SB was 6.7, reflecting slightly worsened global function at baseline. Despite these different baseline CDR-SB values, all three groups are shown as starting at 0 on the y-axis. Given that prior studies have shown that a 1-to-2-point change in CDR-SB reflects a clinically meaningful difference in various stages of AD, these results indicate that each of the interventions did not on average confer a clinically meaningful change relative to the placebo group. Given the different underlying populations in each of these trials, it is not possible to show one control line for all 3 drugs. For simplicity, the control line shown represents the control arm from the TRAILBLAZER-ALZ 2 study involving donanemab. This is because the baseline CDR-SB of trial participants in TRAILBLAZER-ALZ 2 was the closest to the mean CDR-SB across the 3 studies (4.6).

Prices of drugs to manage dementia

Based on the World Health Organization Defined Daily Doses (DDD) or Medicare average wholesale price as of January 2026, the price of medications for dementia are summarized in Figure 14.

Figure 14: Costs of a 30-day supply of medications for dementia



*Monthly prices of lecanemab (for a 70 kg patient) and donanemab are based on Medicare average wholesale price Jan 2026. Other pharmacy prices are from goodrx.com, February 2026. Listed doses are based on Defined Daily Doses by the World Health Organization. All doses shown are generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives. These doses should not be used as a guide for treatment.

Other pharmacological therapies in dementia

A number of other therapies have been suggested for cognitive impairment in dementia, but evidence is insufficient to recommend any of them. Many dietary supplements are heavily marketed to patients despite a dearth of evidence supporting their use and potential for substantial cost burdens.

Table 15: Other treatments proposed for cognitive impairment

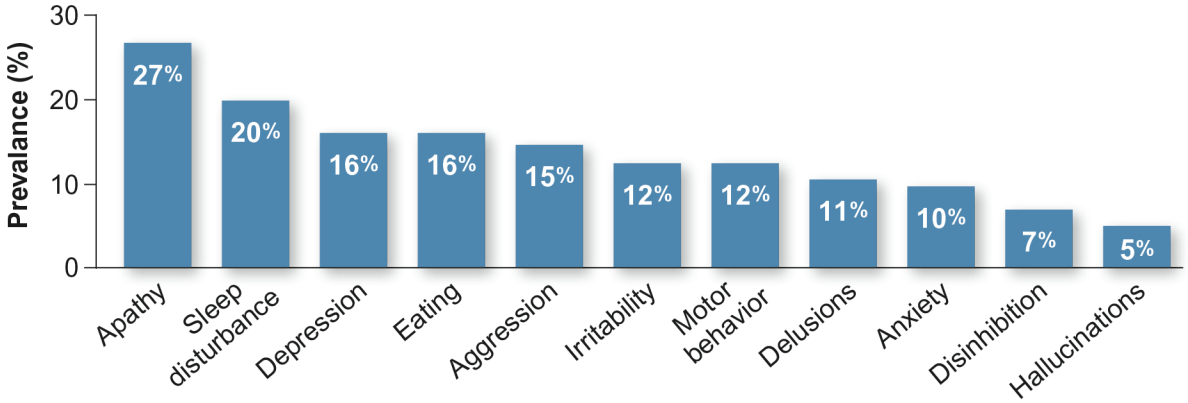
Therapy	Evidence
Vitamin E	Trials investigating vitamin E in patients with MCI and AD have produced mixed results. Some studies suggest that vitamin E 2000 IU/day confers a minimal benefit in delaying functional progression in patients with mild to moderate AD dementia, but other studies found no benefit at this dose in patients with MCI or at a dose of 800 IU/day in patients with mild to moderate AD dementia.[265-268] (Note: high doses of Vitamin E can increase bleeding risk in those on anticoagulants, particularly warfarin.)
HMG−CoA reductase inhibitors (statins)	There is insufficient evidence to recommend statins for reducing the risk of, or for the treatment of, dementia (including AD). Two large studies in patients with mild to moderate AD suggested no benefit.[269,270]
Estrogen	A Cochrane review concluded that there is no evidence that estrogen maintains or improves cognitive function in women who already have Alzheimer's disease.[271] The Women's Health Initiative Memory study found that conjugated equine estrogen (with or without progesterone) in postmenopausal women aged ≥65 years did not improve global cognitive function, or decrease the risk of MCI or dementia, and may actually adversely affect these outcomes.[272-275]
NSAIDs	NSAIDs and aspirin are not recommended for the prevention or treatment of Alzheimer's disease. Multiple trials in mild to moderate AD dementia have failed to demonstrate benefit.[276] Although aspirin is widely prescribed for patients with a diagnosis of vascular dementia, there is no good evidence to support this practice.[277]
Folic acid, vitamin B_6 and vitamin B_{12}	Systematic reviews and RCTs have found no evidence that combined treatment with folic acid, vitamin B_6 and vitamin B_{12} has beneficial effects on cognitive function in either healthy people, or in those with cognitive impairment or dementia.[278-280]
Ginkgo biloba	A 2009 Cochrane systematic review and a subsequent trial found no convincing evidence that ginkgo biloba has predictable and clinically significant benefit for patients with dementia or cognitive impairment[281] A 6−year RCT with 3,069 people aged ≥75 years with normal cognition or MCI found no advantage of ginkgo biloba over placebo in reducing the incidence of Alzheimer's disease or dementia.[282]
Omega−3 fatty acids	Trials of docosahexaenoic acid (DHA) and other omega−3 fatty acids in patients with mild to moderate AD dementia have demonstrated no benefit.[283,284,]

BOTTOM LINE: None of the medications available meaningfully alter the course of dementia. Anti-amyloid monoclonal antibodies are currently limited to patients with MCI or mild dementia positive for AD biomarkers, while cholinesterase inhibitors can be used at any point in dementia treatment and memantine can be added in moderate to severe dementia cases. Patients and families should decide with clinicians whether medication treatment is right for them. Many over-the-counter options have no proven benefit; stopping their use could reduce pill burden and unnecessary expenses.

Managing behavioral and psychological symptoms of dementia (BPSD)

Dementia is often accompanied by symptoms such as yelling, physical aggression, apathy, hostility, sexual disinhibition, defiance, wandering, psychotic symptoms (hallucinations or delusions), emotional lability, and paranoid ideation and behavior.[285,286] In a cohort study of community-dwelling adults with dementia, 61% engaged in at least one neuropsychiatric disturbance and 32% had moderate-to-severe disturbance at some point during their illness.[287] Higher rates of BPSD (i.e., 50%−80%) have been reported among residents of nursing care facilities.[288]

Figure 15: Prevalence of BPSD symptoms among patients with dementia from Cache County Study (N=362)[289]



Many medications have been prescribed to help manage real or perceived behavioral problems in older patients with dementia; these include antidepressants, benzodiazepines, and antipsychotic medications (APMs). Since at least the 1980s, however, the widespread use of APMs to manage behavioral problems has been questioned because of evidence that APMs offer minimal benefits as chronic treatment for behavioral problems, while posing significant risks including extrapyramidal symptoms, metabolic derangements, cardiac events, pneumonia, stroke, and death.[290-294] Non−drug strategies can often effectively address many behavioral issues with far fewer risks than drugs. In specific clinical circumstances, APMs may have a limited role, but such instances are far less common than would justify current levels of use.

BPSD overview

BPSD can range from behaviors that are merely annoying to those that endanger the patient and/or others. Apathy and sleep disturbances are most common, followed (in descending order) by depression, eating disorders, aggression, irritability, motor behaviors, delusions, anxiety, disinhibition, and hallucinations.[289] The symptoms with the greatest potential for harm are aggression, psychosis, and mood disorders.[287] This set of symptoms is often used as a single primary outcome measure in clinical trials for treatments of BPSD, which can make it difficult to assess the efficacy of a given treatment for specific BPSD symptoms.[287]

The term “agitation” is somewhat non-specific and may include verbal (e.g., screaming, cursing) and/or physical (e.g., hitting, biting, kicking) behaviors. It is helpful, when creating treatment plans, to be as

specific as possible about the targeted behavior. In addition, the term “psychosis” should not be seen as synonymous with the symptoms of schizophrenia; the psychosis that can accompany dementia is managed very differently than the psychosis of a primary psychotic disorder like schizophrenia.

