PACE Pharmaceutical Assistance Contract for the Elderly

Alosa Health
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Dealing with cognitive impairment

Prevention, management, and advance care planning

Dealing with cognitive impairment:

Prevention, management, and advance care planning

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The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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

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Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians and other healthcare providers.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits™.* Clinicians should claim only the credit commensurate with the extent of their participation in the activity.

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 or other types of dementia. 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 (BPSD), and reviews best practices for advance care planning.

The education program has several components, which include:

1. Written evidence report (print monograph)
2. Summary document of 4-5 key messages
3. "Academic detailing" educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
4. Reference cards for easy access to key materials
5. Patient education information (brochure/tear off sheets)

Its goal is to critically review and synthesize the most current clinical information on these topics into accessible, non-commercial, evidence-based educational material, to be taught interactively to providers by specially trained clinical educators.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family medicine, and geriatrics, and other health care professionals who deliver primary care.

Learning Objectives:

Upon completing this activity, participants will be able to:

- Describe the risk factors for dementia and evidence around interventions to prevent cognitive impairment
- Identify patients with cognitive impairment, rule out reversible causes, and optimize overall health
- Design a series of conversations to establish and update an advance care plan for patients with dementia
- Recommend treatment of dementia with cholinesterase inhibitors or memantine based on severity, and monitor for side effects to determine treatment course
- Identify causes of behavioral and psychological symptoms of dementia, establishing a plan to address causes with non-pharmacologic options, reserving antipsychotic medications for distressing or dangerous circumstances.

Disclosure Policy:

Harvard Medical School has long held the standard that its continuing medical education courses be free of commercial bias.

In accord with the disclosure policy of the Medical School as well as standards set forth by the Accreditation Council for Continuing Medical Education, course planners, speakers, and content reviewers have been asked to disclose any relevant relationship they, or their spouse or partner, have to companies producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients. In addition, faculty have been asked to list any off-label uses of pharmaceuticals and/or devices for investigational or non-FDA approved purposes that they plan to discuss.

Such disclosure is not intended to suggest or condone bias in any presentation, but is elicited to provide the course director and participants with information that might be of potential importance to their evaluation of a given presentation.

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The following committee members from Harvard Medical School's Continuing Medical Education program also reviewed this educational activity: John Kevin Tucker, MD; Jane Segilson Sillman, MD; Morgan Soffler, MD; Raul Gonzalez, MD; James Burns, MD; Molly Hayes, MD; Mary Lou Townsend, MEd; Gyorgy Baffy, MD, PhD; and Michiya Nishino, MD, PhD. None of these committee members have any relevant financial relationships to disclose.

Media used:

Printed educational material.

Instructions for Participation and Credit:

There are no fees to participate in this activity. To receive credit, participants must (1) read the statements on target audience, learning objectives, and disclosures, (2) study the educational activity, and (3) complete the post−test and activity evaluation. To receive *AMA PRA Category 1 Credit*™, participants must receive a minimum score of 70% on the post−test.

Tests and evaluations should be submitted to Alosa Health via email, mail or fax.

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The activity will take approximately 1.5 hours to complete.

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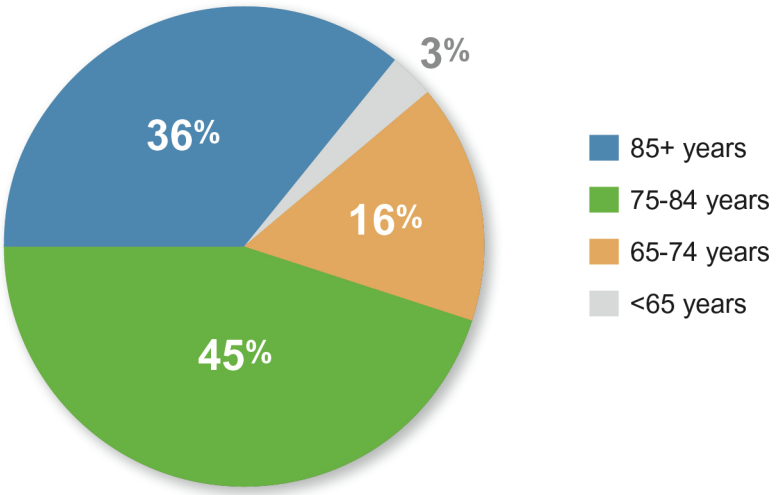
Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

Table of Contents

The challenge of Alzheimer's disease

As of 2019, an estimated 5.8 million people have Alzheimer's dementia (AD) in the U.S., with prevalence increasing with age.[1] One in 10 people over the age of 65 has AD with prevalence rising to 1 in 3 in people over age 85 (Figure 1).[1] Mild cognitive impairment (MCI), an intermediate stage on the spectrum between normal cognitive aging and dementia, is also common, with estimated prevalence of 15%−20% in adults aged 65 and older.[1]

Figure 1: Ages of people with Alzheimer's disease in the US, 2016[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, from 11.6% in 2000 to 8.8% in 2012.[2] The reasons for this trend are unclear, but could be related to better management of comorbid conditions such as hypertension, diabetes, and obesity. Nonetheless, the rise in the total population of older adults will drive a steady increase in the numbers of people experiencing Alzheimer's disease and other dementias in coming decades.

Primary care clinicians must be adept at evaluating older adults for dementia or MCI and be prepared to manage cognitive impairment and related medical issues, maintaining 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, provides recommendations about screening and evaluation, and summarizes current evidence for both preventing future dementia and managing current dementia with non-pharmacological and pharmacological approaches. This activity also provides detailed guidance about ways to manage behavioral and psychological symptoms of dementia (BPSD), which are very common and often challenging for medical providers and non-professional caregivers.

The spectrum of cognitive impairments

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 memory (i.e., the ability to recall general facts and concepts, vocabulary, and language) and procedural memory (i.e., how to perform mental or physical tasks of daily living).[3] Cognitive skills that typically decline with age include: episodic memory (i.e., remembering where objects are and the "what," "where," and "when" of daily life); processing speed; ability to learn new information; and the ability to multi-task or shift between tasks.[3]

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 tests, but not serious enough to interfere with daily life, although greater effort, compensatory strategies, or accommodation may be required.[4] 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, general medical illness vs. being a herald of dementia caused by underlying neuropathology, is uncertain in any given patient. Nonetheless, patients with MCI nearly always progress to more severe levels of dementia, and greater cognitive impairment at the time of MCI diagnosis is associated with faster progression.[5] Clinical studies of older adults with MCI reveal a relatively rapid conversion to a diagnosis of AD (14%-19% per year.[6,7]

Dementia[*] is a syndrome involving impairment in cognitive functioning that interferes with a person's ability to carry out usual activities. It can involve impairments in: (1) memory; (2) language; (3) reasoning, judgment, and handling of complex tasks (i.e., executive dysfunction); (4) higher−order perceptual/motor functioning; and/or (5) personality, behavior, or comportment. Dementia is not diagnosed when changes in cognition and function can be accounted for by a reversible physiological condition (i.e., dehydration, urinary tract infection, or drug side effect), an acute state of confusion, delirium, or another mental disease (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 can vary widely.

Types of dementia

AD is the most common, but not the only, cause of dementia. The cardinal features of the major types of dementia are summarized in Table 1 (following page).

[*] 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. The key feature of NCDs is that the primary clinical deficit is in cognitive function is acquired rather than developmental.

Table 1: Major types of dementia[1,4]

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 (mixed−picture dementia).
Vascular dementia (VD)	Between 5% and 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. Progressive subcortical small vessel ischemia may cause slow progression.
Dementia with Lewy bodies (DLB)	5%−10% of dementia cases	Involves any 2 of the following: visual hallucinations, parkinsonism or 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.
Frontotemporal dementia (FTD)	< 10% of cases of dementia	Early changes in personality (disinhibition, apathy, loss of empathy) and/or language (primary progressive aphasia).	Apathy, emotional blunting and disinhibited behaviors may make it difficult to differentiate from depression or bipolar disorder.
*Prevalence figures do not sum to 100% because of the wide variability in prevalence estimates and the possibility that patients may experience more than one type of dementia simultaneously.			

Dementia can also be a secondary manifestation of a range of conditions, including:[4]

- traumatic brain injury
- substance abuse or medication side effects
- HIV
- Huntington's disease
- Parkinson's disease
- prion disease
- normal pressure hydrocephalus
- chronic traumatic encephalopathy (see below)

Delirium

In contrast to dementia, delirium is an acute, reversible mental disorder characterized by impaired attention, disorganized thinking, and an altered level of consciousness.[4] Delirium generally follows a rapidly waxing and waning course. Other 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.[4]

To distinguish delirium from dementia, establishing the time course is critical by obtaining collateral information about cognitive function prior to the acute presentation. 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 result in improvement in the delirium.

Although delirium is distinct from dementia, patients with dementia are at higher risk of developing delirium. Delirium may also herald the onset of MCI or dementia, in that 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.

Chronic traumatic encephalopathy (CTE)

Alzheimer's disease and CTE have long been recognized as sharing some similar neuropathological features, mainly the presence of neurofibrillary tangles and hyper-phosphorylated tau proteins, but have generally been described as distinct entities. Neurotrauma has been associated with an increased risk of developing dementia and accelerates the progression of disease.[8] The diagnosis of CTE requires a prior history of neurotrauma (generally repetitive), and the demonstration of specific neuropathological features, namely tauopathy. CTE has been diagnosed in individuals with extensive exposure histories, ranging from traditional impact-acceleration injuries to blast exposure. People at highest risk include football players, wrestlers, boxers, and soldiers.

Symptoms reported retrospectively by family, friends, and colleagues, following the diagnosis of CTE fall into four domains: mood, behavior, cognition, and motor.[8] Mood disturbances such as irritability, depression, and apathy are common in CTE. Behavioral changes are also common including, but not limited to, impulsivity, aggression, and judgment issues. Sometimes these behavioral changes are associated with violent outbursts. Cognitive changes can be severely debilitating. Short-term memory loss and learning deficiencies are frequently reported. Motor deficits, particularly in older subjects, include decreased reaction time, eye movement disorders, and recurrent falls.

As with Alzheimer's disease, no disease-modifying treatments exist for CTE, the emphasis being on prevention by avoiding repeated head trauma and/or using protective equipment.

Risk factors for cognitive impairment

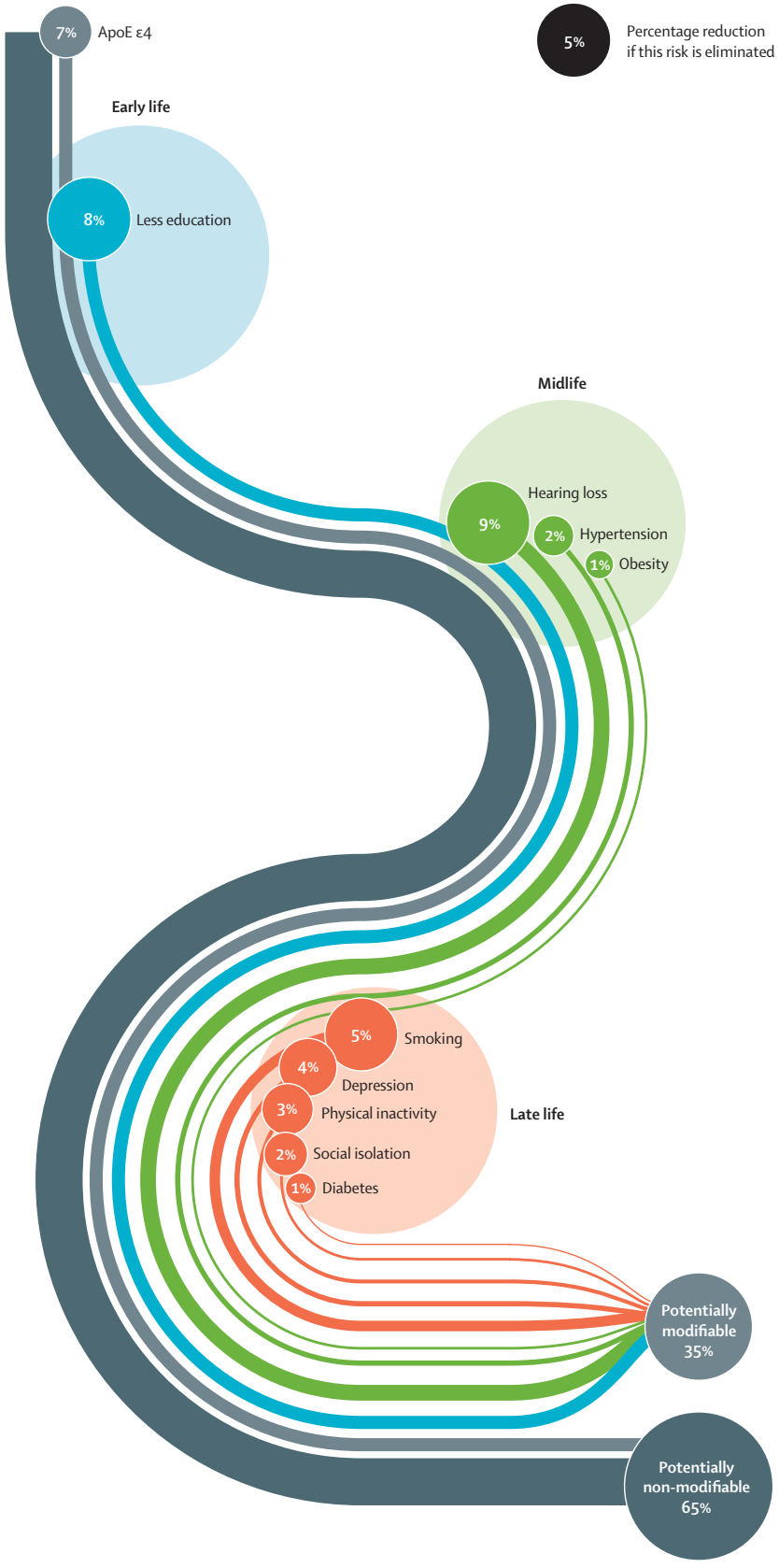
Many conditions and diseases increase the risk of cognitive impairment and dementia. Genetic, environmental, and lifestyle risk factors play interrelated roles. Non−modifiable risk factors for dementia include:

- older age
- family history
- female sex
- Down syndrome
- lower IQ
- genetic factors (e.g., APOE4)

Potentially modifiable risk factors for dementia have been getting increasing attention as research has shown how significant such factors can be, and with the recognition that effective prevention efforts will still be needed even if disease-modifying treatments eventually emerge. One recent systematic review and meta-analysis estimated that about 35% of dementia is attributable to a combination of nine potentially modifiable risk factors (see Figure 2 on following page):[9]

- education only to ages 11 or 12 (limited educational attainment)
- midlife
  - hearing loss
  - hypertension
  - obesity
- later-life
  - smoking
  - depression
  - physical inactivity
  - social isolation
  - diabetes (both Type 1 and Type 2)

Figure 2: Percentage reductions in risk of dementia for modifiable risk factors across the lifespan[9]



Additional potentially modifiable risk factors include:

- adverse drug effects
- excessive alcohol consumption or other forms of substance use disorder
- poor nutrition
- thyroid, kidney, or liver disease
- cardiac disease, including coronary artery disease and heart failure

The following sections summarize the evidence base for the modifiable risk factors included in Figure 2.

