Chapter 73: Alzheimer Disease

Kristin M. Zimmerman; Emily P. Peron; Ericka L. Crouse; Lana J. Sargent; Sarah E. Hobgood

UPDATE SUMMARY

Update Summary

June 24, 2023

The following sections and tables were updated:

- Addition of Lecanemab-irmb in Tables 73-3 and 73-7 and in section "Anti-amyloid Monoclonal Antibody"
- Addition of details regarding FDA approval of brexpiprazole to section "Pharmacotherapy of Neuropsychiatric Symptoms—Antipsychotics"

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 53, Alzheimer Disease.

KEY CONCEPTS

KEY CONCEPTS

1. Alzheimer disease (AD) is the most common cause of dementia, the prevalence of which increases with each decade of life.
2. The etiology of AD is unknown, and current pharmacotherapy neither cures nor arrests its pathophysiology.
3. Amyloid plaques and neurofibrillary tangles (NFTs) are the pathologic hallmarks of AD; however, the definitive cause of this disease is yet to be determined.
4. AD affects multiple areas of cognition and is characterized by a gradual onset with a slow, progressive decline.
5. A thorough physical examination (including a neurologic examination), as well as laboratory and imaging studies, are required to rule out other disorders and diagnose AD before considering pharmacotherapy.
6. Pharmacotherapy for AD focuses on impacting three domains: (1) cognition, (2) neuropsychiatric symptoms, and (3) functional ability.
7. Nonmedication therapy and social support for the patient and family are the primary treatment interventions for AD.
8. Cholinesterase inhibitors and memantine are used to treat cognitive symptoms of AD, whereas immunotherapies may have the potential to be disease-modifying.
9. Aducanumab and lecanemab, amyloid beta-directed antibodies, were Food and Drug Administration (FDA) approved recently for AD via accelerated approval. Two other agents have been designated breakthrough therapy and are continuing to be evaluated.
10. Appropriate management of vascular disease risk factors may reduce the risk for developing AD and may prevent the worsening of dementia in people with AD.
11. A thorough behavioral assessment with careful examination of environmental factors should be conducted, and a plan put in place before initiating medication therapy for behavioral symptoms.

BEYOND THE BOOK

BEYOND THE BOOK

Visit the Mini-Cog website at http://mini-cog.com. At the top of the screen select from the "Mini-Cog Versions" drop-down menu the "Standardized Mini-Cog Instrument" tab:

1. Review the three-step process and scoring guidelines. You do not need to print this document, as you can simply draw a circle on a blank piece of paper for your partner to use while you take notes on a separate piece of paper.
2. Work with a classmate to practice administering the Mini-Cog to each other and scoring it accordingly.
3. If you get stuck or are not sure how to score an item, return to the "Mini-Cog Versions" drop-down menu and select "Administering the Mini-Cog" and/or "Scoring the Mini-Cog."
4. You may have questions after working through this exercise, perhaps related to test logistics or next steps. If that is the case, consider returning to the "Mini-Cog Versions" drop-down menu and visiting the "FAQs" page.

This activity is intended to increase your familiarity with a brief, freely available dementia screening tool that is often used in clinical settings and as part of the Medicare Annual Wellness Visit. The Mini-Cog can be administered by any health professional or trained lay health worker.

INTRODUCTION

I now begin the journey that will lead me into the sunset of my life.

—Ronald Reagan

Dementia is an umbrella term used to define the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities that interferes with a person's daily life and activities. Mild cognitive impairment (MCI) often proceeds dementia, but not all cases progress to dementia. There are a variety of diseases and pathologies that cause dementia, with Alzheimer disease (AD), which is a gradually progressive dementia affecting cognition, behavior, and functional status, being the most common. The exact pathophysiologic mechanisms underlying AD are not entirely known, and no cure exists.[1] Although medications may reduce AD symptoms for a time, the disease is eventually fatal.