Some BPSD symptoms fluctuate over the course of dementia, while others are more persistent. One study of patients with mild AD found that wandering and purposeless/inappropriate activities persisted or increased in severity over two years in about 85% of patients who had these symptoms, while paranoid ideation persisted in approximately 66% of the patients who had it.[295] Hallucinations and depressive symptoms were the least persistent symptoms: less than half of the patients with depressive symptoms still had the symptoms one year later. Depressive symptoms often occur in the early stages of dementia; as dementia progresses, other behavioral and psychological symptoms often come to predominate.[296]

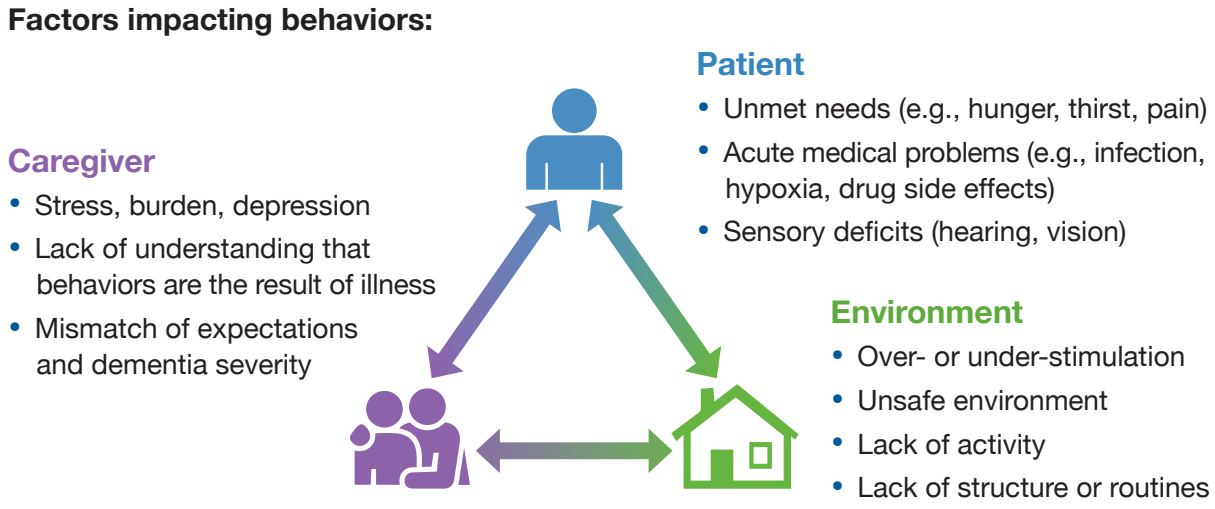
BPSD can sometimes be difficult to differentiate from delirium, which can cause similar symptoms but generally has an abrupt onset, with time-limited symptoms characterized by incoherent and disorganized speech, which may be provoked by a concurrent physical illness or medication/substance reaction.[19]

Acute vs. non−acute BPSD

Management of BPSD should be based on the characteristics and severity of the symptoms. Therefore, it is helpful to differentiate between two broad classes of BPSD: acute and non−acute. People with acute BPSD are in severe distress, may have severely disruptive or dangerous behaviors, and may pose an imminent danger to themselves or others. People with non−acute BPSD do not have symptoms that rise to this level of urgency. Instead, their symptoms may be inconvenient or annoying, may disrupt their functioning, or otherwise may erode quality of life. Non−acute BPSD calls for a different clinical and behavioral approach than acute BPSD, using a different spectrum and order of therapeutic options. APMs may sometimes be needed for management of crises caused by acute BPSD but are seldom appropriate for the ongoing management of non−acute BPSD.

One approach to handling patients with identified BPSD is “describe, investigate, create, and evaluate” (DICE). This approach was developed by a multidisciplinary panel of dementia care experts organized by the University of Michigan Program for Positive Aging to address interlinked risk factors at the level of patients, caregivers, and the environment (Figure 16).[297,298]

Figure 16: Potential causes of BPSD addressed in the DICE model[297]



Step 1: Describe. Elicit a thorough description of symptoms and the context in which they occur from caregivers and the person with dementia (if possible). Note possible antecedents or triggers, the symptoms that are most distressing or problematic, and treatment goals. (Note: if the situation poses a safety risk, consider a psychotropic drug to reduce harm.)

Step 2: Investigate. Search for potentially modifiable underlying causes of BPSD including clinical conditions, drug adverse effects, psychological issues, and environmental stressors. Include an evaluation of the caregiver's relationship with the person with dementia, their communication styles, expectations, estimations of the patient's abilities, and their level of stress. As above, if the situation poses a safety risk, consider a psychotropic drug to reduce harm.

Step 3: Create. Create and implement a treatment plan that targets identified causes with non-pharmacologic approaches and, if appropriate, pharmacological approaches. Include the person with dementia, if possible, in the plan creation, as well as caregivers.

Step 4: Evaluate. Assess whether the treatment plan was implemented effectively, whether targeted symptoms improved, whether the patient's and caregiver's distress were reduced, and whether there were any unintended consequences to any elements of the plan. Assessment should be ongoing, and if psychotropic drugs were prescribed, evaluate whether a dose reduction or discontinuation is possible.

Identifying potentially reversible triggers can be challenging if the patient's cognitive impairment is severe. Family and caregivers may be able to help by describing the patient's routine and normal level of functioning.

Adverse drug effects

Adverse drug effects are one of the most common reversible conditions in geriatric medicine, and many medications routinely used by older adults can cause or worsen behavioral and psychological problems.

For example, anticholinergic agents used for a variety of indications can increase the risk of visual hallucinations, agitation, irritability, delirium, and aggressiveness. Psychotropics, such as benzodiazepines, can impair cognition, be disinhibiting, and contribute to gait instability and falls. Identifying possible drug–related triggers for BPSD presents an opportunity to effect a cure by stopping the offending drug or lowering the dose. This has led to the recommendation that "any new symptom in an older patient should be considered a possible drug side effect until proven otherwise."[299]

BOTTOM LINE: Manage BPSD based on the characteristics and severity of the symptoms. People with acute BPSD are in severe distress, have severely disruptive or dangerous behaviors, and may pose an imminent danger to themselves or others. People with non−acute BPSD do not pose an emergency situation, although their symptoms may be inconvenient, may disrupt their functioning, or otherwise may diminish quality of life. Non−acute BPSD calls for a different clinical and behavioral approach than acute BPSD, using a different spectrum or order of therapeutic options.

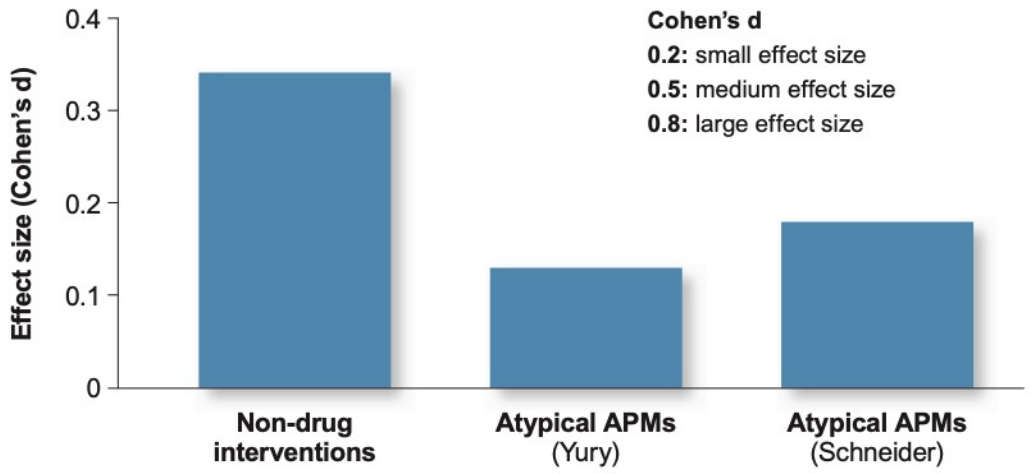
Non−drug management strategies

General principles

Non−drug management of BPSD can often produce equivalent outcomes, in a much shorter time, and at less risk than drug treatment, and is thus the first choice for managing behavior problems.[300] Although some studies of non−drug interventions are relatively small, un−controlled, or non−randomized, the evidence supporting the efficacy of non–pharmacological interventions is broad. In part, the apparent weakness of non-drug studies may reflect the relative lack of research funding for non−drug vs. pharmacologic interventions. In addition, many of the methodologies used in drug testing (e.g., blinding and random assignment) are more challenging in studies that test the efficacy of non−drug interventions. Many trials also use combinations of specific strategies, which can make it difficult to assess the quality of evidence for individual non−pharmacological interventions.

Effect sizes in studies of non−pharmacologic interventions for BPSD tend to be modest, although the same is true for effect sizes generally found in studies of the efficacy of APMs. In general, effect sizes for non−pharmacologic interventions are actually higher than those typical of drug studies. For example, a meta–analysis of 13 non−drug interventions for BPSD found a pooled–estimate standardized effect size of 0.34 (95% CI: 0.04–0.26; P=0.006).[300] This compares with a net effect size of 0.13 from a 2007 meta−analysis of studies comparing atypical APMs to placebo, and an effect size of 0.18 in a 2006 meta−analysis of APMs in the treatment of BPSD (Figure 17).[301,302]

Figure 17: Comparison of effect sizes for non-drug and drug interventions for BPSD[300-302]



Evidence for non-pharmacological interventions

Non−pharmacological interventions can target patients themselves, or those who care for them. Both types of interventions may reduce the incidence of BPSD and/or reduce caregiver burden. Interventions generally fall into three broad categories:

1. **Unmet needs interventions** assume that BPSD may sometimes represent a form of communication about an underlying need, such as for stimulation (e.g., repetitive speech or calling out as an expression of a need for auditory stimulation). Symptoms may also be a response to inadequately treated pain, other discomfort, or isolation.
2. **Learning and behavioral interventions** address the possibility that BPSD may be the product of unintentional reinforcement (e.g., a patient with dementia learns that he or she can get attention by screaming).
3. **Environmental vulnerability and reduced stress–threshold interventions** assume that some behavior problems result from a mismatch between the person's environment and their abilities to cope with the situation (e.g., a nursing home resident becomes agitated by too much noise or loud music).