Education

Higher levels of educational achievement may be linked with lower risks 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.[10] 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:[2]

- 12 years: 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.[11]

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.[12] Hearing loss was associated with a greater risk of dementia in a meta-analysis of three studies (RR 1.94; 95% CI: 1.38-2.73) which is the highest of the mid-life risk factors.[9]

Blood pressure control

The harmful effects of hypertension on cognitive function were recognized as early as the 1960s, when a study on psychomotor speed among air traffic controllers and pilots demonstrated reduced performance in individuals with hypertension.[13] Hypertension has been associated with reduced abstract reasoning (executive dysfunction), slowing of mental processing speed, and, less frequently, memory deficits.[14]

Although Alzheimer's dementia and vascular dementia have traditionally been considered distinct entities, evidence suggests that these conditions often coexist.[15] In an analysis of 4,629 individuals with AD, 80% showed evidence of vascular pathology and 32% had a diagnosed cerebrovascular disease (some patients had both conditions).[16] Hypertension disrupts the structure and function of cerebral blood vessels, leads to ischemic damage of white matter regions critical for cognitive function, and may promote Alzheimer pathology.[17]

Consistent evidence shows an association between hypertension in midlife with altered cognitive function in both midlife and late life.[17] The association of blood pressure (BP) in late life with cognition is less clear, with evidence of both harmful and beneficial effects of high BP on cognition. 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 not conclusive. The 2019 Systolic Blood Pressure Intervention Trial (**SPRINT-MIND**) tested the effect of more intensive blood pressure (BP) control on cognitive outcomes in persons without diabetes or preexisting stroke.[18] 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 no significant difference in the rate of newly-diagnosed dementia was observed (146 cases in the intensive group vs. 176 cases in the standard group; HR 0.83; 95% CI: 0.67-1.04), but the rate of mild cognitive impairment was modestly lower in the intensive group (14.6 vs. 18.3 cases per 1000 person years; HR 0.81; 95% CI: 0.69-0.95).[18]

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 starting many years before clinical onset. A combination of pre-dementia apathy, loss of initiative, and reduced olfactory function could explain this association.[19]

Exactly how obesity might contribute to dementia risk remains poorly understood. Obesity in midlife and at older ages is associated with brain atrophy.[20,21] Evidence also suggests that a variant of the fat mass and obesity-associated (FTO) gene affects brain structure, causing deficits in the frontal and occipital lobes.[22] Obesity is also likely to influence cognition through its impact on vascular risk factors and pathology.[23]

An analysis of data from the UK 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.[23] A similar pattern was found in a systematic review and meta-analysis of 13 studies found that having obesity below the age of 65 years had a positive association on incident dementia (RR 1.41; 95% CI: 1.20–1.66), but the opposite was seen in those aged 65 and over (RR 0.83; 95% CI: 0.74–0.94).[24] The authors of this study speculate that the findings may reflect the fact that maintaining one's weight, even if it's overweight, is a marker of health, whereas unplanned weight loss in later years may reflect a decline in health.

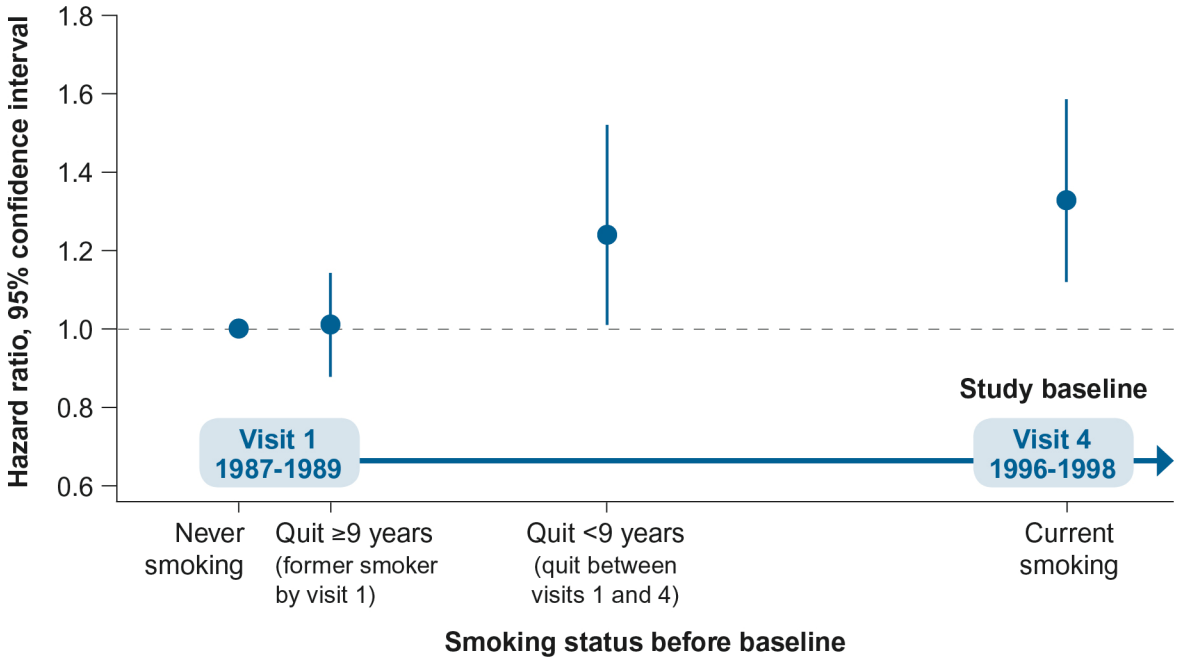
Smoking

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.[25] Observational data support an association between current smoking and dementia or cognitive decline,[26] although the extent of the contribution of smoking to dementia and cognitive decline 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).[27] Participants who quit smoking more than nine years before baseline had no significant increase in dementia risk compared to never-smokers.

Figure 3: Association between smoking status and risk of dementia[27]



Depression

Depressive symptoms can be a part of the clinical presentation of dementia, which can blur the causal relationship between the two conditions. 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.[28] The mechanism is likely to be multifactorial, as depression is linked to cerebrovascular pathology, and affects stress hormones, neuronal growth factors, and hippocampal volume.[29]

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).[30]

Social isolation

A growing body of evidence suggests that social isolation is a risk factor for dementia and it increases the risk of associated risk factors such as hypertension, coronary heart disease, and depression.[9] Social isolation may also result in cognitive inactivity, which is linked to faster cognitive decline and low mood.

Longitudinal studies suggest that social interaction may prevent or delay dementia but there is a lack of intervention study evidence that social activity prevents cognitive decline or dementia. People who live alone, have never married, are divorced or widowed have an increased risk of all-cause dementia.[31] A recent meta-analysis of social activity found that incident dementia risk was elevated for people with more limited social activity participation (RR 1.41; 95% CI: 1.13-1.75) and less frequent social contact (RR 1.57; 95% CI: 1.32-1.85).[32] The relatively short follow-up period in some studies precludes strong conclusions about the direction of causation.

Diabetes

Observational studies have long suggested that patients with diabetes have an elevated risk of developing AD, but the relationship has not been clear. Diabetes contributes to vascular dysfunction, which increases stroke risk, but in autopsy studies, patients with diabetes don't have more amyloid plaques or tau tangles than people without diabetes.[33]

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).[34] 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).[35]

Exercise and physical activity

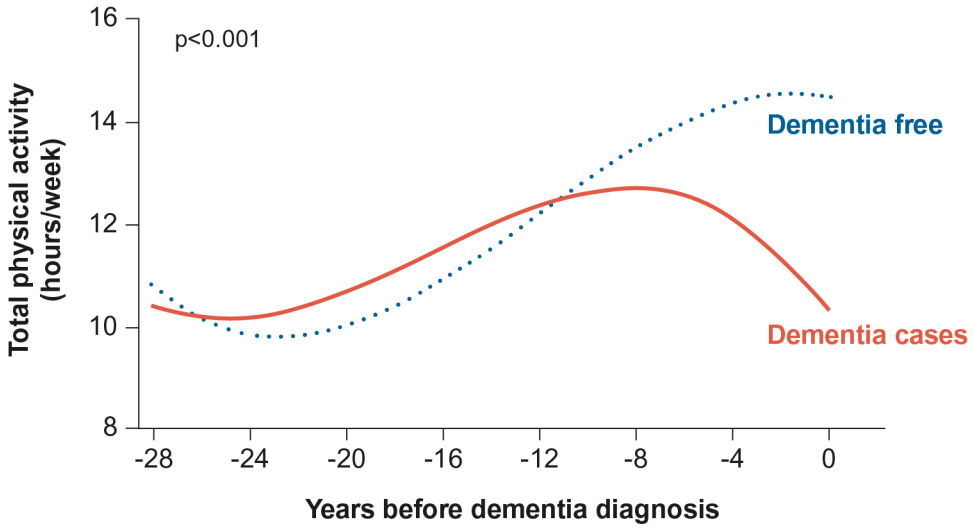
The potential mechanisms for physical exercise to improve cognition or prevent dementia are indirect effects on other modifiable risk factors such as obesity, insulin resistance, hypertension, hypercholesterolemia and general cardiovascular fitness. There may also be direct neurological effects such as increased neurogenesis, cerebral blood flow, and levels of brain derived neurotrophic factor.[36]

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

One meta-analysis of 15 prospective cohort studies following 33,816 individuals without dementia for 1-12 years, found that physical activity was negatively associated with cognitive decline, with high levels of exercise being the most protective (HR 0.62; 95% CI: 0.54-0.70).[37] In this study, even low-to-moderate exercise appeared beneficial (HR 0.65; 95% CI: 0.57-0.75). Another meta-analysis of 16 studies with 163,797 participants without dementia found that participants in the highest physical activity groups (compared to those in the lowest-activity group) had a significantly lower risk of AD (RR 0.55; 95% CI: 0.36-0.84).[38]

However, a recent 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 (Figure 4). In fact, physical activity in people with dementia began to decline up to nine years before diagnosis.[39]

Figure 4: Reduced physical activity in years prior to dementia diagnosis[39]



Randomized trials of exercise interventions for cognition in healthy older adults have been less successful than might have been expected in light of the positive associations seen in longitudinal cohort studies. Recent meta-analyses have either reported no overall evidence that exercise improves cognition in healthy older adults,[40] or that benefits are limited to specific cognitive domains. A 2014 meta-analysis reviewed 25 studies of aerobic exercise, resistance training or tai chi.[41] Fifteen of these 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 vs. 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 control (two studies, 156 participants).[41]

A 24-month trial with 1,766 sedentary older adults without cognitive impairment did not show 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) or talks about health education with 10 min. of stretching weekly (Table 2).[42]

Table 2: Cognitive outcomes in a trial of physical activity[42]

Outcome	Physical activity		Health education		Odds ratio	p-value
	# / total	%	# / total	%	(95% CI)	
Mild cognitive impairment	70/686	10.2	62/682	9.1	1.14 (0.79-1.62)	0.48
Dementia	28/743	3.8	29/747	3.9	0.96 (0.57-1.63)	0.88
Mild cognitive impairment or dementia	98/743	13.2	91/747	12.1	1.08 (0.80-1.46)	0.61

Anticholinergic medications

Anticholinergic drugs (e.g., some antihistamines, antidepressants, and medications for gastrointestinal and bladder disorders) can have short-term adverse effects, including confusion and memory loss in older people, and some evidence exists for long-term adverse effect on cognition.[43]

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.[43] The greatest risk were associated with antipsychotics and bladder antimuscarinics, and the population attributable fraction of these medications for dementia is 10%.[9]

Benzodiazepines

Many observational studies have examined the relationship of benzodiazepine use and dementia risk, with mixed results and a frequently-acknowledged limitation that reverse causation may explain the observed associations (i.e., that benzodiazepines may be prescribed for prodromal symptoms of dementia such as anxiety or insomnia). However, 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 associated with a significantly increased risk of dementia (OR 1.39; 95% CI: 1.21-1.59).[44]

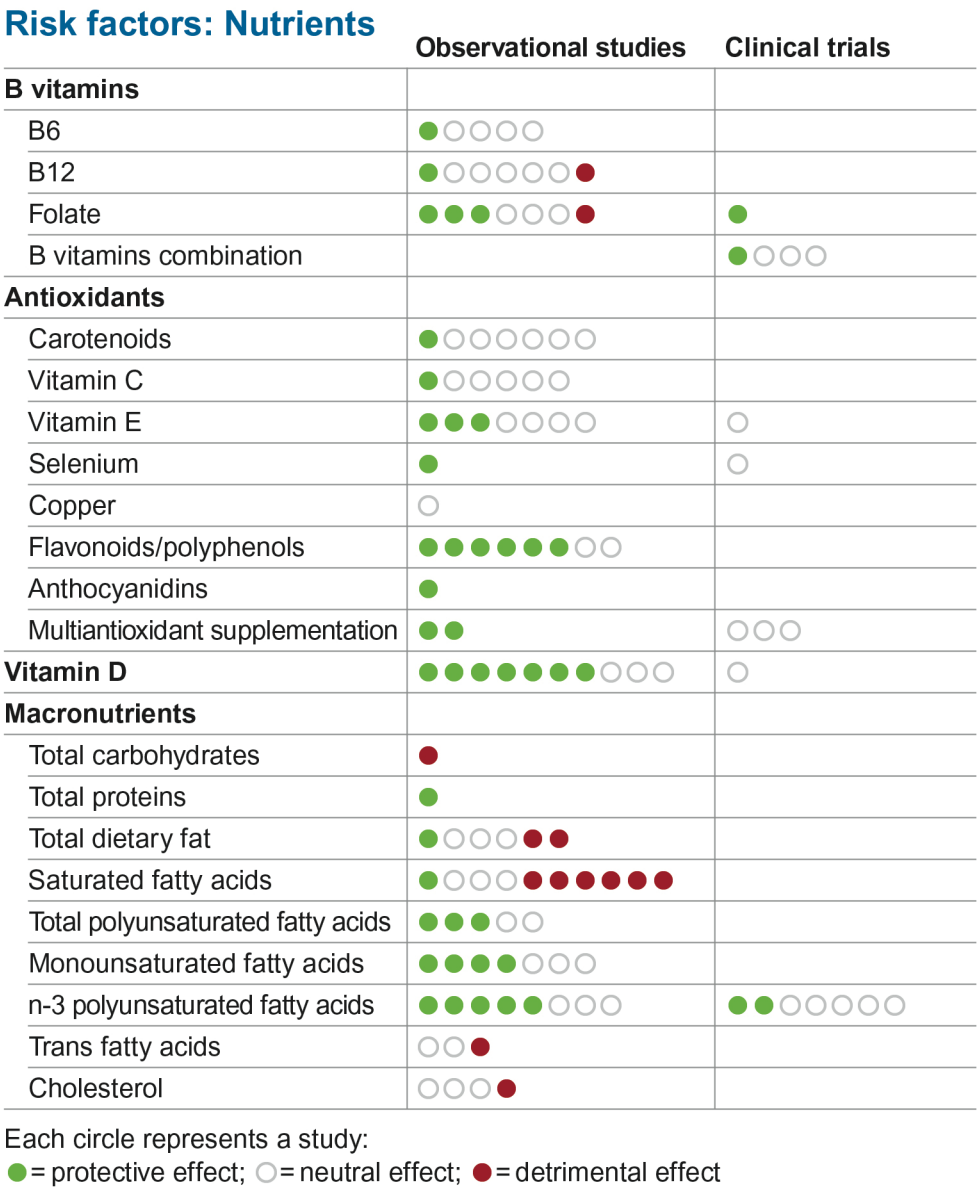
Benzodiazepine deprescribing

Deprescribing benzodiazepines (i.e., tapering supervised by a health care professional) can involve substitution of other drugs (e.g., melatonin or trazodone), 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%.[45] 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.[46] 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.[46]