Behaviors likely to respond to non−pharmacological interventions include: aggression, disruption, shadowing, depression, and repetitive behaviors. Non−pharmacologic interventions should be matched to the specific needs and capabilities of the patient, and they can be used concurrently with any medications that might be employed.[303-305]

Table 16: Evidence supporting non−pharmacological strategies for BPSD

Interventions supported by large, randomized or controlled clinical trials	
Staff or caregiver training/education programs	• Education in geriatric psychopharmacology for nursing home staff with goal of avoiding unnecessary psychoactive medications[306] • Planning activities with caregivers for their care recipients[300,307] • Modifying care recipient's physical and social environment (e.g., removing clutter, removing hazards, organizing, task simplification)[308,309] • Interdisciplinary skills training for nursing home staff[310]
Potentially helpful interventions supported by evidence from small, uncontrolled studies	
Environmental modifications[311,312]	• Support normal sleep/wake cycles • Structure activities to reduce boredom • Reduce unnecessary stimulation • Create home−like environment
Music therapy[313]	• Receptive music therapy (listening to music by a therapist who sings or selects recorded music for the recipients) • Active music therapy (recipients engage in music-making by playing small instruments, with possible encouragement to improvise with instruments, voice, or dance.) Also: music played when doing routine daily care, etc.
Bright light therapy[314]	• Exposure to simulated or natural lighting to promote circadian rhythm synchronization
Aromatherapy[315]	• Use of plant and herb-based essential oils (indirect inhalation via room diffuser, direct inhalation, aromatherapy massage, or applying essential oils to the skin)
Exercise plus caregiver training behavior modification[316]	• Home-based exercise program combined with caregiver training in behavioral management techniques
Pet therapy[314,317]	• Several small studies suggest that the presence of a dog may reduce aggression and agitation and promote social behavior in people with dementia
AI companions/pet robots[318]	• Increasingly being used but evidence to date is low-quality • Robots feasible and acceptable but costly • Problems include speech recognition issues and challenges interfacing with robots

As the disease progresses, patients with AD and related dementia typically have greater difficulty communicating with others. Here are some recommendations for communication strategies that may help prevent BPSD or help calm a patient in distress:[297]

- identify yourself and others if the patient does not remember
- explain what is happening, when it is happening, one step at a time
- use calm, reassuring tones
- ensure you can be heard
- avoid negative words and tone
- ask one thing at a time
- speak slowly

- allow the patient sufficient time to respond
- offer simple choices
- help the patient find words for self-expression, and confirm your own understanding of what has been said
- lightly touch to reassure, calm, or redirect
- use relaxing sensory stimuli, such as music or soft lighting if they enjoy it
- take time and allow silence, so the patient can process information

Management of physiological factors

A number of common though often−overlooked physiological factors may play a primary or contributing role in BPSD, and these should be explored whenever feasible before pharmacological interventions are attempted:[319]

- symptoms resulting from conditions such as
  - pain
  - constipation
  - nocturia
  - hunger or thirst
  - dehydration
- medical conditions such as
  - urinary tract infections
  - alcohol or substance misuse
  - hyponatremia
  - hyper– or hypothyroidism
  - hypercalcemia
  - vitamin B_{12} or folic acid deficiency

Dietary and eating−related issues should be carefully assessed. An inability to chew properly or swallow easily can increase agitation, and therefore a patient's dental integrity, use of dentures, and swallowing ability should be assessed. If a patient's appetite or cycle of hunger/satiety is not synchronized with the timing of meals provided, consider options to individualize the availability of food and/or food choice. Difficulty preparing or eating meals, confusion about mealtimes, apathy, agitation, and paranoid ideation about food and fluids may all contribute to weight loss, which is common in patients with dementia. Avoiding alcohol and caffeine can promote improved sleep.

Environmental strategies

Behavioral and psychological symptoms are often understandable responses to a wide range of factors that make life uncomfortable, frightening, worrisome, irritating, or boring for people with dementia. Paying close attention to such environmental factors, and eliminating or correcting them, should be the first priority for caregivers, whether in a home or an institution.[319] This requires patience, diligence, and a willingness to see the world through the eyes and other senses of the person whose behaviors are difficult. Because sensory deficits are common in older adults, and because vision and hearing deficits can increase fearfulness, anxiety, and agitation, any patient with non−acute BPSD should be assessed for these deficits. If present, these deficits should be corrected promptly with glasses, improved lighting, magnifying devices, hearing aids, or other approaches.

Other environmental factors that can worsen BPSD include: temperature (too hot or too cold), noise (in or outside the room or dwelling unit), lighting (too much, too little, or quality), unfamiliarity (new people, new furniture, new surroundings), disrupted routines, needing assistance but not knowing how to ask, being uncomfortable from sitting or lying in one position for too long, or inability to communicate easily because of language or speech difficulties.

Management of psychological factors

Patients with BPSD may benefit from psychological interventions such as individual, family, or group psychotherapy, depending on their level of cognitive functioning. Such interventions may help patients understand or express their feelings, correct or address cognitive errors or maladaptive thinking patterns, and suggest practical steps for changing behaviors or responses to different situations.

Dementia care management

Dementia care management is a collaborative care model integrating multi-professional and multimodal strategies to improve outcomes for dementia patients and caregivers including medication management and caregiver support and education. A meta-analysis of 13 trials evaluating the dementia care management model suggested some short-term improvements in patient and caregiver outcomes although the trials were too heterogeneous to allow strong conclusions.[320] A cluster randomized trial of general practices in Germany (n=634) found that a dementia care management approach reduced neuropsychiatric symptoms and modestly reduced caregiver burden after one year of follow-up.[321] A 2025 pragmatic trial involving 2,176 patient/caregiver dyads randomized to health system dementia care (NP or Pas) vs. community-based dementia care (social worker, nurse, therapist) vs. usual care found no treatment differences between groups in terms of cognition, functional status, or quality of life.[322]

BOTTOM LINE: Use non−drug interventions first for managing non−acute BPSD: focus on identifying and correcting any reversible environmental, psychological, or physiological factors that might be causing or contributing to symptoms, and then try specific approaches shown to be potentially helpful in addressing BPSD.

Pharmacologic management of BPSD

The evidence base for drug treatment of BPSD is generally modest. Until 2023, there were no FDA–approved medications for this indication.[323-325] The atypical antipsychotic brexpiprazole (Rexulti) is now approved for the treatment of BPSD, however no compelling evidence suggests that brexpiprazole provides increased benefit or reduced harm compared to other atypical antipsychotics.

There has been a dearth of guidance from large, randomized trials about medication use for BPSD.[326,327] As such, treatments have evolved anecdotally based on clinicians using many classes of medications off−label, including pain medications, cholinesterase inhibitors, NMDA modulators, antidepressants, anticonvulsants, dextromethorphan-quinidine, anxiolytics, and antipsychotics. What is clear from the evidence, however, is that some of these medications, particularly antipsychotics, can have serious harms.

If BPSD is not disruptive, dangerous, or distressing to the patient or caregiver (i.e., the patient has non–acute BPSD), medications are usually not warranted, although they may be indicated for non−BPSD

symptoms such as depression, anxiety, or psychosis. If a medication must be used, it is critical to focus on one or more specific target symptoms or behaviors. This kind of focus can provide a clear basis for ongoing monitoring and symptom re−evaluation.

Pharmacologic interventions are generally ***not*** warranted to address behaviors such as:

- wandering
- unsociability
- poor self–care
- restlessness
- nervousness
- fidgeting
- hoarding
- sexual disinhibition, if non-aggressive
- “sundowning” (increased confusion and restlessness in early evening)
- shadowing (constantly following or mimicking caregivers)
- uncooperativeness without aggressive behavior
- inattention or indifference to surroundings

Given the inherent difficulty of determining efficacy if multiple medications are used to address a given condition, any trial of a medication for BPSD should be completed with a single medication whenever possible. If the single medication works poorly, it should be discontinued after an adequate trial period, and an alternative medication should be initiated. Approaching prescribing judiciously can help prevent the unnecessary and potentially harmful accrual of multiple psychotropic agents (i.e., psychotropic polypharmacy) in a given patient. Assess suboptimal responses to determine whether the partial effect was due to developments other than the medication (e.g., a change in clinical status) or issues with adherence or dosing. Do not automatically assume that the medication should be continued and/or another medication added for additional effect. Before any medication is administered, inform patients (as feasible), family members, and/or caregivers of the possible risks of pharmacotherapy.

Psychotropic medications traditionally used for BPSD may cause a variety of serious adverse effects including confusion, falls, fractures, delirium, and over−sedation. Older patients are particularly vulnerable to injury from psychotropic medications because of slower metabolic clearance, increased central nervous system sensitivity, and reduced physiologic reserve. The FDA-approved medication for agitation, brexpiprazole, was associated with a number of side effects including nearly twice the rate of dizziness and somnolence compared with placebo.[326] In older patients, start with low doses of the medications and titrate to a minimal effective dose to reduce the likelihood of adverse events.

After starting a medication, monitor patients closely for both adverse effects and drug–drug interactions. If a medication is successful in addressing a specific target symptom, reassess the patient regularly and adjust dose accordingly, and try titrating the dose downward when it is safe to do so. Behavioral and psychological symptoms of dementia are subject to remission on their own, and patients may not need these medications for long periods, even if successful.

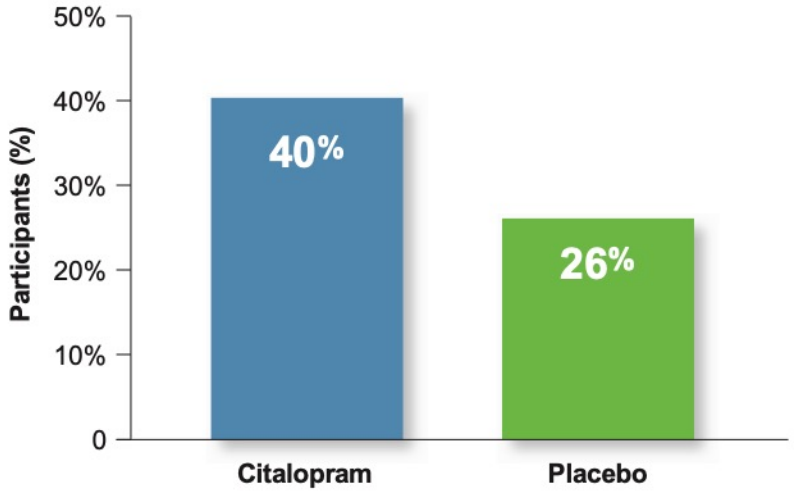
Antidepressants

Up to 40% of patients with dementia have substantial depressive symptoms at some stage of their illness, and some of the symptoms of depression (e.g., irritability, sleep disturbances) overlap with those of BPSD.[323] Alleviating depression in patients with dementia has been reported to lessen behavior

disturbances, improve activities of daily living, and reduce caregiver distress, although study results are mixed and effect sizes are small.[289] Recent systematic reviews found that evidence is of variable quality and does not provide strong support for the efficacy of antidepressants for treating depression in dementia.[328,329]

However, there is some evidence to suggest that antidepressants may be helpful for non-depression, non-acute BPSD.[325] Among the classes of antidepressants, selective serotonin reuptake inhibitors (SSRIs) have been the most widely studied. A Cochrane review of antidepressants for BPSD found modest evidence for efficacy and tolerability with sertraline and citalopram.[330] For example, a trial randomized 186 patients with AD and significant agitation to citalopram 30 mg or placebo for nine weeks. Improved scores on the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) scale showed that 40% of patients on citalopram compared to 26% of patients on placebo had moderate or marked improvement in severity of agitation in AD (Figure 18).[331]

Figure 18: Participants with AD and moderate or marked improvement in agitation[331]



Sertraline and citalopram appear to be tolerated reasonably well compared to placebo or antipsychotics.[330] Another review assessed 19 trials of antidepressants (including eleven trials with SSRIs and three trials with trazodone) for the treatment of BPSD. Effectiveness was demonstrated in 11 of the 19 trials and these agents were well−tolerated in 14 of the trials.[325] A 12−week randomized controlled trial in non–depressed patients with dementia showed that the SSRI citalopram was as effective as the antipsychotic risperidone in decreasing “psychosis” and agitation, with a better side effect profile.[332]

Citalopram now carries a warning about QTc prolongation, and the maximum dose recommended was reduced to 40 mg (20 mg in older adults).[333] Its S–isomer, escitalopram, was not found to be effective for agitation in a 2025 trial (N=143) and drug-related QT interval prolongation was observed in this study (7.2% in the escitalopram group compared to 2.5% in the placebo group for men (P=0.02) and 10% in the escitalopram group compared to 3% in the placebo group for women (P=0.04).[334]

A Cochrane review of two small trials of trazodone found that it was not more effective compared with placebo in controlling BPSD.[335] Another small randomized controlled trial compared the SSRI fluvoxamine and risperidone (n=60).[336] The medications were equally effective but the side effects were less severe with fluvoxamine and there was one sudden death on risperidone (probably due to a myocardial

infarction). Small trials of other SSRIs, including fluoxetine and paroxetine, for BPSD found minimal evidence that the drugs were better than placebo.[337-339]

It may be prudent to consider one or two trials of either sertraline or citalopram for non−acute BPSD, even in the absence of overt symptoms of depression, before proceeding to other medications. In using these drugs, it is important to be alert to the possibility of SSRI−induced adverse effects including:

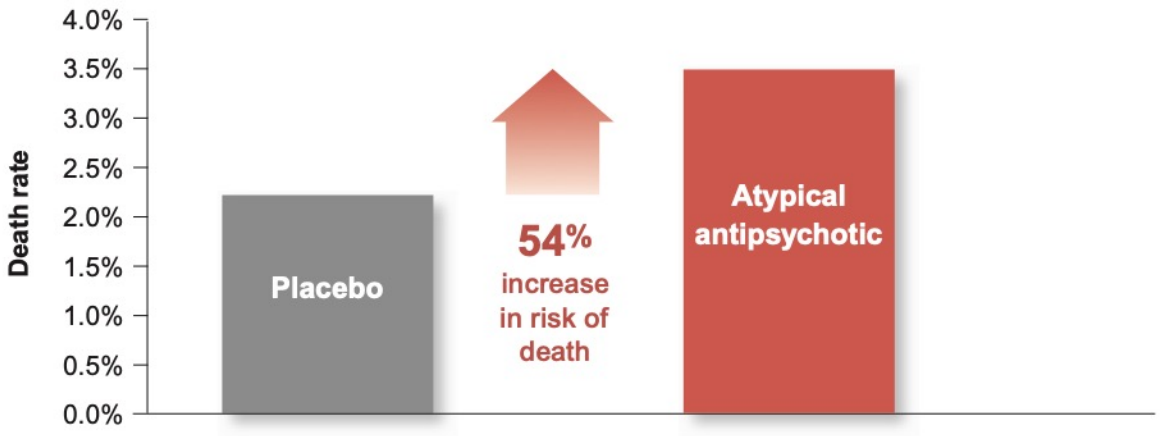
- syndrome of inappropriate antidiuretic hormone (SIADH) leading to hyponatremia, which is more common in older patients, especially those taking a thiazide diuretic[340,341]
- increased risk of upper GI bleeding in patients with other risk factors such as concurrent use of NSAIDs, anticoagulants, and antiplatelet agents[342]
- increased risk of falling and resulting fracture[343]

BOTTOM LINE: The antidepressants citalopram and sertraline appear to have favorable risk–benefit profiles for addressing non−acute BPSD. One or two trials of these medications should be the first−line approach after non−drug strategies have been tried. Before prescribing an SSRI for BPSD, rule out hyponatremia, review medications, and check for a history of GI bleeding.

Antipsychotic medications

APMs should be avoided in patients with non−acute BPSD until other interventions have been tried. They have minimal efficacy for the symptoms typical of non–acute BPSD and have a relatively high risk of side effects, including stroke and death.

Figure 19: Meta-analysis of 15 RCTs shows atypical APMs increase mortality risk at 12 weeks in patients with dementia[290]



Prior to the approval of brexpiprazole, there were no APMs approved in the U.S. for any BPSD symptoms despite at least 17 randomized controlled trials, most of them unpublished.[301] Meta–analyses of these previous studies indicated limited efficacy and significant potential for harm from side effects.[344] A Cochrane review had found some evidence that typical APMs might decrease agitation and psychosis slightly and that atypical APMs reduce agitation slightly.[345] However, the authors concluded that the apparent effectiveness of the drugs may be explained by the natural course of BPSD; simple sedation

may also account for some of their observed effects. A 2018 Cochrane review found low-quality evidence that discontinuation of antipsychotics seemed to have little or no important effect on BPSD, which the authors surmised may be because most BPSD are intermittent and do not usually persist for more than three months.[346] Thus, although APMs may help control acute BPSD in certain patients, they must always be used carefully.