Nutrients

A wide range of vitamins, antioxidants, and macronutrients have been examined for potential roles in either contributing to, or protecting from, dementia. As illustrated in Figure 5, most studies have been observational, some with conflicting results. The few clinical trials that have been conducted suggest a protective effect for folate, B-vitamin combinations, and omega-3 polyunsaturated fatty acids found in flaxseed and fish (also known as n-3 polyunsaturated fatty acids).[47]

Figure 5: Observational studies and clinical trials of nutrient roles in dementia[47]



Food and dietary factors

Figure 6 (on the next page) summarizes the mostly observational evidence for the effects of various beverages, foods, and dietary patterns on dementia risk. Clinical trial data show protective effects for olive oil, nuts, and a Mediterranean diet.[47]

Figure 6: Observational studies and clinical trials of nutrient roles in dementia[47]

Risk factors: Food and diet

	Observational studies	Clinical trials
Alcohol		
Moderate total intake vs abstinence	●●●●●●●○	
Moderate vs high total intake	●●●	
Moderate wine consumption	●●●●●○	
Moderate beer consumption	○○●●	
Moderate other spirit consumption	○○○○●	
Coffee and tea		
Coffee	●●●●●○○○○	
Tea	●●○○○○	
Caffeine	●●●○	
Food groups		
Fish and seafood	●●●●●○○	
Meat	○○	
Vegetables	●●●●●	
Fruits	●●○○	
Fruits and vegetables	●●●	
Juices	●○	
Legumes	○○	
Dairy	●●●	
Olive oil		●●
Nuts		●●
Dietary patterns		
Mediterranean diet	●●●●●●●●●●○○○	●●○
DASH diet	●●○	
MIND diet	●●●●	

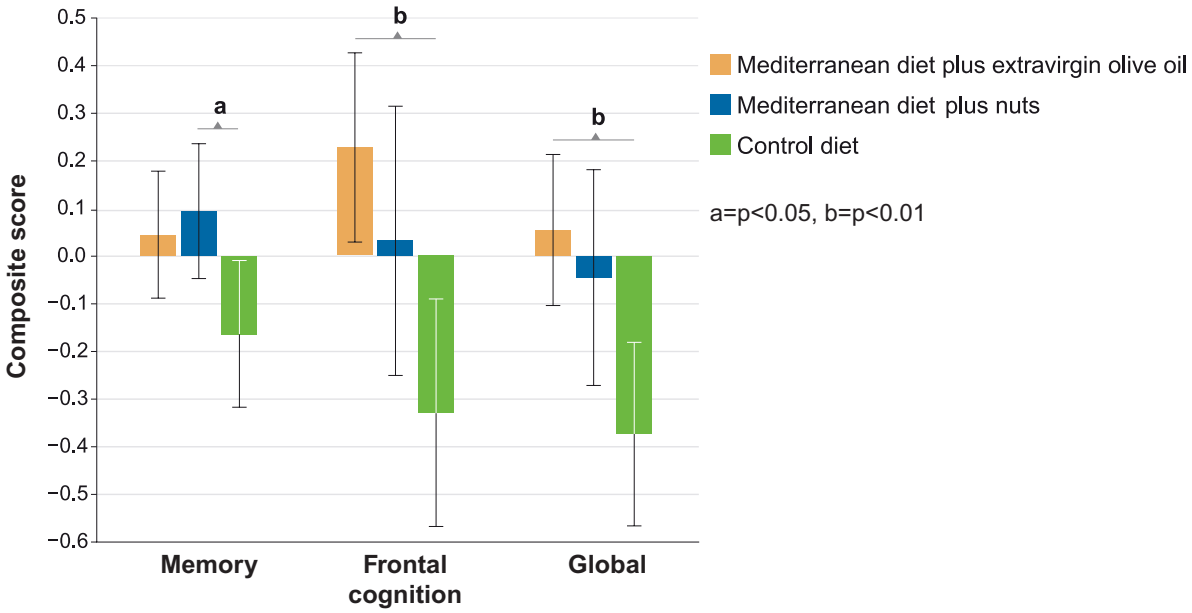
Each circle represents a study:
●= protective effect; ○= neutral effect; ●= detrimental effect

DASH=Dietary Approaches to Stop Hypertension; MIND=Mediterranean-DASH Intervention for Neurodegenerative Delay.

Adherence to a Mediterranean−type diet may be associated with slower cognitive decline in individuals diagnosed with MCI. These findings, however, are often based on observational studies.[48-50] An example is a retrospective study of 482 patients with MCI followed for a mean of 4.3 years, which 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.[48]

The **PREDIMED** trial of 447 cognitively healthy people randomized to three dietary groups (Mediterranean diet plus olive oil; Mediterranean diet plus nuts; and a control diet) with a median follow-up of 4.1 years found improvements in memory and frontal cognition in the two intervention groups compared to declines in cognitive functioning in the control group.[51]

Figure 7: Improvements in cognition with Mediterranean diet[51]



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

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. 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.[52,53] 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).[54]

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

A cross-sectional analysis of data from the Rush Memory and Aging Project (n=456) shows 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.[55]

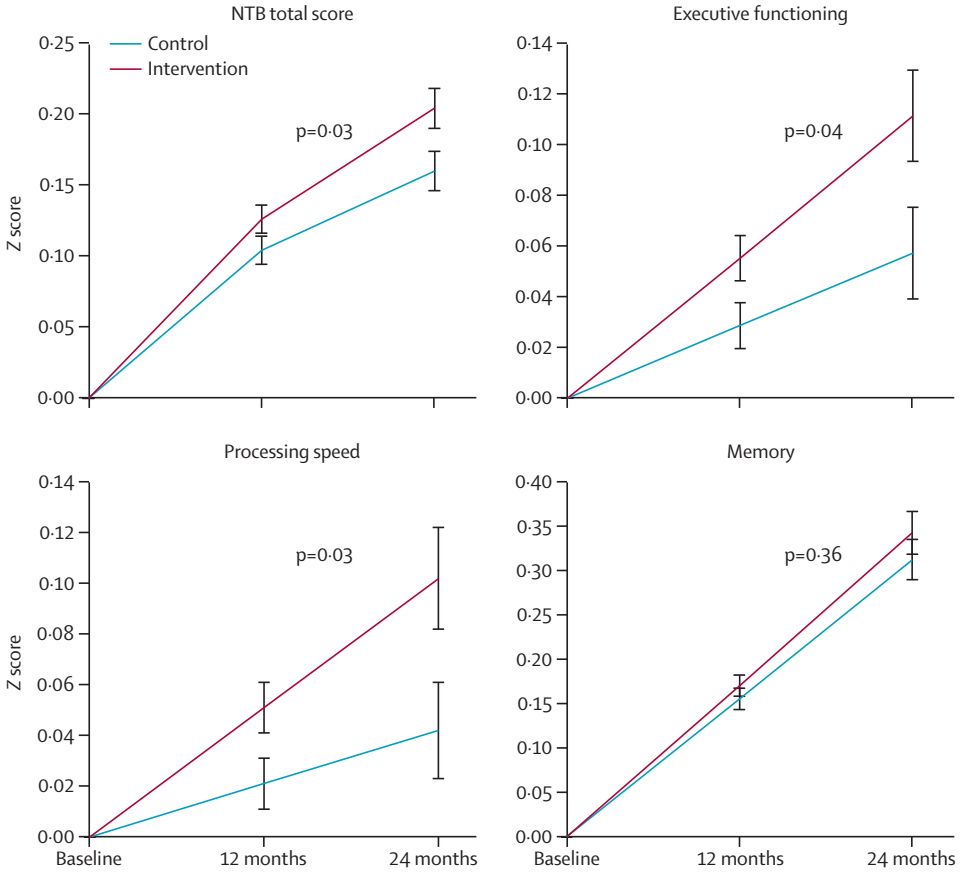
BOTTOM LINE: approximately 35% of dementia is attributable to a combination of nine potentially modifiable risk factors, and prevention efforts aimed at these risk factors will still be needed even if disease-modifying treatments eventually emerge.

Multimodal interventions for prevention

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.[56] 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 statistically significant (but clinically questionable) mean improvements versus the control group in a composite measure of cognition (neuropsychological test battery [NTB] total score), executive function, and processing speed, but not memory (Figure 8).

Figure 8: Results from FINGER multimodal intervention to improve cognitive function[56]



Note: when interpreting effect sizes such as Z scores, consider that 0.20 is a small effect size, 0.50 is a moderate effect size, and 0.80 is a large effect size.

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.[57] 3,526 participants from general practices were 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 otherwise. If indicated, medication was given for hypertension, diabetes or dyslipidemia. After 6.7 years, no significant differences in dementia incidence were observed between the intervention and usual care group (HR 0.92; 95% CI: 0.71-1.19). The authors thought the negative findings may have been related to the relative lack of cardiovascular risk factors in the study population, reducing the possibility of risk reduction.

The Multidomain Alzheimer Preventive Trial in France (**MAPT**) randomized 1,680 older adults with memory complaints, 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.[58] 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.[59] 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 15-point scale, P=0.04) and no significant difference in cognitive function as measured by the MMSE.

Screening for cognitive impairment and dementia

In 2020, the U.S. Preventive Services Task Force (USPSTF) released updated guidance about screening for cognitive impairment in older adults, concluding 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.[60] 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 screening.[61] 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,[60] which may include the following scenarios:

- patients with subjective cognitive complaints, conveyed either by the patient or a knowledgeable informant
- patients with mood or anxiety complaints, conveyed either by the patient or a knowledgeable informant
- selected patients at risk for adverse safety outcomes (e.g., living alone, poor medication adherence, working in professions in which cognitive dysfunction places them or others at risk)

If cognitive impairment is suspected, it is important to use a validated instrument because routine history and physical examinations are not sensitive for detecting such impairment. Although no disease−modifying treatments exist for dementia (i.e., treatments leading to a permanent slowing of the

disease progression), patients and caregivers may benefit from a better understanding of cognitive impairment as well as from interventions aimed at safety, optimizing cognition, planning for the future, and enhancing overall well-being. Medicare covers testing and screening for cognitive impairment as a part of annual wellness visits.

Screening for cognitive impairment can be quick. Examples of screening instruments that take five minutes or less to administer include: the Clock Drawing Test (CDT), 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.[62] 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 clinical Alzheimer-type dementia from normal cognition.[63] For example, the clock-drawing test had a 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, and the Montreal Cognitive Assessment had sensitivity of 0.94 and specificity of 0.94 in two studies (all for distinguishing AD from normal cognition). Accuracy was lower for all tests for distinguishing Alzheimer's from MCI.

Because a diagnosis of dementia requires both objective evidence of cognitive impairment and loss of function in usual activities, 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.[64] 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 (see Appendix 1). The patient is first asked to repeat and remember 3 unrelated words, allowing a maximum of 3 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 3 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%−85.2% for detecting signs of dementia, when validated against clinical diagnostic criteria as a gold standard.[62]

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.[65]

In comparison, the pooled sensitivity and specificity from 108 studies of the Mini−Mental State Examination (MMSE) is 81% and 89%, respectively.[66] 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 represent more efficient means of selecting which patients require a more detailed diagnostic evaluation.

The Montreal Cognitive Assessment (MoCA) includes 18 questions that assess orientation, memory, language, attention, and executive function.[66] 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 sensitivity 89%, specificity 75% vs. MMSE sensitivity 62% and specificity 87%).[66] As of September, 2020, clinicians will need to complete an online training and certification program before accessing and using MoCA.[67]

Neuropsychological testing may be useful if a diagnosis is unclear. The testing involves evaluating multiple cognitive domains: attention, orientation, executive function, memory, language, calculations, mental flexibility, conceptualization and has a sensitivity of 80-98% and specificity of 44-98%.[68,69]

Table 3: Dementia screening and diagnostic tool sensitivity and specificity[65,66,68]

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

*Compared to clinical diagnosis

BOTTOM LINE: universal screening for cognitive impairment in older adults without recognized signs and symptoms of cognitive impairment is not supported by evidence, although patients with cognitive or mood complaints and those at risk for adverse safety outcomes may benefit from an appropriate evaluation.

Short screening tests and questionnaires can reliably identify cognitive impairment (which may, or may not, be due to dementia) beyond routine history and physical examination alone. The purpose of screening is to identify patients who should undergo a more detailed evaluation to help determine underlying causes or factors contributing to cognitive impairment.

Diagnosing dementia

A focused differential diagnosis of dementia or MCI should be considered 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 onset, progression over days to weeks, 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; (2) a meaningful decline in function; and (3) evidence of cognitive dysfunction on a mental status examination or formal neuropsychological testing.[70] Selected labs and studies are recommended to establish a clinical diagnosis regarding the cause of dementia and to assess potentially reversible or modifiable factors.

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 and changes that have arisen

due to cognitive dysfunction; (3) conducting a focused review of other pertinent information from the patient's medical history, social history, family history, and review of systems.

The medical history should also assess:

- drug and alcohol intake
- family history of cognitive impairment, dementia, neurological, or psychiatric conditions
- bowel/bladder incontinence
- review of mood, anxiety, sleep, and pain
- history of head trauma, encephalitis, meningitis, seizures, or other neurological or psychiatric illness
- review of medications with potential to affect cognition, including over-the-counter products and herbal remedies or dietary supplements
- educational and occupational history

Eliciting examples of a patient's cognitive functioning from both patients and informants may help determine what domain(s) of cognition are affected. 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. AD dementia typically causes impairment of episodic memory out of proportion to impairments in other cognitive domains early in its time course.

Table 4: 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 activities of daily living	Finding it hard to plan or complete everyday tasks. Individuals 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 substitutes 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.	*Temporarily misplacing keys or a wallet*
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*
12. Psychosis	Having hallucinations (audio or visual) and/or delusions (often paranoid in nature).	*Hallucinations and delusions are never normal*

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 that merit attention.

Detailed cognitive examination

A detailed assessment of cognitive domains can confirm the profile of impairment suggested by the history, and also provides an additional measure of severity. In many cases the Montreal Cognitive Assessment (MoCA) provides sufficient information to aid in generating a differential diagnosis and can be administered in only about 10 minutes. The MoCA has 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.[71] AD and other 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.

Physical, laboratory, and imaging 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 signs that might suggest stroke or tumor
    - gait
    - assessment for motor neuron disease
- laboratory
    - comprehensive metabolic profile
    - complete blood count and differential
    - thyroid stimulating hormone (TSH)
    - vitamin B_{12} level
    - urinalysis

In early 2020, a diagnostic test of plasma phosphorylated tau181 was shown to have high accuracy for differentiating between AD and frontotemporal degeneration, although the test is not yet available for clinical use.[72]

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.

Although the American Association of Neurology recommends either head CT or MRI in the initial evaluation for dementia, particularly among those with focal signs, the recommendation is controversial because of the low probability that findings would alter management.[73] Imaging may be reasonable 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 treatable malignancy.[73]

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 in patients with atypical presentations, as well as discriminating from non-neurodegenerative conditions, such as depression.[74] FDG-PET and SPECT are the only functional neuroimaging methods currently widely available for clinical use.

Amyloid PET tracers that measure brain amyloid lesion burden may help differentiate AD from other causes of dementia.[75] These tracers have been approved by regulatory agencies in the United States and elsewhere as qualitative assessments of amyloid plaque density. 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: for amyloid PET, 0.91 and 0.92; for FDG-PET 0.89 and 0.74; for SPECT 0.64 and 0.83; and for MRI 0.91 and 0.89.[76]

A consensus opinion of the Amyloid Imaging Task Force, the Society of Nuclear Medicine, and the Alzheimer's Association concluded that amyloid imaging is not appropriate in patients who meet the core

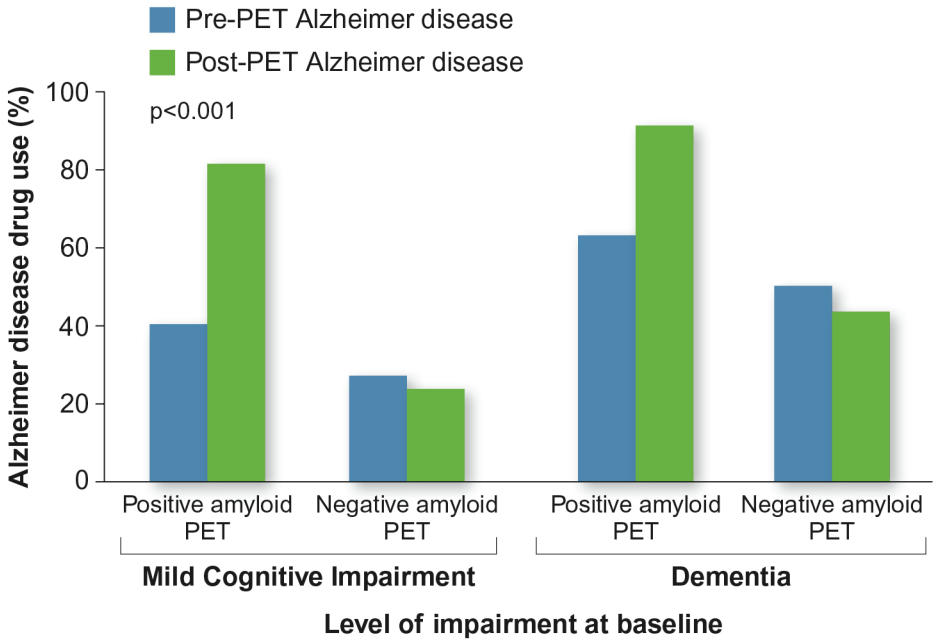
clinical criteria for probable AD and have a typical age of onset, and such a scan should not be used to determine dementia severity.[77] Currently, these scans are not covered by many health insurances plans.

Amyloid PET imaging may be appropriate in patients with focal signs of dementia when all three of the following criteria are met:[77]

- etiology remains unclear after a comprehensive evaluation by a dementia specialist
- AD is high on the differential diagnosis
- knowledge of amyloid PET status is expected to alter diagnosis and management

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.[78] The etiologic 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 AD medications rose significantly after positive PET scans in patients with MCI or dementia, and declined marginally in patients with negative PET scans (Figure 9).

Figure 9: Changes to medication therapy after amyloid PET scan[78]



Genetic testing

Genetic testing for AD is not routinely recommended because results are neither sensitive nor specific.[79] Referral to a genetic counselor for consideration of testing for gene mutations associated with familial AD is only recommended for patients with early−onset AD and family history of dementia or those with a family history suggesting an autosomal dominant mode of transmission. Of note, less than 1% of AD cases are due to familial autosomal dominant gene mutations, such as amyloid precursor protein, presenilin 1, and presenilin 2, which show 95-100% penetrance.[79] Apolipoprotein E (APOE), however, 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. Because having an APOE4 allele is neither

necessary nor sufficient to cause AD, numerous consensus statements and articles have recommended against using APOE genotyping for predicting AD risk.[79]

Cerebrospinal fluid testing

Some studies have examined the use of cerebrospinal fluid (CSF) markers for predicting conversion from MCI to dementia, the most common being:

- increased levels of phosphorylated tau protein
- 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

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. These tests do not have an established role in the evaluation of patients with MCI in the clinical setting, however, a 2014 Cochrane review of 14 observational studies evaluating CSF Aß42 for predicting conversion from MCI to AD found significant variation in assay thresholds, which precluded summary estimates of sensitivity and specificity.[80] Sensitivity in individual studies ranged from 36 to 100 percent and specificity ranged from 29 to 91 percent. The authors concluded that a low CSF Aß42 is of marginal clinical utility.

BOTTOM LINE: patients who screen positive on an initial screening for cognitive impairment should undergo further evaluation to confirm the diagnosis and rule out reversible causes such as depression, vitamin deficiency, NPH, alcohol or medications affecting cognition, or disorders of thyroid, kidney, or liver.

Clinicians should determine how much of the assessment process to complete themselves and consider referrals where appropriate. Genetic testing is not necessary except in patients with early−onset or rapidly progressive dementia and a family history, or those with a family history suggesting an autosomal dominant mode of transmission.

Advance care planning for dementia

Advance care planning (ACP) is a continuous, dynamic process of reflection and dialog between people with dementia or other serious illness, those close to them, and with their health care providers about the person's 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 own 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.

Although many patients, and practically all health care providers know about ACP, the majority of patients have not completed the most common documents involved in ACP. A systematic review of 150 studies with 795,909 patients found that only 37% had completed advance directives, 29% had a living will, and

33% had defined health care proxies.[81] The completion rate for advance directives was similar between those with chronic illnesses and healthy adults.

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 they have not already been completed). 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 providers should take it upon themselves to do so, unless others have already done 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. Clinicians should assume full mental capacity and regard dementia as a progressive condition situated on a continuum of mental functioning.[82] 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 a living will, a health care proxy, power of attorney, and do not resuscitate (DNR)/do not intubate (DNI)/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 if they have 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 by the end of follow-up 55% had died, 41% had experienced pneumonia, 53% had febrile episodes, 86% had problems eating, and 41% had "burdensome" interventions in the last three months of life.[83]

Table 5: Events experienced by nursing home residents with advanced dementia[83]

Events	18-month incidence
Eating problems	86%
Death	55%
Febrile episodes	53%
Pneumonia	41%
Burdensome interventions in last 3 months of life	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 (Table 6 on the following page), and recognize that these preferences may change with time, hence requiring repeated inquiries. Patients should also establish clear health care agents who can make the patient's wishes known in the event that they are incapacitated and unable to do so.

Table 6: Goals of care applied to two common dementia-related issues[83]

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	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 the patient experience. A 2017 trial randomized 302 dyads of nursing home residents with advanced dementia and their decision makers to either a video focused on goals-of-care and a structured discussion about ACP vs. a general information video and usual care.[84] 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).

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 solicit treatment preferences and goals-of-care.

Managing dementia

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 no disease-modifying treatment for dementia yet exists, appropriate use of available interventions may have a substantial positive effect on the well−being of patients.[85] In some cases, this could mean the difference between the ability to continue living independently and the need for institutional care.

When managing dementia, particularly AD, it is 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.[86] (Note that a high score on the FAST tool, combined with the presence of other medical conditions may qualify a patient for hospice benefits.[83])

Table 7: Major FAST stages and characteristics of Alzheimer's disease[86]

Stage	Stage name	Characteristic	Expected untreated AD duration (months)	Mental age (years)	MMSE (score)
1	Normal aging	No deficits whatsoever	--	Adult	
2	Possible mild cognitive impairment	Subjective functional deficit	--		28-29
3	Mild cognitive impairment	Objective functional deficit interferes with a person's most complex tasks	84	12+	24-28
4	Mild dementia	Independent activities of daily living become affected, such as bill paying, cooking, cleaning, traveling	24	8-12	19-20
5	Moderate dementia	Needs help selecting proper attire	18	5-7	15
6	Moderately severe dementia	Needs help putting on clothes, bathing, toileting, incontinent (urinary and fecal)	3.6-9.6	2-5	1-9
7	Severe dementia	Not able to speak, walk, sit up, smile, hold up head	12-18	0-1.25	0

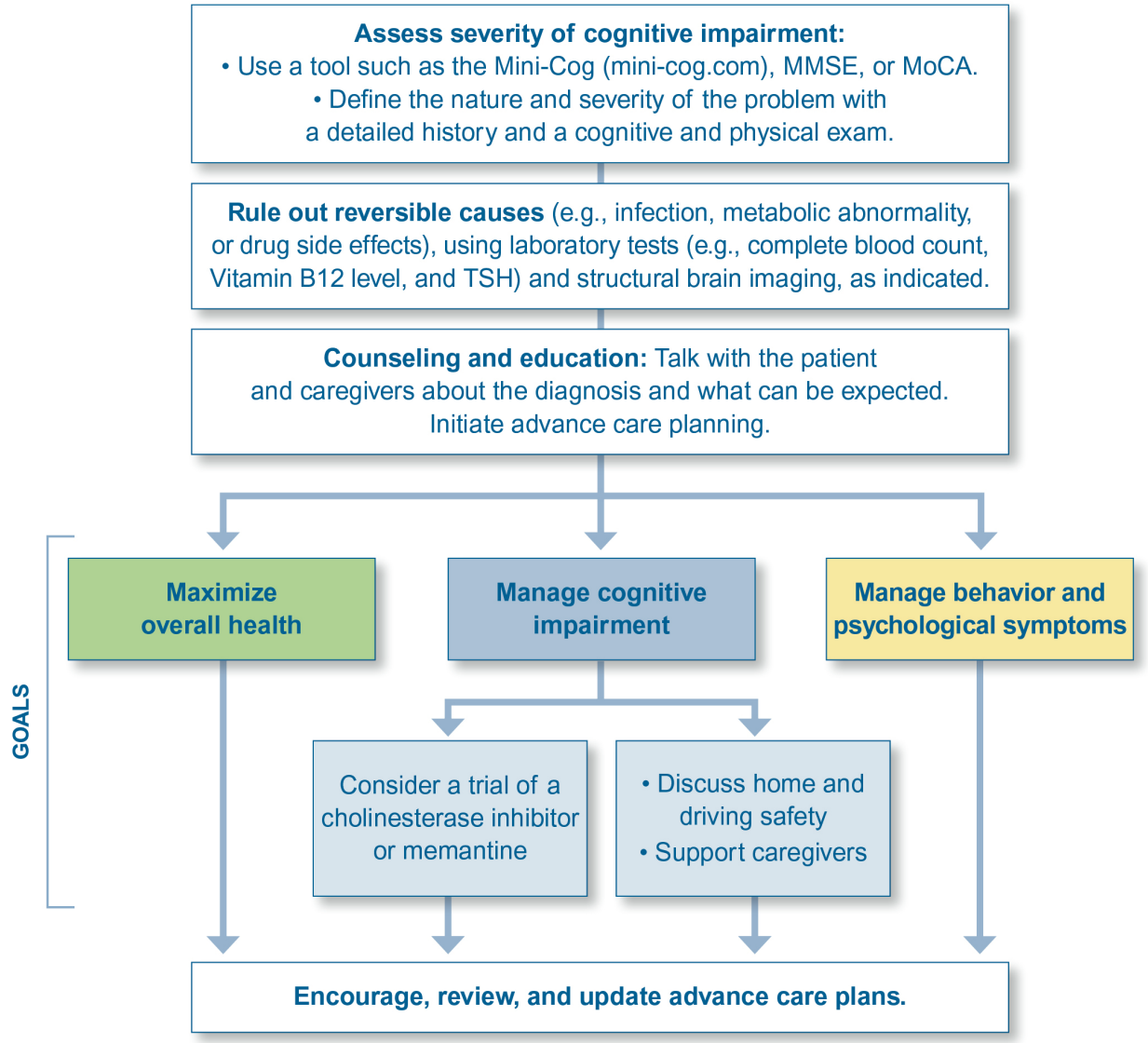
Questionnaires such as the Weintraub Activities of Daily Living Questionnaire can also be useful for staging.[87] Consultations with medical, neurological, or psychiatric subspecialties may be helpful, depending upon the circumstance. Geriatric psychopharmacologists, geriatric psychiatrists, neuropsychiatrists 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 offer strategies for: dealing with specific or recurrent problematic situations; providing psychotherapy when appropriate; providing guidance about services such as day programs, home services, respite care, and dementia care units; providing guidance about financial and legal planning; and making 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).[88] Developed at the University of Bradford, England, in the 1980s, DCM is a process of continuous quality improvement aimed at 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: bradford.ac.uk/dementia/dcm/Introduction-to-Dementia-Care-Mapping)

Managing a patient with dementia requires the physician to focus on present issues while keeping an eye on preparations for the future (Figure 10). A patient's wishes pertaining to end of life care and surrogate medical and financial decisions should be discussed early on, while he or she has the capacity to make informed decisions in these areas, generally before a moderate stage of dementia is reached (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.

Figure 10: A framework for screening and management



Non-pharmacological options for dementia management

A range of interventions have been explored as ways to help manage dementia. Such interventions fall into three main strategies: increasing brain cognitive reserve; reducing brain inflammation; and reducing brain damage via vascular, neurotoxic, or oxidative stress factors.

Optimizing general health

Identifying and treating non−neurological conditions that may negatively affect cognition is an important first step towards the goal of optimizing cognitive status. General medical illnesses, medications, and psychiatric illnesses can affect frontal−associated brain networks important for attention and executive functions. Treating such illnesses may boost cognition and provide patients with more reserve with which to compensate for the effects of the underlying cause of their MCI or dementia.

Examples of medical conditions and medications with the potential to exacerbate cognitive dysfunction include:[89]

- medical conditions
  - cardiac, pulmonary, renal, or hepatic disease
  - endocrine dysfunction, particularly hypothyroidism
  - depression
  - anxiety
  - delirium
  - sleep disorders, particularly obstructive sleep apnea and insomnia
  - chronic pain
  - vitamin B12 deficiency
  - NPH
- medications
  - anticholinergic medications
  - antihistamines
  - benzodiazepines
  - non-benzodiazepine sedative/hypnotics
  - opioid analgesics
  - alcohol

Treatment of neuropsychiatric symptoms of dementia, including depression and anxiety, can secondarily benefit cognition (see section on BPSD below).