Use APMs simultaneously with behavioral treatments, and only if potentially reversible or remediable causes have been ruled out. Indications include:

- physically aggressive or violent behavior that poses a danger to the patient or others
- hallucinations or delusions that are distressing to the patient, lead to dangerous behavior, or significantly impair normal functioning

If an APM is necessary, first try oral medication if the patient will accept it. In a non-cooperative agitated patient with acute BPSD, a parenteral agent may be indicated. Haloperidol may be used in an emergency situation, but it should not be used long-term.[236]

Typical antipsychotics

Reviews and meta-analyses of clinical trials involving typical antipsychotics (e.g., haloperidol, thioridazine, and chlorpromazine) in the management of BPSD found modest improvement in aggression over 3-8 weeks of treatment compared to placebo.[236,347-349] No consistent evidence shows that any one typical antipsychotic is more effective than another,[348] and there are insufficient data to draw conclusions about the efficacy of typical vs. atypical antipsychotics for BPSD.[350]

Discontinuation rates due to adverse effects were significantly higher with typical antipsychotics than with placebo,[348] and the troublesome adverse effects associated with typical antipsychotics (e.g., extrapyramidal side effects) limit their usefulness. Stroke risk also may be higher with typical antipsychotics compared to atypical antipsychotics.[351] Importantly, recent studies show that haloperidol use is associated with a 50-100% higher risk of death compared to other antipsychotics.[294] Chlorpromazine is no longer recommended for intramuscular treatment in emergencies with aggressive psychotic patients due to its risk of inducing severe hypotension.[352]

Atypical antipsychotics

The evidence base for the effectiveness of atypical antipsychotics for BPSD is generally weak, but at least some degree of confidence in efficacy exists for brexpiprazole, as well as non-FDA approved medications including aripiprazole (Abilify) and risperidone (Risperdal). Olanzapine (Zyprexa) and quetiapine (Seroquel) were not found effective in meta-analyses of their various published and unpublished trials.[226,301,353,354] However, an enduring challenge in interpreting the literature is the dearth of high-quality head-to-head trials examining atypical antipsychotics.

There have been three Phase 3 trials of brexpiprazole in patients with probable AD that all have similar inclusion criteria.[326,327] All patients were deemed eligible for pharmacotherapy and had an assessment of environmental factors, had prior trials of non-pharmacologic interventions (e.g., music therapy, group activities) and scored ≥4 on the Neuropsychiatric Inventory (NPI) agitation/aggression domain.

In total across the three studies, 1048 patients (range of 270-433 patients per trial) were randomized to two different dosing strategies: fixed dose or flexible dose. Patients were followed for 12 weeks in all three studies, and the primary outcome measure was the Cohen-Mansfield Agitation Inventory (CMAI),

which quantifies the frequency of 29 agitation behaviors on a scale of 1-7 based on caregiver response, yielding a score from 29-203.

Doses of brexpiprazole 0.5 mg and 1 mg were no different than placebo. Moreover, the Cohen's D for higher-dose brexpiprazole (2 mg and 3 mg) versus placebo was 0.25, which indicates a relatively small to moderate effect size in line with the standardized effect estimates from other trials exploring the impact of antipsychotics on agitation.[300-302] The changes on the CMAI for all doses were well below the minimal clinically important difference.

Taken together, the effect sizes are relatively modest and similar to those of select other APMs (such as risperidone and aripiprazole). Furthermore, the side effect profile of brexpiprazole appears similar to other APMs. As such, it is unlikely that brexpiprazole represents an APM with a unique mechanism of action for controlling agitation in patients with AD, despite it being the only one in the class to have an FDA approval for this indication.

The **Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD)** study compared the effect of atypical antipsychotic drugs (olanzapine, risperidone, or quetiapine considered together as a group) vs. placebo in 421 outpatients with AD on psychiatric and behavioral symptoms, functional abilities, cognition, care needs, and quality of life over 12 weeks.[355] There were no significant differences between the antipsychotic and placebo groups in measures of cognition, functional skills, care needs, or quality of life, except for worsening of functional skills in the olanzapine treatment group compared to placebo.[355]

The atypical antipsychotic pimavanserin (Nuplazid) may alleviate symptoms of Parkinson's disease psychosis without worsening motor symptoms because it acts on serotonin 5HT2A receptors with no appreciable affinity for dopaminergic receptors.[356] The 2021 **HARMONY** trial employed an open label phase for 12 weeks of pimavanserin in patients who have psychosis with AD, Parkinson's disease dementia, dementia with Lewy bodies, frontotemporal dementia, or vascular dementia.[357] Following the open-label phase, those who had a reduction from baseline of at least 30% in the psychosis score were then randomly assigned to pimavanserin or placebo for up to 26 weeks. The rate of relapse of psychosis was lower in the pimavanserin vs. placebo groups (13% vs. 28%, respectively). However, the effect was driven largely by those with Parkinson's disease dementia, and adverse events were more frequent in the pimavanserin group vs. placebo (41% and 36.6%, respectively) with headache (9.5%) and urinary tract infection (6.7%) being the most common. To date, the FDA has withheld a label for pimavanserin for dementia-related psychosis.

Withdrawal of antipsychotics

Antipsychotics should be tapered slowly to minimize the risk of a withdrawal syndrome (unless significant adverse effects or a drug interaction necessitates abrupt cessation). A reduction in antipsychotic dose by 25−50% every two weeks (splitting pills, if needed, to keep the taper slow) and ceasing medication after two weeks on the minimum dose, is generally recommended. Close attention should be paid to behavior in response to reducing doses, since as previously noted one study of patients with AD showed an increased risk of relapse of psychosis and agitation when risperidone was discontinued.[324] Evidence-driven deprescribing resources and algorithms for antipsychotic discontinuation are available at deprescribing.org

Steps for responsible APM prescribing when it is required:

1. Identify and document the behavior being targeted (e.g., physically aggressive behavior, hallucinations, etc.).
2. Start a trial of APM for a limited duration (e.g., 4 weeks).
3. Start at the lowest dose and gradually titrate to response while monitoring side effects.

Drug	Starting dose	Maximum dose
aripiprazole	2-5 mg	15 mg
brexpiprazole	0.5 mg	3 mg
olanzapine	1.25-5 mg	10 mg
quetiapine	12.5-25 mg	300 mg
risperidone	0.25-0.5 mg	2 mg
paliperidone	1.5 mg	3-6 mg

4. Evaluate the drug effect on the targeted behavior and discontinue if efficacy is weak or side effects are problematic.
5. Once the behaviors/situation is stable, attempt gradual dose reduction while monitoring for recurrence of BPSD symptoms.

BOTTOM LINE: Due to their substantial risks and weak evidence for efficacy, APMs should be used rarely and with considerable caution for non−acute BPSD. APMs may, however, be required to control acute episodes of aggression, self-harm, or dangerous psychotic symptoms. Any benefits of treatment must outweigh the well–established risks, including potentially increasing mortality.

Other pharmacological options for BPSD

Benzodiazepines and similar drugs

Avoid the long–term use of benzodiazepines and similar−acting medications (e.g., zolpidem) in the treatment of both acute and non−acute BPSD, because the risks of these agents may outweigh their benefits in patients over 60.[358] They may cause or exacerbate a range of problems including:[358,359,]

- cognitive impairment
- rebound insomnia (i.e., if taken as needed, patients sleep worse on the nights that they omit it than if they had taken placebo)[360]
- falls
- accidents
- paradoxical agitation
- physical dependence with regular use[361]
- aspiration and its consequences
- death[362]

A low-dose short-acting benzodiazepine can be considered for specific anxiety-provoking activities (e.g., bathing).

Pain medications

Randomized controlled trials have shown that daily pain assessment and a step-wise approach to the use of pain medications may reduce BPSD in patients with moderate to severe dementia in nursing homes.[363,364] A 2011 study of 352 nursing home residents cluster randomized to a stepwise pain treatment protocol including acetaminophen and opioid analgesics reduced agitation by 17% compared to control, with no difference in functional status and cognition, over an 8-week trial.[363] A 2022 Cochrane review, however, found no clear evidence of benefit in an algorithm-based pain management intervention compared to pain education for reducing pain intensity or challenging behavior (although the 2011 study was not included in this Cochrane review).[365]

Cholinesterase inhibitors and memantine

Although some studies of cholinesterase inhibitors and memantine have found small, statistically significant beneficial effects on BPSD as measured by the Neuropsychiatric Inventory and other scales, the clinical significance of these changes is unclear. A 2008 meta-analysis found that treatment of BPSD with cholinesterase inhibitors produced only a very modest benefit limited to patients with mild AD (NPI: -1.92 points [MCID ≤4] in patients with mild AD vs. -0.06 points in patients with severe AD).[366] An updated 2015 review found a small improvement in NPI scores, but also significantly higher study drop-out due to adverse effects.[367] In patients with mild to moderate vascular dementia, cholinesterase inhibitors showed no behavioral or functional benefits, except for a minimal difference on the Alzheimer's Disease Functional Assessment and Change Scale.[368] Rivastigmine may modestly improve BPSD (in particular visual hallucinations) in patients with dementia with Lewy bodies.[369]

The situation for memantine is similar. A 2008 post-hoc pooled analysis of six RCTs of patients with moderate to severe AD found small but statistically significant beneficial effects of memantine on the NPI in treatment and prevention of symptoms such as delusions, hallucinations, disinhibition, irritability, agitation, and aggression.[370] Another pooled analysis of three RCTs showed similar results.[371] However, these effects were so small as to be not considered clinically meaningful.[348]

Dextromethophan-quinidine (Nuedexta)

Nuedexta is a patented combination of two older components: dextromethorphan, (the d-isomer of a sedating semisynthetic morphine derivative) and quinidine (an antiarrhythmic that can cause potentially dangerous QTc prolongation). (Note: this combination is not FDA-approved for the treatment of BPSD, and is instead FDA-approved for pseudobulbar affect, a condition of emotional lability associated with neurologic conditions such as amyotrophic lateral sclerosis, multiple sclerosis, and dementia.)