General lifestyle interventions

Lifestyle changes that can provide psychological, physical, and cognitive benefits include getting 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 about making 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 compliance 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.

Exercise

Physical exercise is associated with a range of benefits in older people, including improving balance and reducing falls,[90] improving mood,[91] and improving function.[92] But, 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).[93] A systematic review of 41 studies found no improvements in memory-related outcomes with exercise.[94] 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.[95] The results of less high quality studies were mixed but did not indicate generalized cognitive improvement compared to control.[94]

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, which was 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.[96]

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.[97] 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.[98] 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 (n=20-40), of low quality, and with substantial heterogeneity between studies.[41,99-101]

Addressing hearing loss

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 of hearing interventions with cognitive outcomes assessed over longer than three years (most of low-to-moderate quality) found that three reported a positive association of hearing aid use with cognitive decline or incident cognitive impairment while three reported no such association.[102] A study involving 20 patients with dementia and their caregivers found that one month after giving the patients a hearing amplification device, participants with high symptom burden at baseline showed improvement in depression and neuropsychiatric outcomes.[103] 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.[103]

Enhancing personal safety

Preserving the safety of patients with dementia can mean reducing their independence, and this dynamic 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.[104]

The ability to drive represents both real and metaphorical freedom that many people are extremely unwilling to give up. But the risks posed by mixing dementia with 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%).[105]

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 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 above and beyond public transportation). More information about driving and dementia can be found at the Alzheimer's Association (bit.ly/Alz_driving) and AAA (seniordriving.aaa.com). Some states require clinicians to report patients with certain 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 potentially hazardous power tools or appliances, and keeping firearms or other weapons in the house. 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 slots for different days and times can help reduce confusion about what medications should be taken when.

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 the adults with impaired executive function at baseline showed improvements of 44% and 51% in measures of executive function and memory at follow-up of between 4-8 months compared to controls.[106] Another pilot RCT compared cognitive training, a health promotion course, and a book-club as interventions for people with subjective memory problems (but not dementia) and found no between-group differences in cognitive outcomes.[107]

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.[108] A review of 15 RCTs of cognitive stimulation in patients with mild-to-moderate dementia found only minimal effects.[109] Nonetheless, despite limited evidence for efficacy, cognitive interventions are increasingly used to help preserve autonomy and quality of life. For people with dementia, the goals are to optimize and extend cognitive and functional skills for the longest possible period.[110]

Three major types of cognitive interventions are:[111]

- **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) compared to donepezil alone in patients with mild to moderate AD. All participants had been treated with donepezil for at least three months.[112] 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). Whether this difference has any meaningful clinical impact is debatable.

A variant cognitive intervention that has been used in patients with AD is the activation of procedural motor memory, which is often preserved in mild and moderate AD. For example, patients with severely impaired recent memory are often able to achieve normal motor learning and skill retention in tasks such as learning to dance.[110]

Dual cognitive support involves activating prior knowledge by linking the recall of new material to personal and salient life events. This type of support may be particularly effective when the information to be recalled has an emotional significance to the patient.[113]

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

Pharmacological interventions

Because not enough is known about the underlying causes and mechanisms of AD and related disorders, the medications available to treat it are of limited efficacy. Two drug classes are FDA-approved to treat dementia−related cognitive dysfunction: cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and N−methyl−D−aspartate (NMDA) receptor antagonist memantine. A product combining memantine and donepezil is also available to decrease polypharmacy/pill burden. These drugs do not alter the underlying pathology of dementia, and clinical trials indicate that on average they confer only modest symptomatic benefits in cognitive performance and functional status.[114] Clinical trials of novel treatments for dementia have been disappointing, although Biogen is reported to be seeking FDA approval for aducanumab based on re-interpretation and re-analysis of data from two previous clinical trials.[115]

Although generally well−tolerated, some carry a significant risk of side effects (reviewed below). In light of these issues, the French Pharmacoeconomic Committee no longer recommends the use of these drugs,[116] while other groups (e.g., the British National Health Service's NICE) urge caution and recommend they only be prescribed by neurologists or physicians with specific expertise in dementia.[117]

We recommend that clinicians offer a trial of these medications only after careful consideration of potential benefits vs. risks within the context of the patient's goal, with a plan in place for monitoring both response and side effects, and for consideration of suspending therapy if no ongoing benefit is evident.

When interpreting the evidence related to drugs approved for dementia, it is critical to keep in mind that these drugs were approved based on changes in test scores, rather than measures of patient functioning or quality of life. Table 8 summarizes the tests most commonly used in clinical trials of dementia drugs and the score changes that are considered clinically important.

Table 8: Common tests and minimal clinically important scores

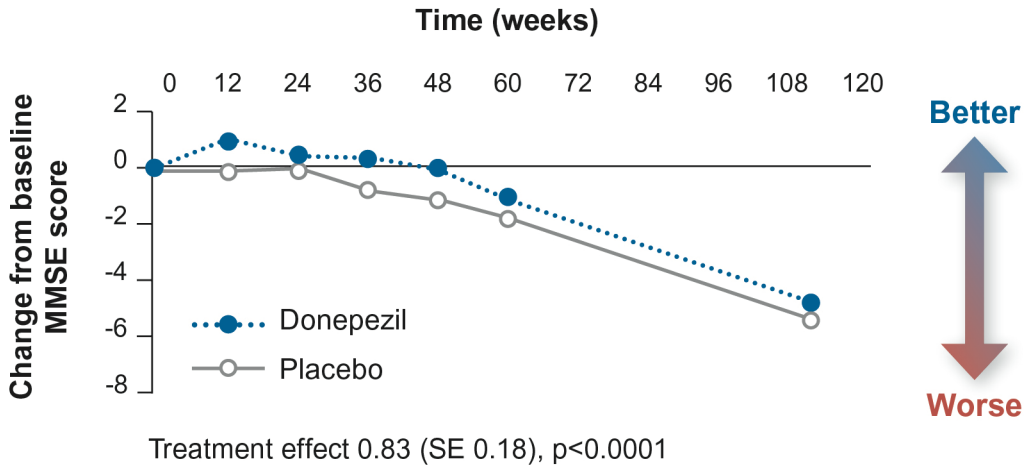
	Scale	Range	Direction	Minimal clinically important difference
Cognition	MMSE	0-30	Higher is better	≥3
	ADAS-Cog	0-70	Lower is better	≥4
	SIB	0-100	Higher is better	≥7
Global	CIBIC-plus	1-7	Lower is better	≥1
Behavior	NPI	0-144	Lower is better	≥4

Cholinesterase inhibitors

The cholinesterase inhibitors donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon) 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.[118] However, attempts to address this underlying pathophysiology have not translated well to clinical benefit.

Most trials of cholinesterase inhibitors are short-term (six months or less) and in community−dwelling patients with mild to moderate AD dementia, and produced clinically marginal effects on cognitive function and global functional status.[119] This benefit, when it occurs, is manifested by a small reduction in the rate of cognitive decline, rather than its reversal. There is no evidence of increasing benefits with longer duration of therapy. For example, one of the few long-term studies was the AD2000 study of 565 community-dwelling patients with mild-to-moderate AD followed for 3 years, which showed benefits in cognitive function and functional status "below minimally relevant thresholds" at 2 years (see Figure 11 on the following page) and no difference in nursing home admission at 3 years.[120]

Figure 11: Modest improvements of MMSE score disappears within 12 months[120]



Treatment effect 0.83 (SE 0.18), p<0.0001

Cholinesterase inhibitors in MCI

A 2012 Cochrane Review of nine studies of cholinesterase inhibitors in patients with MCI found no significant differences on 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.[121]

Cholinesterase inhibitors in AD

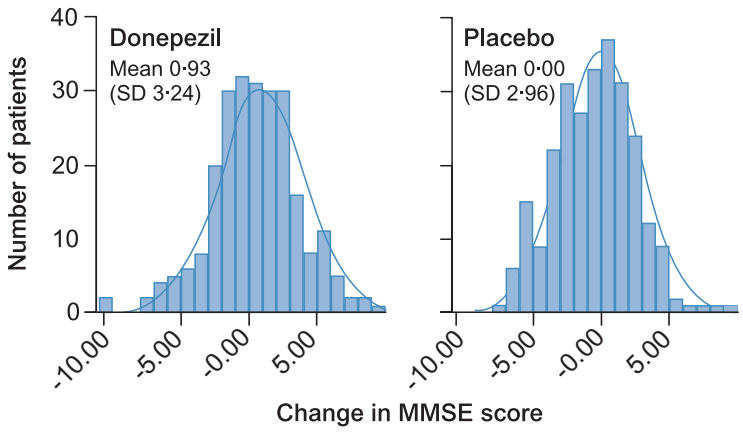
Systematic reviews of RCTs of cholinesterase inhibitors in patients with AD yield only modest results of questionable clinical significance:[122]

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

A 2020 systematic review and meta-analysis of 55 studies evaluating non-BPSD outcomes of drug treatments for AD, found mostly low-strength evidence suggesting that, compared with placebo, cholinesterase inhibitors produced small average improvements in cognition (median 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.[123]

A few studies in community-dwelling patients or nursing home residents with severe AD showed some modest benefit in cognitive function and functional status.[124-128] 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, show 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).[129,130]

Figure 12: Improvement in MMSE scores, donepezil vs. placebo[120]



A randomized double-blind study (n=1467) examined the effect of increasing the dose of donepezil from 10 to 23 mg/day in patients with moderate to severe AD.[131] The results showed a statistically significant, yet 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/d: +2.6 points vs. +0.4 points; P<0.001).[131] A Cochrane meta-analysis of 2 trials comparing donepezil 10 mg/day vs. 23 mg/day found no differences on efficacy outcomes, but fewer participants on 10 mg/day experienced adverse events or withdrew from treatment.[119]

Few studies have compared cholinesterase inhibitors head−to−head; those that have do not suggest superior efficacy for any one over the others.[122]

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[132,133]
- Parkinson's disease dementia: limited clinical improvement from rivastigmine[134] (rivastigmine has a specific approval for PDD[135])
- Vascular dementia: possible improvement in cognition[136,137]
- Frontotemporal dementia: no convincing evidence of benefit[138]

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 does not know what the patient's course would have been in the absence of treatment. 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.[139]

Safety

Medications with anticholinergic activity may reduce the efficacy of the cholinesterase inhibitors and can also cause delirium in patients receiving such treatment.[140] These drugs include antihistamines, tricyclic antidepressants, antipsychotics, and drugs used for urinary incontinence, such as oxybutynin, tolterodine,

and solifenacin. These medications may reduce or negate any beneficial effect on cognition by cholinesterase inhibitors.[141]

The most common adverse effects of cholinesterase inhibitors are gastrointestinal, and include anorexia, nausea, vomiting, and diarrhea.[142] These drugs can also cause dizziness, hypertension, syncope, bradycardia, QT interval prolongation, arrhythmia, angina pectoris and heart block.[141] Meta−analyses suggest that the frequency of dizziness with cholinesterase inhibitors is 10% (8% with donepezil, 10% with galantamine, and 22% with oral rivastigmine).[143] Cholinesterase inhibitors are associated with 53% increase in the risk of syncope, but not with falls, fractures, or accidental injury compared with placebo.[144] In clinical trials, 29% of patients stopped therapy due to adverse effects.[145] Donepezil may cause fewer adverse effects than oral rivastigmine.[122]

Doses of cholinesterase inhibitors should be started low, and slowly uptitrated to minimize adverse effects.[129] 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 differential 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 doses higher than 10 mg/day but are also more likely to experience side effects.[131]

Table 9: Dosing of cholinesterase inhibitors[89]

Drug	Starting dose	Titration	Target dose
donepezil (Aricept)	5 mg once daily	Increase to 10 mg once daily after 4−6 weeks according to response. Further increases in increments of 5 mg to maximum dose of 23 mg/day may be considered in selected patients with marked improvement on lower doses.	10 mg/day
galantamine (Razadyne)	4 mg orally (immediate−release) twice daily 8 mg orally (extended−release) once daily	Increase by 8 mg/day (given in 2 divided doses) every 4 weeks according to response, maximum 24 mg/day Increase by 8 mg/day every 4 weeks, maximum 24 mg/day	16-24 mg/day Maximum dose: 24 mg
rivastigmine (Exelon)−oral	1.5 mg orally twice daily	Increase by 3 mg/day (given in 2 divided doses) every 2 weeks according to response, maximum 12 mg/day	Maximum dose 12 mg/day

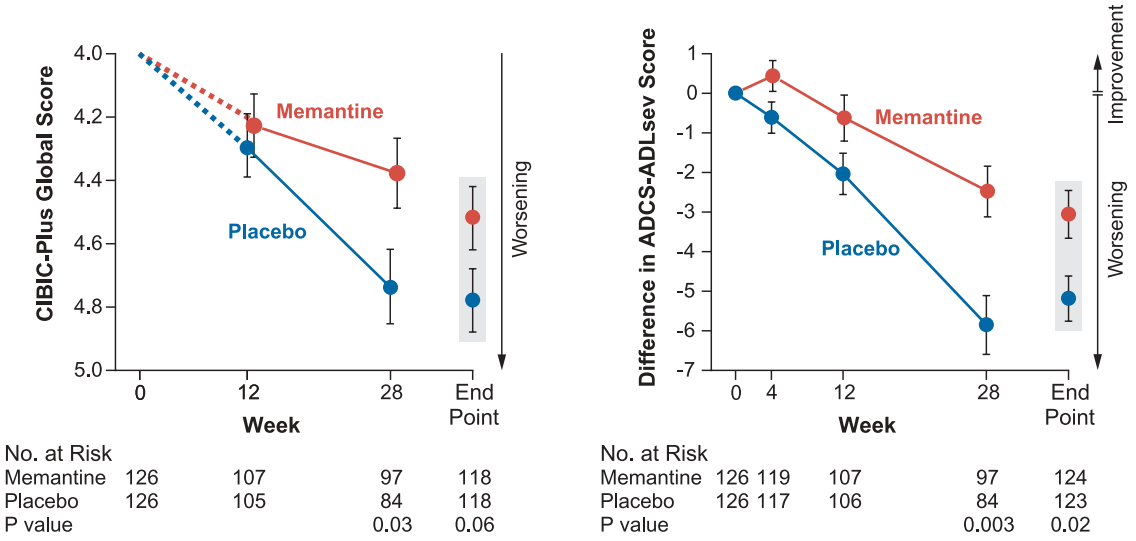
rivastigmine (Exelon) − transdermal	4.6 mg/24 hour patch once daily	Increase to 9.5 mg/24 hour patch once daily after 4 weeks according to response; starting dose varies if switching from oral to transdermal therapy. 13.3 mg/24 hour patch may be considered in selected patients with marked improvement on lower doses.	9.5-13.3 mg/day

NMDA antagonist (memantine)

Memantine (Namenda) is a non−competitive NMDA receptor antagonist. By inhibiting the NMDA receptor, memantine may reduce glutamate−mediated excitotoxicity and thus improve the functioning of neurons.[146]

Clinical trials suggest small cognitive benefits from memantine in patients with moderate to severe AD dementia, but not mild AD dementia.[147-149] Most studies are short-term and were conducted in patients with moderate to severe AD. Some studies show a modest, short-term benefit in terms of cognitive function and functional status. A few studies in patients with mild AD did not show consistent benefits.[149,150] Evidence from two trials with approximately 750 participants suggests a small clinical benefit for memantine in patients with mild-to-moderate vascular dementia (mean improvement 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 dementia.[149]

Figure 13: Modest treatment effect of memantine in moderate-severe AD[147]



Memantine has been well−tolerated in clinical trials.[151] Most studies found the overall incidence of adverse effects and dropout rates due to adverse effects to be similar to that of placebo.[151] Common adverse effects are agitation, urinary incontinence, urinary tract infection, insomnia, and diarrhea.[147] A meta-analysis showed that memantine was not associated with increased risk of falls, syncope, fractures, or accidental injury compared with placebo.[144] In general, memantine is better tolerated than cholinesterase inhibitors (see Table 10 on the following page).[89]

Table 10: Comparison of adverse effects for cholinesterase inhibitors vs. memantine[89]

	Cholinesterase inhibitors	Memantine
Adverse effects	• Nausea/vomiting • Loss of appetite • Increased frequency of bowel movements • Vivid dreams • Insomnia • Local skin irritation (galantamine patch only)	• Dizziness • Headache • Constipation • Hallucination
Cautions	• Peptic ulcer disease • Respiratory disease • Seizure disorder • Urinary tract obstruction	• Cardiovascular disease • 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.

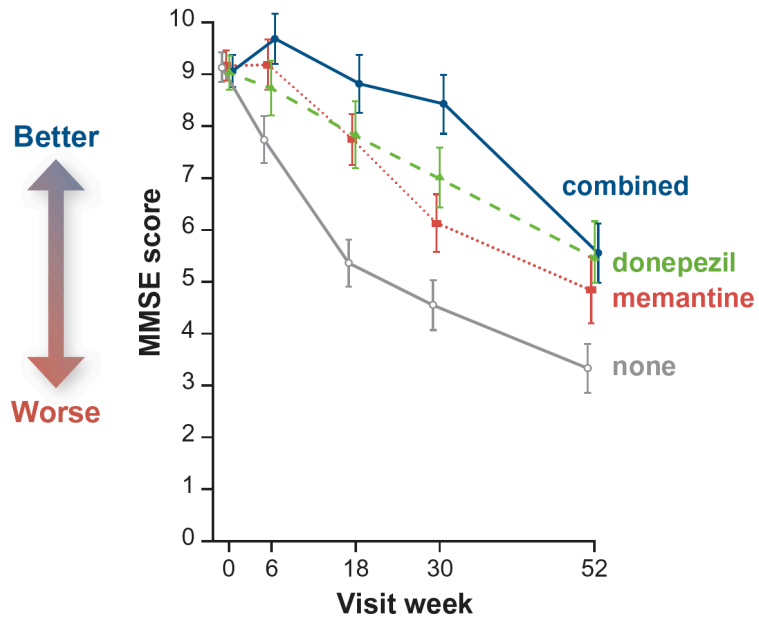
Table 11: Dosing of memantine[89]

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 bid if dose >5 mg per day	20 mg/day
	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

Dual therapy with memantine and a cholinesterase inhibitor

The effect of adding memantine to a cholinesterase inhibitor in patients with moderate to severe AD may initially 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.[152-154] 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.[128]

Figure 14: Addition of memantine to donepezil in patients with moderate-severe AD[153]



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, improved global clinical impression, but not function.[123]

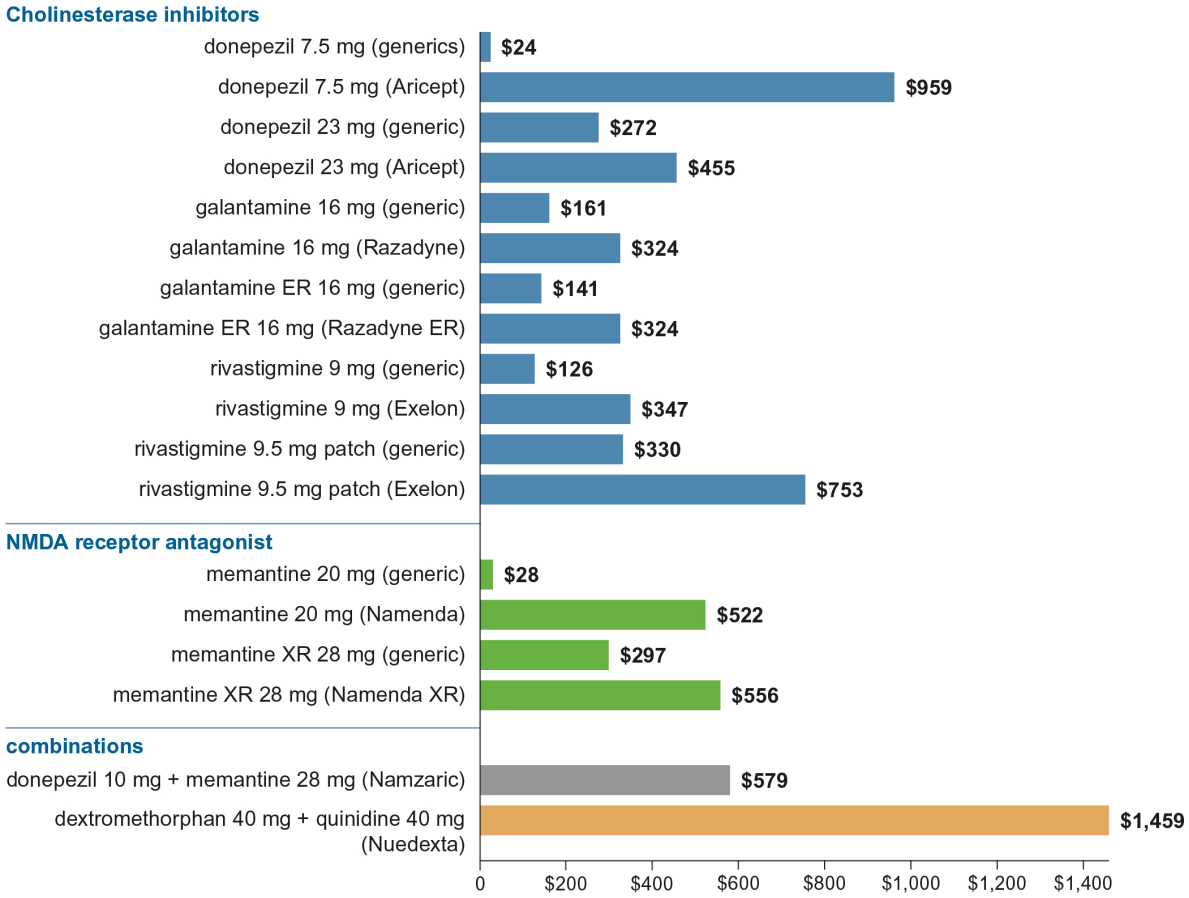
Table 12: Dosing of the combination of memantine and donepezil

Drug	Starting dose	Titration
memantine/ donepezil (Namzaric)[155]	Patients stable on donepezil 10 mg: 7 mg/10 mg once daily in the evening 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	Increase the memantine component by 7 mg/day, no more frequently than weekly to a target dose of 28 mg/10 mg once daily No titration required; patients initiated on maximum dose.

Prices of drugs to manage dementia

Based on the World Health Organization Defined Daily Doses (DDD), the price of cholinesterase inhibitors, memantine or the combination of donepezil and memantine are summarized in Figure 15, as of March 2020.

Figure 15: Costs of a 30-day supply of medications for dementia



Prices from goodrx.com, March 2020. Listed doses are based on Defined Daily Doses by the World Health Organization and should not be used for dosing in all patients. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

Other pharmacological therapies in dementia

A number of other therapies have been suggested for cognitive impairment in dementia. Insufficient evidence exists to recommend any of them.

Table 13: Other treatments proposed for cognitive impairment

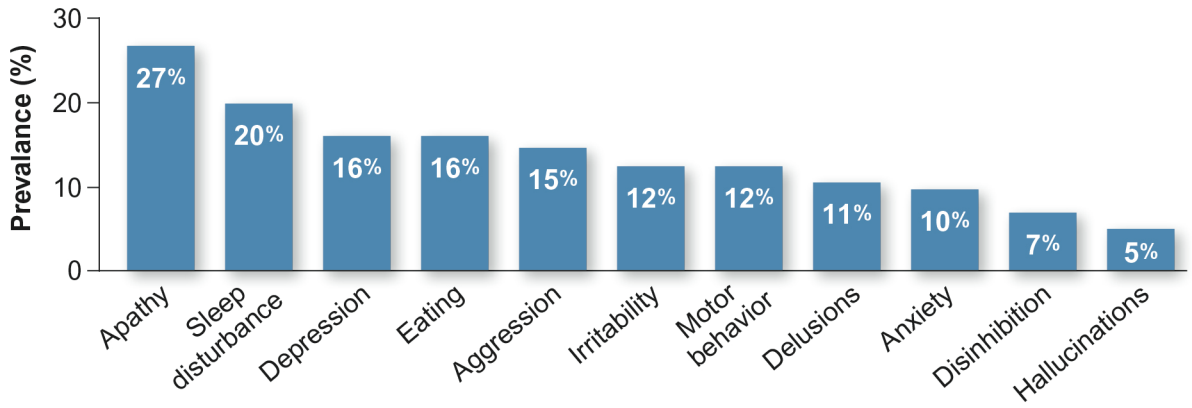
Therapy	Evidence
Vitamin E	Trials investigating vitamin E in MCI and AD dementia have been mixed, with some studies suggesting that vitamin E 2000 IU/day confers a minimal benefit in delaying functional progression in mild to moderate AD dementia and other studies suggesting no benefit at this dose in MCI or at a dose of 800 IU/day in mild to moderate AD dementia.[156,157,158,159] (Note: high doses of Vitamin E can increase bleeding risk in those on blood thinners, 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 dementia suggested no benefit.[160,161]
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.[162] 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.[163-166]
NSAIDs	NSAIDs and aspirin cannot be recommended for the prevention or treatment of Alzheimer's disease. Multiple trials in mild to moderate AD dementia have failed to demonstrate benefit.[167] Although aspirin is widely prescribed for patients with a diagnosis of vascular dementia, there is no good evidence to support this practice.[168]
Folic acid, vitamin B_6 and vitamin B_{12}	Systematic reviews and RCTs have found no evidence that folic acid (with or without vitamin B_{12}), vitamin B_6 alone, vitamin B_{12} in people with low B_{12} levels at baseline. Combined treatment with folic acid, vitamin B_6 and vitamin B_{12} has not shown beneficial effects on cognitive function in either healthy people, or in those with cognitive impairment or dementia.[169-171]
Ginkgo biloba	A 2009 Cochrane systematic review and a subsequent trial found no convincing evidence that ginkgo biloba has predictable and clinically significant benefit on dementia or cognitive function.[172] 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.[173]
Omega−3 fatty acids	Trials of docosahexaenoic acid (DHA) and other omega−3 fatty acids in mild to moderate AD dementia have demonstrated no benefit.[174,175]

BOTTOM LINE: cholinesterase inhibitors (for patients with mild, moderate, or severe dementia) and memantine (for those with moderate or severe dementia) offer, on average, only small benefit of equivocal clinical significance. Side effects with both drugs are common (although generally less severe with memantine) therefore start with a low dose and titrate according to package inserts. Reassess at 3-6 months to determine if risk-benefit relationship warrants continued treatment and discontinue therapy is no ongoing benefit is evident.

Managing 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 behavior.[176,177] In a cohort study of community-dwelling adults with dementia, 61% displayed at least one neuropsychiatric disturbance and 32% had moderate-to-severe disturbance at some point during their illness.[178] Higher rates of BPSD (i.e., 50%−80%) have been reported among residents of nursing care facilities.[179]

Figure 16: Prevalence of BPSD symptoms among patients with dementia from Cache County Study (n=362)[180]



Many medications have been prescribed to help manage real or perceived behavior problems in elderly patients; these include antidepressants, benzodiazepines, and antipsychotic medications (APMs). Since at least the 1980s, however, the widespread use of APMs to manage behavior 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.[181-185] 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 the current high levels of use.

BPSD overview

BPSD can range from behaviors that are merely annoying to those that endanger the patient and/or others. Apathy, depression, and aggression are the most common features, followed (in descending order) by sleep disturbances, anxiety, delusions, and hallucinations.[178,186] The symptoms with the greatest potential for harm are aggression, psychosis, and mood disorders.[178] (Note: the term “agitation,” while occasionally used to describe some of these symptoms, is non–specific and is rarely helpful in creating a treatment plan, and the term “psychosis” should not be seen as parallel to the symptoms of schizophrenia, which can appropriately be managed with antipsychotic medications.) This entire set of symptoms is often used as a single primary outcome measure in clinical trials. As a result, the efficacy of therapies for specific symptoms in AD can be difficult to determine.[178]

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 2 years in about 85% of patients who had these symptoms at baseline, while paranoid ideation persisted in approximately 66% of patients.[186] 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 may predominate.

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 (Table 14).[187]

Table 14: Differentiating delirium from BPSD[187]

	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., the 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)

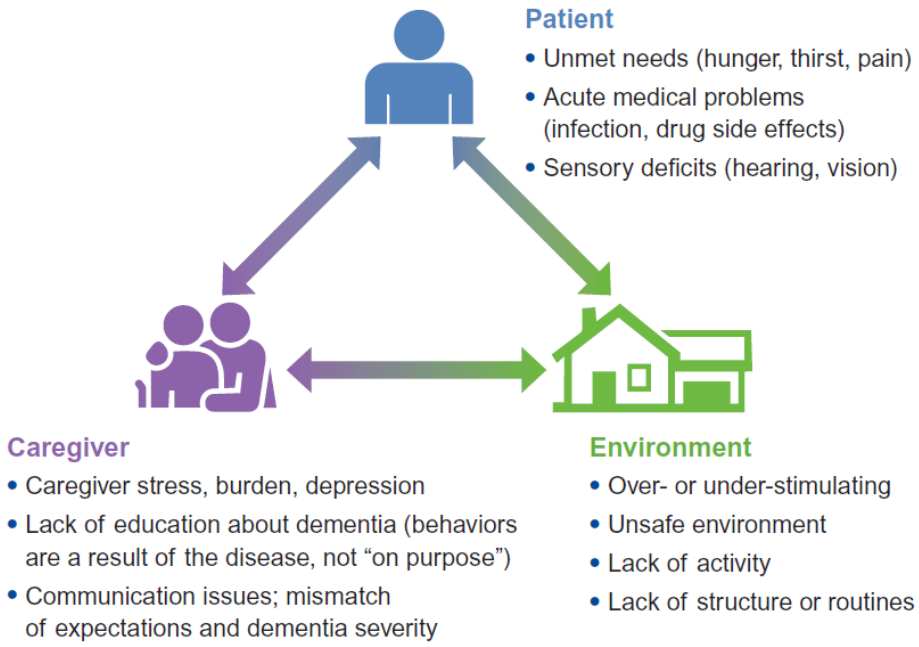
Acute vs. non−acute BPSD

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 pose an imminent danger to themselves or others, or have severely disruptive or dangerous behaviors. 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 range and ordering of therapeutic options (Figure 17). 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) developed by a multidisciplinary panel of 12 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 17).[188]

Figure 17: Factors addressed in the DICE model[188]



Step 1: Describe. Elicit a thorough description of symptoms and the context in which they occur from care givers and the person with dementia (if possible). Not possible antecedents or behavioral triggers, symptoms that are most distressing or problematic, as well as treatment goals. (Note: if the situation poses a safety risk, consider psychotropic drug use to reduce harm and allow for a full description of behavior.)