Anecdotal evidence and limited trial data led to this medication’s assessment for the management of agitation associated with AD. An industry-sponsored phase II trial randomized 220 adults with AD to dextromethorphan-quinidine or placebo.[372] In the primary analysis patients randomized to dextromethorphan-quinidine had reductions of 1.5 to 1.8 on the 12-point NPI agitation/aggression score ($P<0.001$), perhaps attributable in part to the sedating properties of dextromethorphan. However, the combination did not significantly improve quality of life ($P=0.16$) or activities of daily living ($P=0.16$).

Both components in this drug carry the risk of important drug-drug interactions: dextromethorphan taken with any one of several antidepressants can cause a life-threatening serotonergic syndrome, and quinidine, if taken with one of scores of medications that also prolong the Q-T interval, can produce dangerous and potentially fatal arrhythmias.

In the phase II trial described above 61.2% of patients given the combination of drugs had adverse events vs. 43.3% for controls. In the treated group, serious adverse events included femoral fracture, myocardial infarction, and stroke. One common adverse event was falling, which occurred in 8.6% of treated patients vs. 3.9% of those given placebo. Overall, a lack of well-demonstrated benefit and an increase in adverse events compared to placebo limits its usefulness.

Other medications with limited evidence of efficacy for BPSD

The anticonvulsants gabapentin[373] and carbamazepine have been studied in uncontrolled case series or short-term trials in patients with BPSD, with mixed results.[348,374] These agents might be considered at a low dose and in a time–limited trial for dementia–related agitation/aggression if other interventions have been exhausted, with close monitoring for response, adverse effects, and drug interactions.[236,375]

Prazosin (Minipress, Vasoflex, others) is an alpha–1 receptor antagonist used primarily in the treatment of benign prostatic hypertrophy. This class of drugs might have some role in some patients with BPSD, especially to reduce agitation and aggression. A small (n=22) placebo–controlled 8−week study of prazosin found that patients in the treatment group had significantly more improvement on two agitation rating scales, with no differences between the groups in blood pressure or adverse events (at a mean dose of 6 mg).[376] This study needs replication with larger samples of patients.

Several agents have some limited support from case studies and case reviews for the treatment of patients with aggressive sexual disinhibition in whom medical and medication causes have been ruled out. These include SSRI antidepressants (first choice), anti–androgens, luteinizing hormone-releasing hormone (LHRH) agonists, or estrogen.[377,378,]

Investigating the possible relationship between decline of melatonin function and the symptoms of dementia, a Cochrane review of three randomized controlled trials of melatonin therapy found little benefit in the scores on tests of cognition. There was, however, some improvement in behavioral and affective symptoms in patients taking melatonin (2.5 mg/day).[379]

Fall risk with psychoactive drugs

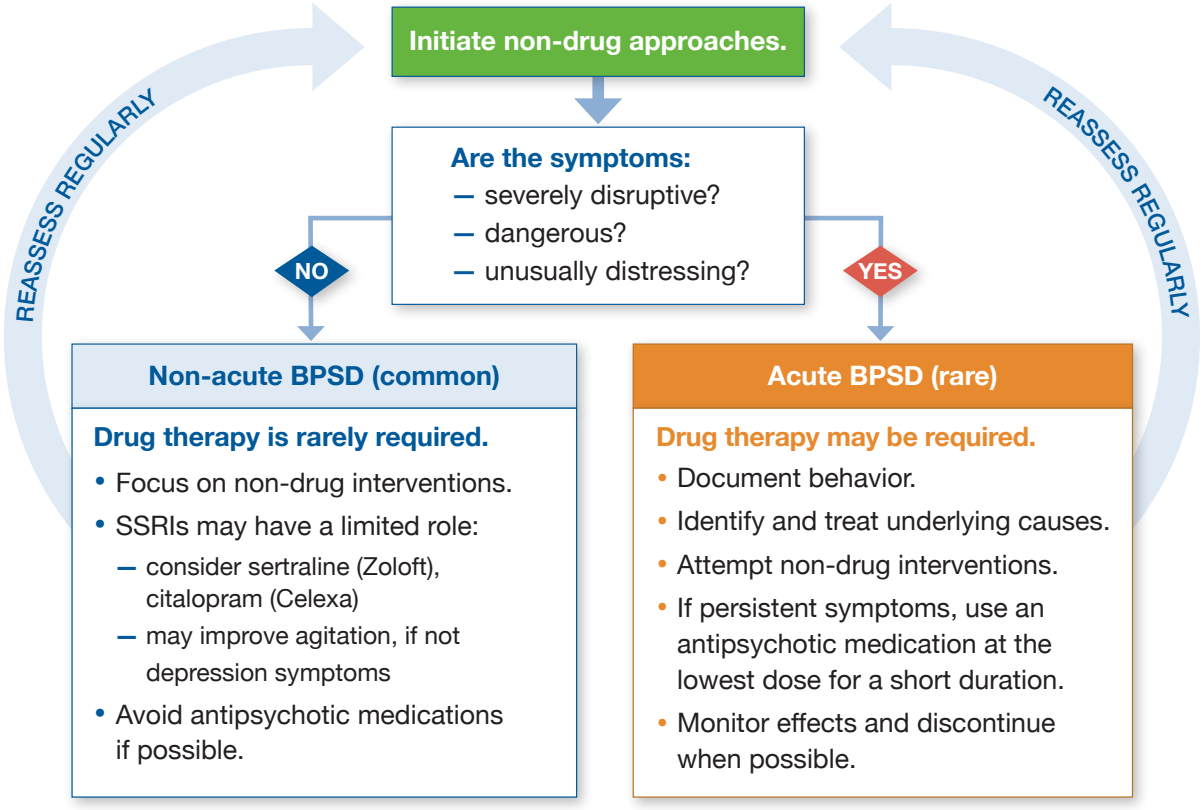
Most of the drug classes reviewed above have been shown to increase the risk of falls, both in the initiation phase and with long-term use in older adults (Table 17).

Table 17: Fall risk with psychoactive drugs used for BPSD[380-382]

Long-term use	Odds Ratio	95% Confidence Interval
Antidepressants (SSRIs, SNRIs, TCAs)	1.72	1.40-2.11
Antipsychotics (typical, atypical)	1.71	1.44-2.04
Benzodiazepines	1.60	1.46-1.75
Sedative/hypnotics	1.31	1.14-1.50
Initiation		
Benzodiazepine plus antipsychotics	11.4	1.50-89.0
Non-SSRI antidepressant (e.g., tricyclics)	4.70	1.30-16.2
SSRI antidepressant	0.80	0.20-3.40

In managing BPSD, follow the general principles summarized in Figure 20 below.

Figure 20: Algorithm for managing BPSD[297]



BOTTOM LINE: To manage BPSD, first rule out reversible causes or triggers. Identify specific target behaviors and set realistic goals for change. Initiate non-drug interventions and continue even if drug treatment is added. Initiate non-APM drug interventions (e.g., SSRI antidepressants) for non-acute BPSD. APMs may be warranted for acute severe BPSD or non-acute BPSD that does not respond to other measures.

Supporting patients with cognitive impairment

A diagnosis of dementia can induce substantial fear about what the future holds for both patients and their families. Direct but compassionate communication about the diagnosis and what can and cannot be predicted is essential to allay concerns, set realistic expectations, and promote an engaged, safe lifestyle.

Although existing treatments for dementia are far from satisfactory, appropriate use of available interventions can have a substantial positive effect on the well−being of patients.[383] In some cases, this could mean the difference between the ability to continue living independently and the need for institutional care.

Consultations with medical, neurological, or psychiatric subspecialties may be helpful, depending upon the circumstance. Geriatric psychopharmacologists, geriatric psychiatrists, neuropsychiatrists or behavioral neurologists can provide guidance with respect to the use of medications.

Social workers and nurses with expertise in dementia may be well equipped to help in a variety of ways. They can offer strategies for dealing with specific or recurrent problematic situations; provide psychotherapy when appropriate; provide guidance about services such as day programs, home services, respite care, and dementia care units; provide guidance about financial and legal planning; and make referrals to community resources. Information and support are also available through non−profit organizations such as the Alzheimer's Association (alz.org), the Association for Frontotemporal Degeneration (theaftd.org), the Lewy Body Dementia Association (lbda.org), CurePSP (psp.org), and other disease−specific groups.