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

Step 3: Create. Create and implement a treatment plan that target 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 care givers, since they will carry out the plan and be evaluating the effects of interventions.

Step 4: Evaluate. Assess whether the treatment plan was implemented effectively, whether targeted symptoms improved, whether the patient and caregiver's distress was 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 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 may 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."[189]

BOTTOM LINE: manage BPSD based on the characteristics and severity of the symptoms. People with *acute* BPSD are in severe distress, pose an imminent danger to themselves or others, or have severely disruptive or dangerous behaviors. 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 range or ordering of therapeutic options.

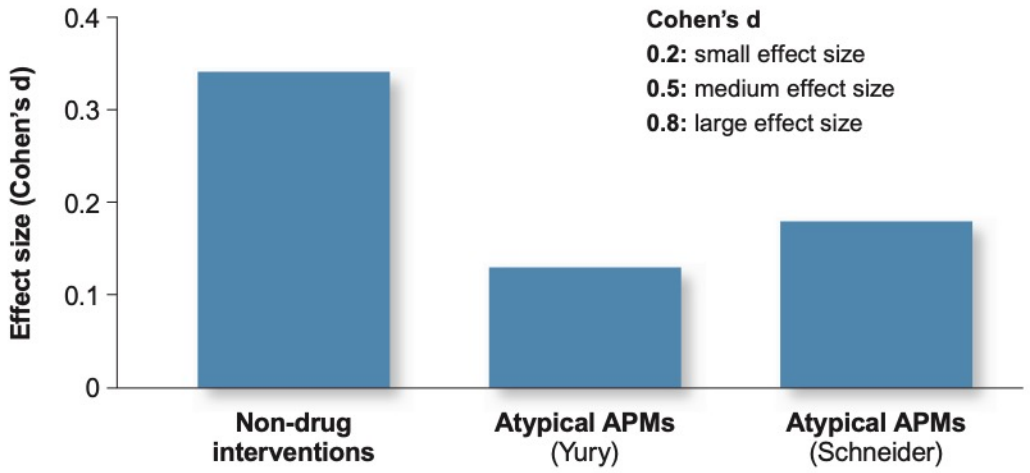
Non−drug management strategies

Non−drug management of BPSD can produce equivalent outcomes, in a much shorter time, and at less risk, than drug treatment and are thus the first choice for managing behavior problems.[190] 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 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 not possible 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.

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.[191] 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.[192]

Effect sizes in studies of non−pharmacologic interventions tend to be modest, although the same is true for effect sizes generally found in studies of the efficacy of APMs. Sometimes effect sizes for non−pharmacologic interventions are higher than those typical of drug studies. For example, a meta–analysis of 13 non−drug interventions for BPSD by Brodaty et al., found a pooled–estimate standardized effect size of 0.34 (95% CI: 0.04–0.26; P=0.006).[190] 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.[193,194]

Figure 18: Comparison of effect sizes for non-drug and drug interventions for BPSD[190,193,194]



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.[195,196]

Table 15: 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[197] • Planning activities with caregivers for their care recipients[190] • Modifying care recipient's physical and social environment (e.g., removing clutter, removing hazards, organizing, task simplification)[198] • Interdisciplinary skills training for nursing home staff[199]
Potentially helpful interventions supported by evidence from small, uncontrolled studies	
Environmental modifications[200,201]	• Support normal sleep/wake cycles • Structure activities to reduce boredom • Reduce unnecessary stimulation • Create home−like environment
Music therapy[202]	• 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[203]	• Exposure to simulated or natural lighting to promote circadian rhythm synchronization.
Aromatherapy[204]	• 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[205]	• Home-based exercise program combined with caregiver training in behavioral management techniques.
Pet therapy[203,206]	• Several small studies suggest that the presence of a dog reduces aggression and agitation, as well as promoting social behavior in people with dementia.

As 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:[188]

- 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 possible before pharmacological interventions are attempted:[207]

- urinary tract infections
- pain
- constipation
- nocturia
- hunger or thirst
- dehydration
- 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. Avoidance of alcohol and caffeine may promote good sleep hygiene.

Environmental strategies

Behavioral and psychological symptoms are often predictable 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.[207] 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, in particular, can increase fearfulness, anxiety, and agitation, any patient displaying non−acute BPSD should be assessed for these deficits, and, if present, they 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.

BOTTOM LINE: use non−drug interventions first for managing non−acute BPSD. These should focus on identifying and correcting any reversible environmental, psychological, or physiological factors that might be causing or contributing to symptoms, and then trying any of the many approaches shown to be potentially helpful for addressing BPSD.

Pharmacologic management of BPSD

The evidence base for drug treatment of BPSD is generally modest, and no medications are FDA–approved for these indications.[208-210] Without guidance from large randomized trials, medication use for BPSD has 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.

In evaluating the evidence base for pharmacologic treatments for BPSD it is helpful to remember that the minimal clinically important difference for scores on the Neuropsychiatric Inventory (NPI), a commonly-used metric, is 4 points or more on the 0-144 scale (lower scores represent better functioning/behavior).

If BPSD are 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, e.g., depression, anxiety, or psychosis). If a medication must be used, it is critical to focus on one or more specific symptoms. 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
- 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 therapeutic trial of a medication for BPSD should be completed with a single medication whenever possible. If the single medication works poorly, the medication should be discontinued, after an adequate trial period, and an alternative medication should be initiated. Assess suboptimal responses to

determine whether the partial effect was due to developments other than the medication (e.g., a change in clinical status); 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.

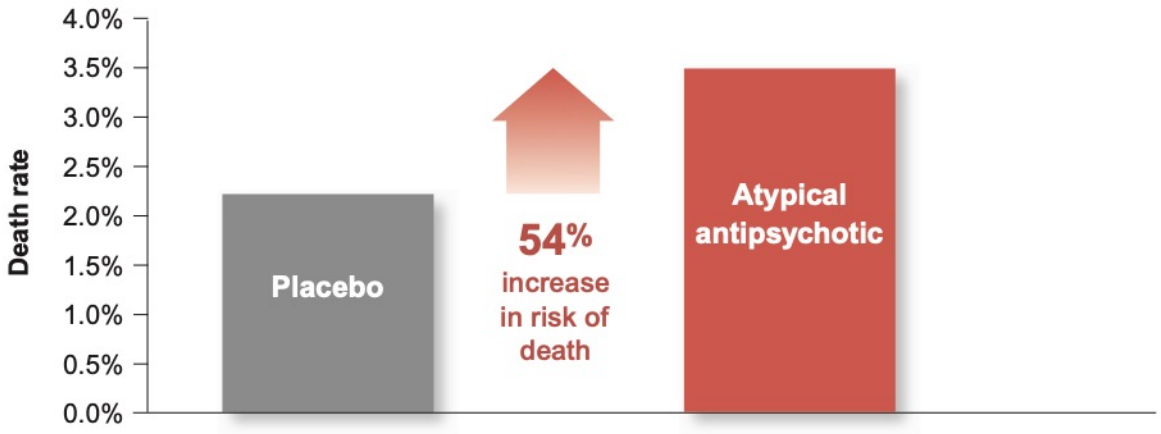
Psychotropic medications traditionally used for BPSD may cause a variety of serious adverse effects including confusion, falls, fractures, delirium, and over−sedation. Elderly patients are particularly vulnerable to injury from psychotropic medications because of slower metabolic clearance, increased central nervous system sensitivity, and reduced physiologic reserve. 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. BPSD symptoms are subject to remission on their own, and patients may not need these medications for long periods, even if successful.

Antipsychotic medications

Antipsychotic medications (APMs) should be avoided in patients with non−acute BPSD until other medications 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[181]



No APMs are approved in the U.S. for BPSD, despite at least 17 randomized controlled trials, most of them unpublished, that sought evidence of effectiveness for this indication.[193] Meta–analyses of these studies has indicated limited efficacy and significant potential for harm from side effects.[211] Thus, although APMs may help control the acute symptoms of BPSD in certain patients, they must always be used carefully and with informed consent.

Reserve APMs for the situations listed below, use them simultaneously with behavioral treatments and only if potentially reversible or remediable causes have been ruled out:

- 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. Aripiprazole and risperidone may provide modest benefit, but other APMs have questionable benefits and/or greater risks.[188] In a non-cooperative 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.[212]

Conventional antipsychotics

Reviews and meta-analyses of clinical trials involving conventional 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.[139,213-215] No consistent evidence shows that any one conventional antipsychotic is more effective than another,[214] and there are insufficient data to draw conclusions about the efficacy of conventional vs. atypical antipsychotics for BPSD.[216]

Discontinuation rates due to adverse effects were significantly higher with conventional antipsychotics than with placebo,[214] and the troublesome adverse effects associated with conventional antipsychotics (e.g., extrapyramidal side effects) limit the usefulness of these agents. Stroke risk also may be higher with conventional antipsychotics compared to “atypical” antipsychotics.[217] Importantly, recent studies show that haloperidol use is associated with a 50-100% higher risk of death compared to other antipsychotics.[185] Chlorpromazine is no longer recommended for intramuscular treatment in emergencies with aggressive psychotic patients due to its risks of inducing severe hypotension.[218]

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 aripiprazole (Abilify) and risperidone (Risperdal), whereas olanzapine (Zyprexa) and quetiapine (Seroquel) were not found effective in meta-analyses of their various published and unpublished trials.[145,193,219,220]

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) versus placebo in 421 outpatients with AD on psychiatric and behavioral symptoms, functional abilities, cognition, care needs, and quality of life over 12 weeks.[221] There were no significant antipsychotic – placebo group differences on 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.[221]

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.[222] But this drug has not been studied in patients with dementia and it carries the same black box warning for mortality as other antipsychotics.

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 and ceasing 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, a

2012 study of patients with AD showed an increased risk of relapse of psychosis and agitation when risperidone was discontinued.[209]

Steps for responsible APM prescribing

1. Identify and document the behavior being targeted.
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
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. Attempt gradual dose reduction while monitoring for recurrence of BPSD symptoms

BOTTOM LINE: due to their significant risks and weak evidence base 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 or psychotic symptoms. The best evidence of efficacy is for aripiprazole and risperidone, depending on the symptom being targeted. None are FDA–approved for this indication, and the benefits of treating the symptom should outweigh the well–established risks, including mortality.

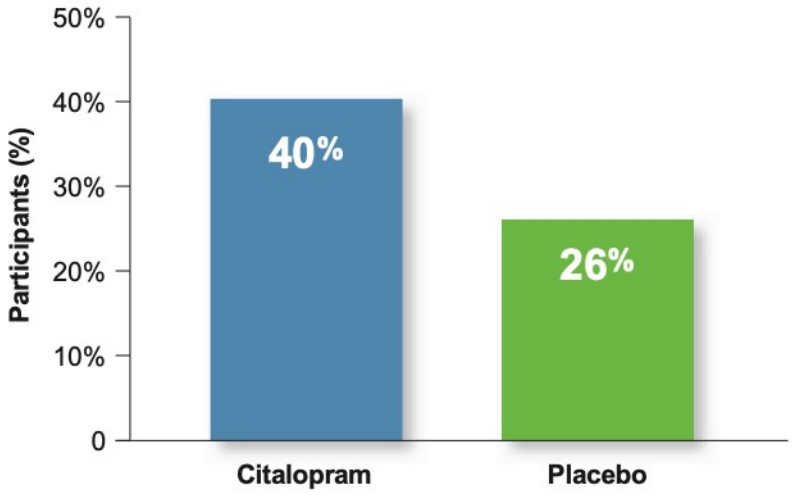
Antidepressants

Up to 40% of patients with dementia have significant depressive symptoms at some stage of their illness, and some of the symptoms related to depression (e.g., irritability, sleep disturbances) overlap with those of BPSD.[208] 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.[180] Even in dementia patients *without* depression, a growing evidence base finds antidepressants helpful for BPSD.[210] Antidepressants, therefore, may be a reasonable choice for treating symptoms of non–acute BPSD. Among the classes of antidepressants, the SSRIs have been the most widely studied.

A Cochrane review of antidepressants for BPSD found modest evidence for efficacy and tolerability with certain agents.[223] In two studies, the SSRIs sertraline and citalopram reduced symptoms of agitation when compared to placebo. A trial randomized 186 patients with AD and significant agitation to citalopram 30 mg or placebo for nine weeks. 40% of patients on citalopram had improved scores on the

Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) scale compared to 26% of patients on placebo (Figure 20). Weighing against this improvement were a modest impairment of cognition in the citalopram group (-1.05 points on MMSE; P=0.03) and QTc prolongation (18.1 msec; P=0.01).[224]

Figure 20: Citalopram for non-acute BPSD[224]



Sertraline and citalopram appear to be tolerated reasonably well compared to placebo or antipsychotics.[223] 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.[210] 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.[225]

Citalopram now carries a warning about QTc prolongation; the maximum dose recommended was reduced to 40 mg (20 mg in the elderly).[226] Its S–isomer, escitalopram, did not produce this abnormality and is therefore the preferred form of this drug, although no trial has evaluated escitalopram in patients with BPSD.

A Cochrane review of two small trials of trazodone found that it was not more effective compared with placebo in controlling BPSD.[227] Another randomized controlled trial compared the SSRI fluvoxamine and risperidone (n=60).[228] The medications were equally effective but the side effects were less severe with fluvoxamine; there was one sudden death on risperidone, probably due to a myocardial infarction. A 1997 pilot study found that fluoxetine was no better than placebo for reducing agitation in 15 outpatients with AD.[229] Two small trials have evaluated paroxetine for BPSD with mixed results: the trial comparing paroxetine to piracetam in 16 patients showed benefit for paroxetine,[230] although the study comparing paroxetine vs. placebo in 10 patients found no significant effects.[231]

It may be prudent to consider one or two trials of either sertraline or escitalopram for non−acute BPSD, even in the absence of overt symptoms of depression, before proceeding to other medication options. In using these drugs, it is important to be alert to the possibility of SSRI−induced Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Secretion leading to hyponatremia, which is more common in elderly patients, especially those taking a thiazide diuretic.[232,233] SSRIs can also increase the risk of upper GI

bleeding in patients with other risk factors such as concurrent use of NSAIDs, anticoagulants, and antiplatelet agents.[234] Finally, SSRIs (along with other classes of antidepressants) can significantly raise the risk of falling and resulting risk of fracture.[235]

BOTTOM LINE: the antidepressants escitalopram and sertraline appear to provide the most favorable risk–benefit profile for addressing non−acute BPSD, with or without depression. One or two trials of these medications should be the first−line approach after all 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.