One general approach to managing patients with dementia is Dementia Care Mapping™ (DCM).[384] Developed at the University of Bradford, England, DCM is a process of improving the quality of person-centered care over time. Caregivers are encouraged to consider care from the point of view of the person living with dementia and to continually monitor the health and wellbeing of patients, changing care dynamically in response to observations and feedback. (For more information see: https://www.bradford.ac.uk/dementia/training-consultancy/dcm/)

Managing a patient with dementia requires the clinician to focus on present issues while keeping an eye on preparations for the future (Figure 14). A patient's wishes pertaining to end of life care and surrogate medical and financial decisions should be discussed early on (generally before a moderate stage of dementia is reached) while he or she has the capacity to make informed decisions in these areas, (see section on advance care planning below). Legal consultation with an elder law attorney may be appropriate, particularly for patients who have shared assets with a living spouse or partner.

Advance care planning for dementia

Advance care planning (ACP) is a continuous, dynamic process of reflection and dialogue between people with dementia or other serious illness and those close to them, and with their health care providers, about preferences and values related to end-of-life care. The goal is to ensure that the medical care a patient receives is aligned with his or her values and wishes and avoids unwanted or unnecessary treatments (e.g., feeding tubes, emergency department visits, and hospitalizations). Although they are both collaborative endeavors, ACP differs from shared decision-making in that ACP is focused on future treatment and care, whereas shared decision making is focused on making a current decision about treatment. ACP also typically involves the creation, or amending, of such documents as living wills, power of attorney, and health care proxies.

Although many patients and practically all health care professionals know about ACP, most people have not completed the most common documents involved in ACP. Even among people with dementia, 30% of patients had no ACP documentation at the time of their death.[385] A systematic review of 150 studies with nearly 800,000 patients found that only 37% had completed advance directives, 29% had a living will, and 33% had defined health care proxies.[386] The completion rate for advance directives was similar between those with chronic illnesses and healthy adults. However, a more recent study found that patients with dementia completed ACP less frequently and might be more likely to receive higher-intensity end of life care than those with cancer.[387]

ACP documents such as advance directives and health care proxies should be written when the person still has legal capacity, and completed as soon as possible following a diagnosis of dementia (if not already done). Because laws vary from state to state, advance directive forms must be appropriate to and recognized by the state in which care is being or will be provided.

Because research shows that ACP conversations are not often initiated by the person living with dementia, health care professionals should take it upon themselves to do so. A diagnosis of dementia should not automatically be equated with such a loss of mental capacity that a conversation about advance care is not possible.[388] Discussions about advance care should include descriptions of the kinds of issues common in dementia, such as loss of cognition, reduced physical functioning, swallowing problems, and infections. Documents that may be involved include do not resuscitate (DNR), do not intubate (DNI), and do not hospitalize (DNH) orders.

Explore the person's disease awareness and expectations and their ideas about their disease trajectory. If the person lacks awareness or is reluctant to talk about end-of-life issues, do not insist. Instead, explore their perceptions of what quality of life means to them, and ask about any fears or concerns about the future. Try to understand the whole person by exploring their life story, values, norms, and preferences.

In discussing advance care, it can be helpful for clinicians to know the typical pattern of dementia progression, particularly for issues related to pneumonia and eating difficulties. Data from a cohort study of 323 nursing home residents with advanced dementia (global deterioration scale stage 7) followed for 18 months found that complications are very common by the end of follow-up.[389]

Table 18: Events experienced in past 18 months by nursing home residents with advanced dementia[390]

Events	18-month incidence
Eating problems	86%
Death	55%
Febrile episodes	53%
Pneumonia	41%
Burdensome interventions in last 3 months of life (e.g., tube feeding, ER visit)	41%

Attempt to solicit from patients their preferences for end-of-life care, which can range from "comfort only" (symptomatic treatments and palliative care/hospice) to "life prolongation" (hospitalization and life support) or some in-between level of care, and recognize that these preferences may change with time, hence requiring repeated inquiries. Patients should also identify health care agents who can make the patient's wishes known in the event that they are incapacitated and unable to do so.

Table 19: Goals of care applied to two common dementia-related issues[389]

Goals of care	Pneumonia	Eating problems
Comfort	Antipyretics and oxygen	Palliative hand feeding (may not provide sufficient calories)
Life prolongation	Hospitalize for life-prolonging treatment, including mechanical ventilation and ICU care	Tube feeding (Note: professional societies recommend against tube feeding because it does not improve survival, malnutrition, or rate of aspiration)
In-between	Antibiotics, while avoiding hospitalization	Palliative hand feeding with aspiration precautions

Providing patients with clear, visual information about the realities of advanced dementia and the differences between comfort care and life prolongation care can improve their experience. A 2017 trial randomized 302 dyads of nursing home residents with advanced dementia and their decisionmakers to either a video focused on goals-of-care and a structured discussion about ACP, vs. a general information video and usual care.[391] After nine months of follow-up, those in the intervention group reported better quality of communications, greater goal concordance (88.4% vs. 71.2%, P=0.001), and fewer hospital transfers (RR 0.47; 95% CI: 0.26-0.88).

Hospice care, either in-home, in a dedicated hospice facility, or in some other setting, provides comfort-focused support, symptom relief, and an emphasis on quality of life in the last phase of life. Proxies of people living with dementia enrolled in hospice report improved care satisfaction and better psychosocial outcomes compared to those not enrolled in hospice.[392] To be eligible for the Medicare hospice benefit, patients must be at or beyond FAST Stage 7 (i.e., be unable to walk, dress, or bathe without assistance; have intermittent or constant urinary or fecal incontinence, and have no consistently meaningful verbal communication) as well as at least one of the following medical conditions in past year:

- aspiration pneumonia
- pyelonephritis
- sepsis
- decubitus ulcer (multiple, stage 3-4)
- recurrent fever after antibiotic treatment
- inability to maintain sufficient fluid/caloric intake with 10% weight loss during previous 6 months or albumin <2.5 g/dL

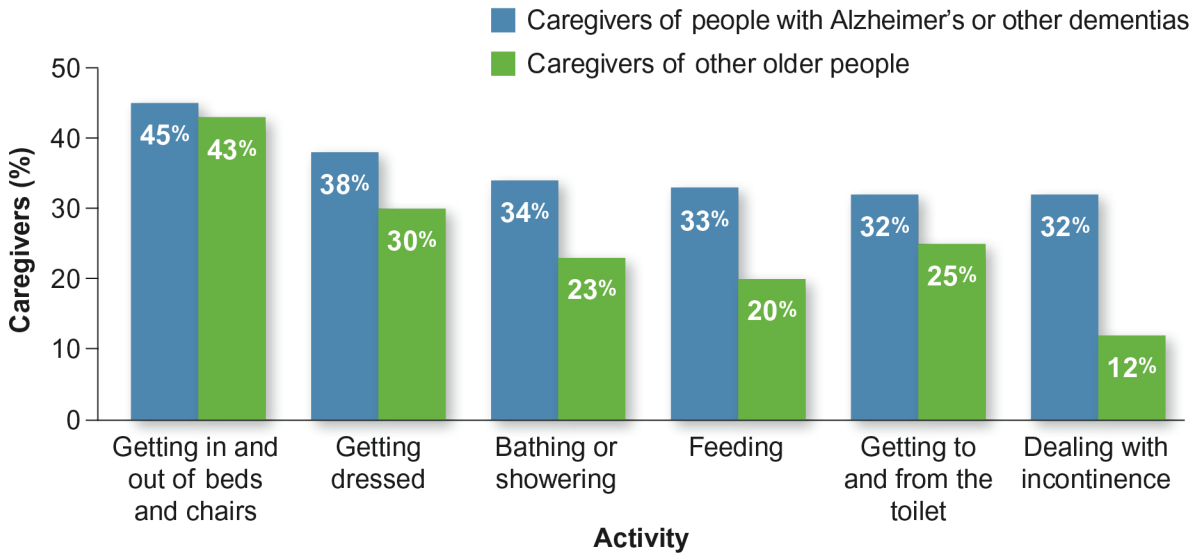
BOTTOM LINE: Advance care planning is a dynamic, continuous process to ensure goal-concordant care in patients with dementia. Start conversations early, discuss the expected clinical course, and identify treatment preferences and goals of care.

Caregiver support

More than 11 million family members and friends provide unpaid care for a person with AD or another dementia in the United States.[393] The effectiveness of long−term management of patients with dementia

is largely dependent on these caregivers. It is therefore important for clinicians to assess the role and needs of the caregiver and be prepared to offer support and referral to other professionals, organizations, or resources that may help them remain healthy. Caregiver burden is a real and common concern.

Figure 21: Common community caregiver tasks[153]



Caring for a person with AD can be very demanding, and these caregivers are at increased risk for depression and illness.[394] In a study of 254 caregivers of patients with AD, 85% reported some degree of depression, and 84% felt that caring for the elder was a burden.[395] These factors can also increase the chances that an elder will be abused.