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.[236] They may cause or exacerbate a range of problems including:[236,237]

- 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)[238]
- falls
- accidents
- paradoxical agitation
- physical dependence with regular use[239]
- aspiration and its consequences
- death[240]

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.[241,242] A 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.[241]

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 NPI 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 in patients with mild AD vs. -0.06 points in patients with severe AD).[243] An updated 2015 review found a small improvement in NPI scores, but also significantly increased study drop-out due to adverse effects.[244] 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.[245] Rivastigmine may modestly improve BPSD (in particular visual hallucinations) in patients with DLB.[246]

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.[247] Another pooled analysis of three RCTs showed similar results.[248] However, these effects were not considered clinically meaningful.[214]

If a patient is undergoing a trial of a cholinesterase inhibitor or memantine for cognitive impairment, whenever possible wait to see if this will be helpful for the BPSD before starting another medication.

Dextromethophan-quinidine (Nuedexta)

Nuedexta is a patented combination of two old components: dextromethorphan (DM), the d-isomer of a semisynthetic morphine derivative that reduces agitation by modulating several neurotransmitters, including serotonin and glutamate; and quinidine (Q), an antiarrhythmic that can cause potentially dangerous QTc prolongation. (Note: DM-Q is *not* FDA-approved for the treatment of BPSD.)

Anecdotal evidence and limited trial data led to its assessment for the management of agitation associated with AD. An industry-sponsored phase II trial randomized 220 adults with AD to DM-Q or placebo.[249] In the primary analysis patients randomized to DM-Q had reductions of 1.5 to 1.8 on the 12-point NPI agitation/aggression score ($P<0.001$). However, the drug combination did not significantly improve quality of life ($P=0.16$), activities of daily living ($P=0.16$) or the MMSE score ($P=0.05$).

Both components in this drug carry the risk of important drug-drug interactions: DM taken with any one of several antidepressants can cause a life-threatening serotonergic syndrome. 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 the DM-Q patients had adverse events vs. 43.3% for controls. In the DM-Q group, serious adverse events included femoral fracture, myocardial infarction, and stroke. One common adverse event was falling, which occurred in 8.6% of DM-Q patients vs. 3.9% of those given placebo.

Medications with limited evidence of efficacy for BPSD

The anticonvulsants gabapentin and carbamazepine have been studied in uncontrolled case series or time−limited trials in patients with BPSD. Results are mixed.[250] 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.[139,251]

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 BPSD, especially to reduce agitation and aggression in some patients with dementia. 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).[252] This study needs replication with larger samples of patients.

Patients with aggressive sexual disinhibition, in whom medical and medication causes have been ruled out, might be appropriate candidates for treatment with an SSRI antidepressant (first choice), or anti–

androgens, luteinizing hormone-releasing hormone (LHRH) agonists, or estrogen, since these agents have some support from case studies and case reviews.[253,254]

A number of studies suggest a 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, however some improvement in behavioral and affective symptoms in patients taking melatonin (2.5 mg/day).[255]

Fall risk with psychoactive drugs

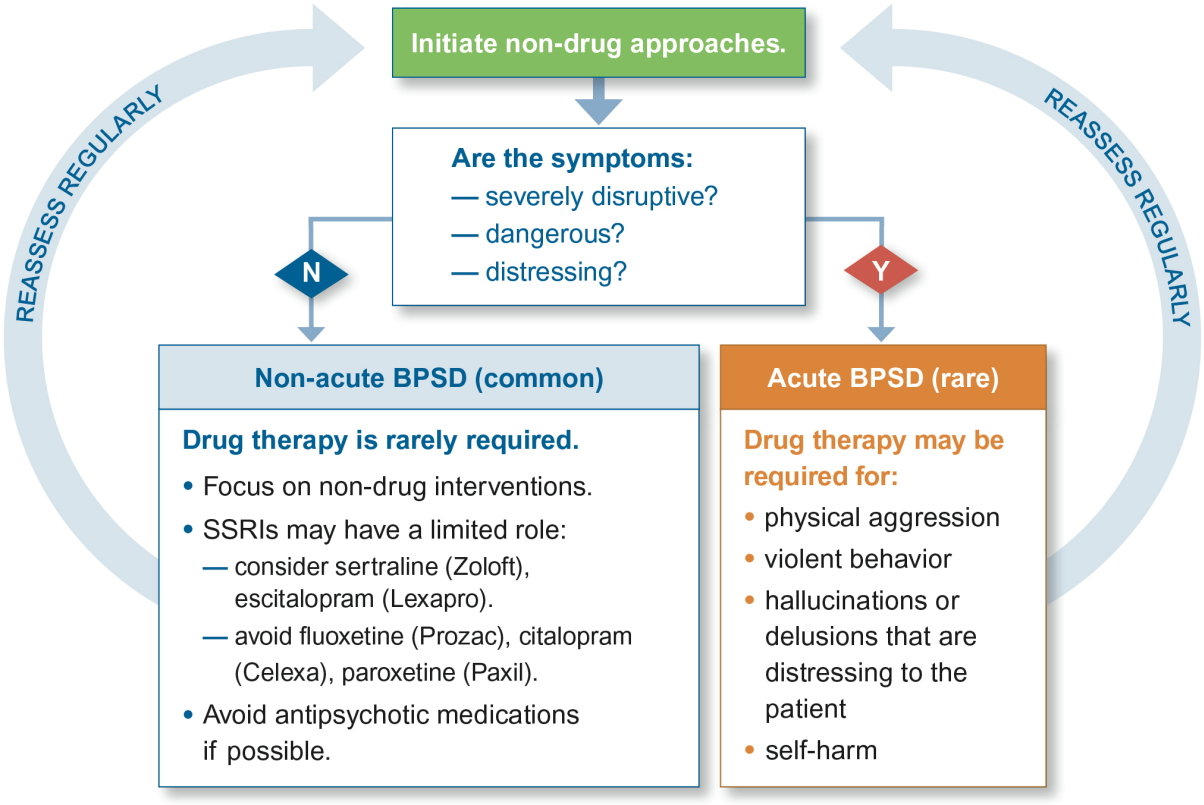
All of the drug classes reviewed above (except SSRI antidepressants) have been shown to increase the risk of falls, both in the initiation phase and with long-term use (Table 16).

Table 16: Fall risk with psychoactive drugs used for BPSD[256-258]

Long-term use	OR	95% Confidence Interval
Antidepressants	1.72	1.40-2.11
Antipsychotics	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	4.70	1.30-16.2
SSRI antidepressant	0.80	0.20-3.40

BOTTOM LINE: in managing BPSD follow the general principles summarized in Figure 21 on the following page.

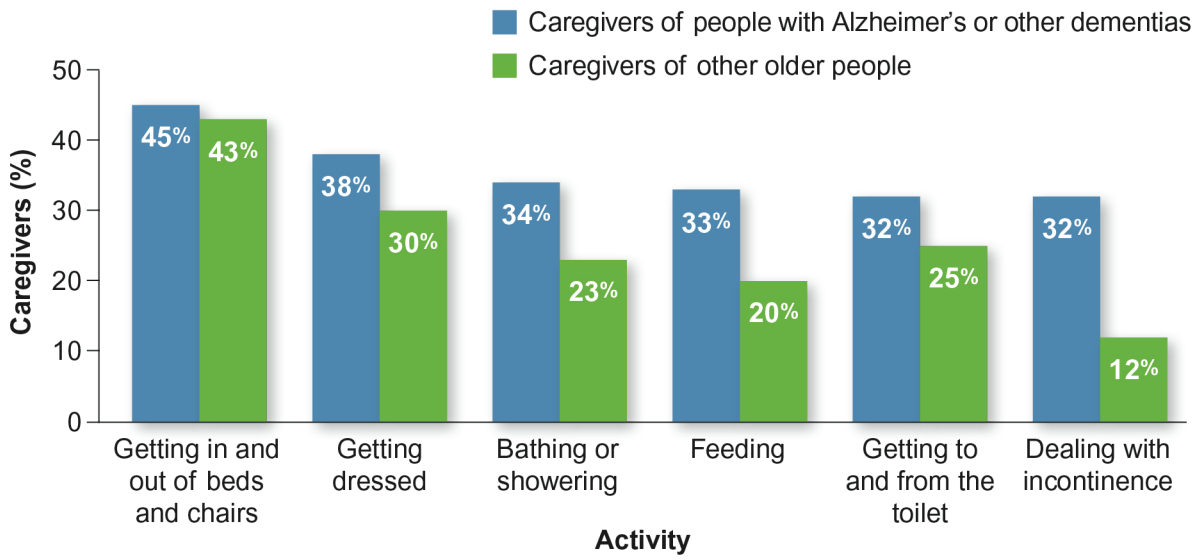
Figure 21: Algorithm for managing BPSD[188]



Caregiver support

At least 15 million family members and friends provide unpaid care for a person with AD or another dementia in the United States.[1] The effectiveness of long−term management of patients with dementia is largely dependent on these caregivers; as such, it is 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.

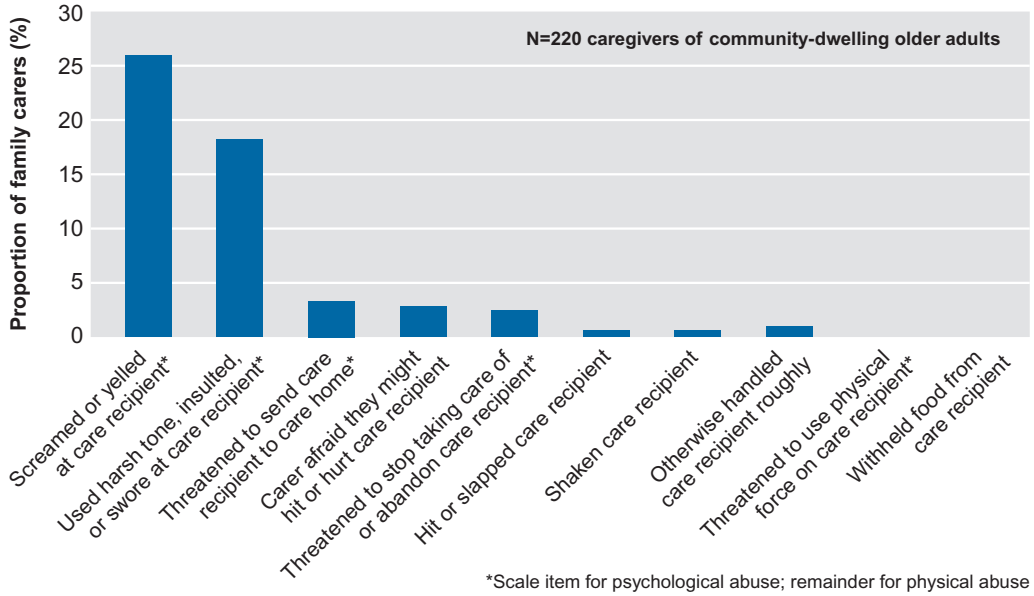
Figure 22: Community caregiver tasks[1]



Caring for a person with AD can be very demanding, and such caregivers are at increased risk for depression and illness.[259] 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.[260] These factors can 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 were self-reported.[261]

Figure 23: Self-reported caregiver behaviors[261]



Ideally, caregivers would receive assistance in caregiving, periodic assessment of their own health and welfare, support from family and friends, and respite care. 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.[262] Pharmacologic interventions for the person with dementia (e.g., use of anticholinergics or antipsychotic medications) show 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.[262]

Teaching caregivers how to change or modify their interactions with the patient has been reported to be effective.[205,263] 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. Programs of counseling and support for caregivers have also been shown to substantially increase the time spousal caregivers were able to care for AD patients at home.[264] Patients whose spouses received the intervention experienced a 28% reduction in the rate of nursing home placement compared with usual care controls, with a difference in time to placement of 557 days.[264]

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.[265] Discussing the benefits and disadvantages of institutional care with caregivers can be challenging, particularly in cases where 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.[266] 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 is also important to help caregivers understand that just because a person's declarative memory is failing, his or her emotional responsiveness likely remains intact.[267] Recent research suggests that people with even severe declarative or short−term memory loss continue to feel the emotions of an event even after they have forgotten the event itself.[267] They may continue to feel sad from an upsetting event, for example, or feel 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.

Here are some suggestions for supporting caregivers and reducing their stress:[262]

- Engage the caregiver as a member of the care team.
  - ask about caregiving problems, health status, and elder abuse
- Encourage the caregiver to improve 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
- Encourage use of technology (e.g., mobility monitors, lift systems for transfers).
- Refer for assistance with care (e.g., Alzheimer's Association, home care services).

BOTTOM LINE: caring for a person with dementia is demanding and raises the risk for physical and mental disorders. Family and other caregivers need support and attention from primary care providers and social workers to maintain their own health and to be able to continue caring for the person with dementia.

Conclusions

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 the physician or team managing dementia are:

- To look for and address any underlying 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 such as concurrent medical conditions and adverse drug effects, that can worsen the underlying cognitive decline

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, although patients with cognitive or mood complaints and those at risk, particularly those with depression, post-traumatic stress disorder (PTSD), and traumatic brain injury (TBI), stand to benefit from early screening and diagnosis. The short screening tests and questionnaires reviewed in this document can reliably identify cognitive impairment and dementia compared to routine history and physical examination alone. Screening is used to identify patients who should undergo more detailed evaluations by neurologists or other specialists to determine underlying causes or factors contributing to cognitive impairment, as well as to track the progress of the condition.

A range of non−pharmacological strategies exist to stabilize cognition and to improve quality of life for both patients with dementia and their caregivers, and these should be fully explored given their lack of adverse effects. 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 therapeutic trials being time−limited and guided by regular assessment of response. Unfortunately, in most cases, this determination is unavoidably subjective.

Goals in managing BPSD include identifying and modifying triggers and initiating non−drug interventions first in most patients. If medication treatment is necessary, consider empirical pain management, SSRI antidepressants, cholinesterase inhibitors, or memantine, as appropriate in the individual patient. APMs should be used only if other alternative therapies are unsuccessful. Frequent reassessment of the need for ongoing medication use as well as monitoring for specific side effects are critical.

Appendix 1: The Mini−Cog Test

The Mini−Cog Test uses a 3-item recall test and the clock drawing test to assess delayed recall and executive functioning.[268] It is a non−specific test designed to quickly screen for gross abnormalities and a trigger for further evaluation. This test may be too simple to monitor treatment response.

Ask patient to repeat and remember 3 items (e.g., ball, car, man).

Clock drawing test (CDT)

"This is a clock face. Please put in the numbers and hands to show 10 minutes after 11 o'clock."

Ask patient to recall the 3 items above.

Impairment in the clock drawing test or item recall test warrants more detailed assessment with the Mini-Mental States Exam (MMSE) or another instrument.

SCORING

3 recalled words	Negative for cognitive impairment
1-2 recalled words + normal CDT	Negative for cognitive impairment
1-2 recalled words + abnormal CDT	Positive for cognitive impairment
0 recalled words	Positive for cognitive impairment

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About this publication

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

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