In a study of 220 caregivers of community-dwelling older adults, a range of negative or abusive behaviors toward the person being cared for were self-reported by caregivers, including yelling or screaming at the person or threatening them with sending them to an institution. Some of these caregivers reported they were afraid they might hit or hurt the care recipient.[396]

Ideally, caregivers would receive assistance in their responsibilities, periodic assessment of their own health and welfare, support from family and friends, and respite care, but this often does not occur. A variety of psychosocial and pharmacological interventions have shown mild to modest efficacy in mitigating caregiver burden and distress. In meta-analyses, psychosocial interventions (e.g., support groups or educational interventions for caregivers of dementia patients) have shown positive effect sizes ranging from 0.09-0.23.[397] Pharmacologic interventions for the person with dementia (e.g., use of anticholinergics or antipsychotic medications) show caregiver effect sizes ranging from 0.18-0.27. Many studies have shown improvements in caregiver burden-associated symptoms (e.g., mood, coping, self-efficacy) even when caregiver burden itself was minimally improved.[397]

Teaching caregivers how to change or modify their interactions with the patient can be effective.[316,398] For example, caregivers can be taught communication skills such as: not interrupting, allowing time for responses, minimizing distractions, speaking slowly, and avoiding talking about the patient as though he or she is not present.

Caregivers need to understand that nursing home placement or extensive in−home services might be needed at some point and that this should not be considered a failure on their part.[399] Discussing the benefits and disadvantages of institutional care with caregivers can be challenging, particularly in cases in which the patient has previously expressed a desire to avoid such care. It can be helpful to remind caregivers that earlier comments may have been made without a full appreciation of the current circumstances, and that expectations almost always change with chronic illnesses.[400] Stressed or "burned−out" caregivers cannot provide the best care, and decisions that avoid this situation can therefore be in the patient's best interest.

It's also important to help caregivers understand that just because a person's memory is failing, his or her emotional responsiveness may well remain intact.[401] People with even severe declarative or short−term memory loss have been found to continue to feel the emotions of an event even after they have forgotten the event itself.[401] They may continue to feel sad from an upsetting event, for example, or happy after a positive event. Thus, a visit or telephone call from a family member might have a lingering positive influence on a patient's mood even if the patient quickly forgets the visit or call.

Some suggestions for supporting caregivers and reducing their stress include:[397]

- engage the caregiver as a member of the care team.
  - ask about caregiving problems, health status, and elder abuse
- encourage the caregiver to ensure their own self-care.
  - suggest respite care and home meal delivery service to relieve caregiver
- provide education and information.
  - offer skills training about safe transfer, support groups, and social worker help
- encourage use of technology (e.g., mobility monitors, lift systems for transfers).
- refer for assistance with care (e.g., Alzheimer's Association, Best Programs for Caregiving at bpc.caregiver.org, home care services).

Guiding an Improved Dementia Experience (GUIDE) model

Starting in 2024 and running for eight years, this program from the Centers for Medicare & Medicaid Services incentivizes comprehensive care coordination for patients with dementia and their caregivers. GUIDE programs provide care navigation support, caregiver training and education, connections to community resources and a respite care benefit. The aim is to delay nursing home placement, improve quality of life for patients and caregivers, and reduce expenses.

To be eligible for GUIDE programs, patients must:

- have a diagnosis of dementia
- be enrolled in traditional Medicare A and B plans
  - Patients with Medicare Advantage plans may have access to similar programs
  - The LIFE program in Pennsylvania provides similar services, and patients using this benefit are not eligible for GUIDE
- Not be living in a long-term nursing home.

Clinicians typically refer eligible patients to active GUIDE programs. Patients and caregivers may also request access directly by contacting GUIDE programs in their area. Links to resources and materials about GUIDE can be found at AlosaHealth.org/Dementia.

Considerations for people with cognitive impairment living alone

Clinicians should be aware that many older adults with cognitive impairments or dementia live alone and do not have family members or informal caregivers to support them. It is estimated that one in four older adults with cognitive impairments live alone.[402] A qualitative study of 76 clinicians, social workers, and other professionals found that many factors make serving older adults living alone with cognitive impairment more challenging than serving those living with others.[403] One of those challenges is the fact that, as evidenced in one study of 1,569 older adults with cognitive impairment living alone, nearly half used high-risk medications such as opioids, insulin, or anticoagulants.[404] When helping patients who live alone, consider having a home safety evaluation conducted, suggest they wear a fall alert monitor, and help people get electronic medication dispensers to reduce risks of medication errors.

BOTTOM LINE: Caring for a person with dementia is demanding and raises the risk for physical and mental disorders in the caregiver. Family and other caregivers need support and attention from primary care providers, social workers, and other health care professionals to maintain their own health and to be able to continue caring for the person with dementia. Health-care providers need to pay special attention to, and, as possible, provide additional supports for, those with dementia without a local reliable caregiver.

Putting it all together

Accurately diagnosing dementia in patients with either suspected cognitive impairment or known risk factors is essential to facilitate timely interventions, which may improve health and overall quality of life. The chief roles of health care professionals are:

- to look for and address any underlying or reversible causes of cognitive impairment, including drug side effects
- to counsel and educate patients and caregivers about non-pharmacological and pharmacological interventions that can reduce stress and anxiety and optimize safety and quality of life
- to address exacerbating factors in those with dementia, such as concurrent medical conditions and adverse drug effects, that can worsen the underlying cognitive decline
- to counsel patients and caregivers regarding the expected course of dementia, facilitate advance care planning, and ensure goal-concordant care

Primary care providers play a pivotal role in the diagnosis and care of people with dementia. They are frequently the point of first contact with the healthcare system and often remain a key source of ongoing care throughout this challenging long-term illness.

Universal screening for cognitive impairment is not necessary. For those with symptoms or who have risk factors for dementia, the short cognitive tests and functional questionnaires reviewed in this document can reliably identify cognitive impairment and dementia beyond what can be learned from a standard routine history and physical examination alone. Such testing can identify patients who should undergo more detailed evaluations by neurologists or other specialists for further workup, and perhaps to assess whether a patient is a candidate for monoclonal antibody treatment, despite its limited efficacy, important risks, and substantial patient-caregiver burden.

Non−pharmacological strategies can help support functional status and preserve quality of life for both patients with dementia and their caregivers, and these should be fully explored given their lack of adverse effects. Medications such as cholinesterase inhibitors and memantine may modestly reduce cognitive decline and non-cognitive symptoms of dementia in some patients. Given the small benefits and frequent side effects of these drugs, caution is advised in their use, with limited duration of therapeutic trials guided by regular assessment of response. Unfortunately, in most cases, this determination is unavoidably subjective.

Goals in managing patients with behavioral and psychological symptoms of dementia include identifying and modifying triggers and initiating non−drug interventions first in most patients. If medication treatment is necessary, consider non-opioid pain management, SSRI antidepressants, cholinesterase inhibitors, or memantine, as appropriate in the individual patient. Antipsychotic medications should be used only if there is a risk of the patient harming themselves or others, and alternative therapies are unsuccessful. Frequent reassessment of the need for ongoing medication as well as monitoring for specific side effects are critical.

Appendix I: Advance care planning reimbursement

Clinicians can be reimbursed for advance care planning as either an optional element of a patient's wellness visit (same day/same provider) or as a separate Medicare Part B "medically necessary service" (deductibles and coinsurance apply). No additional co-pay is required for ACP conversations held as part of an annual wellness visit. Billable advance care planning can be provided in any setting, including telephone or telehealth visits, and the patient does not have to be present (i.e., discussions can be with a family member of surrogate). Special rules apply for Federally Qualified Health Centers, Rural Health Clinics, and patients enrolled in hospice.

Table 1: CPT codes for advance care planning

CPT Codes	Billing Code Descriptors
99497	Advance Care Planning including the explanation and discussion of advance directives such as standard forms (including the completing of such forms, when performed), by the physician or other qualified health professional; first 30 minutes, face-to-face with the patient, family members, and/or surrogate
99498	(add-on) Each additional 30 minutes (List separately in addition to the code for the primary procedure)

Table 2: ACP minutes and corresponding CPT codes and units

ACP minutes	CPT codes
15 or less	Don't bill any ACP services
16 – 45	CPT code 99497 (1 unit)
46 – 75	CPT code 99497 (1 unit) and CPT code 99498 (1 unit)
76 – 105	CPT code 99497 (1 unit) and CPT code 99498 (2 units)

Here are some tips for documenting ACP conversations:[405,406]

- There are no limits on the number of times you can report ACP for a given patient in a given time period – but reimbursement for annual wellness visits are limited to once per year
- Briefly summarize the conversation
- The amount of detail needed is proportional to the length and complexity of the conversation
- Document the starting and stopping times and names of participants
- Note any ACP forms that were completed
- No diagnosis is required, but reference the diagnostic code for a serious illness if applicable

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