Alzheimer disease profoundly affects the family as well as the patient. The need for supervision and assistance increases until the late stages of the disease, when people with AD become totally dependent on a caregiver for all basic needs. To address the growing AD crisis facing the United States, the first national strategic plan, the National Alzheimer's Plan, was released in 2012 with the goal of coordinating efforts across the federal government to prevent and treat AD, increase public awareness, and improve the quality of care and support for patients and their caregivers.[2] The US Department of Health and Human Services has since updated this strategic plan to include a timeline for achieving its goal to "develop effective prevention and treatment modalities by 2025."[2]

EPIDEMIOLOGY

1 AD is the most common cause of dementia, accounting for 60% to 80% of cases, although multiple etiologies can result in dementia (Table 73-1).[3,4] This chapter focuses exclusively on dementia of the Alzheimer type. However, the reader is encouraged to use the nonpharmacologic approaches and management of behavioral problems outlined in this chapter as a general treatment approach for other types of dementia that may share similar features with AD.

TABLE 73-1

Common Types of Dementia

Alzheimer disease
Vascular dementia
Dementia with Lewy bodies
Mixed dementia
Others (eg, Parkinson disease dementia, Frontotemporal dementia, Huntington disease, Creutzfeldt–Jakob disease)
Potentially reversible causes of cognitive dysfunction (eg, normal pressure hydrocephalus, thyroid dysfunction, vitamin B_{12} deficiency, delirium, depression, Wernicke–Korsakoff syndrome, infectious and autoimmune encephalitis)

Data from References 2 and 5.

Approximately 6.2 million adults age 65 years and older in the United States have AD, and by the year 2050, this number is projected to double.[3] Factors determining age of onset and rate of progression remain largely undefined. Onset can be as early as age 30 years, resulting in the arbitrary age classifications of early-onset (younger than age 65 years) AD (EOAD) and late-onset (age 65 years and older) AD (LOAD).[3] Though increasing age is the greatest risk factor for AD, AD is not a normal part of aging.

In people age 65 years and older, survival following AD diagnosis is typically 4 to 8 years but may be as long as 20 years.[3] AD is the fifth leading cause of death for those age 65 years and older in the United States; however, death among people with AD is often not a direct result of the disease but rather the functional impairments that accompany it.[3] Among the most common causes of death in people with AD is pneumonia, possibly resulting from swallowing difficulties and immobility in the terminal stage of the disease.[3] Those diagnosed with AD spend, on average, more years in the most severe stage of the disease than any other stage, and much of this time is spent in a nursing home.[3]

ETIOLOGY

Genetics

2 The exact etiology of AD is unknown; however, several genetic and environmental factors have been explored as potential causes. Genetic factors have been linked to both EOAD and LOAD, although dominantly inherited forms of AD account for less than 1% of cases.[6] More than half of early-onset, dominantly inherited cases of AD can be attributed to alterations on chromosomes 1, 14, or 21. These alterations largely impact the processing of a large membrane protein called amyloid precursor protein (APP). APP is typically broken down by three major secretase enzymes—α-, β-, and γ-secretase—into nonpathologic fragments as well as potentially pathologic 38 to 43 peptide-long β-amyloid peptide (Aβ) fragments. Of these enzymes, α-secretase is responsible for ensuring that APP is broken down into nonpathologic fragments. Relative alterations in the activity of β- and/or γ-secretase may prove pathologic.[7] As a result, these enzymes may be considered potential therapeutic targets.

Rare, autosomal dominant forms of EOAD have been found in *APP* and the presenilin genes (*PSEN1* and *PSEN2*). Scientists have identified more than 160 mutations in *PSEN1* and *PSEN2*, and these mutations result in increased activity of γ-secretase, which may yield larger and more harmful Aβ fragments.[8,9] The *APP* is encoded on chromosome 21. Only a small number of EOAD cases have been associated with mutations in the *APP* gene, resulting in overproduction of Aβ or an increase in the proportion of Aβ ending at peptide 42.[8,9] Presence of these mutations, however, is often indicative of disease development.

Genetic susceptibility to LOAD is primarily linked to the apolipoprotein E (*APOE*) genotype. Hypothetically, *APOE* (a cholesterol transport gene) may be implicated in the pathogenesis of the disease. There are three major subtypes or alleles of *APOE—*2*, **3*, and **4*. Inheritance of the *APOE*4* allele accounts for much of the genetic risk in LOAD.[10] The mechanism through which *APOE*4* confers an increased risk is unknown, although *APOE*4* is associated with factors that may contribute to AD pathology, such as abnormalities in mitochondria, cytoskeletal dysfunction, and low glucose usage.[11] The risk for AD is two- to threefold higher in individuals with one *APOE*4* allele and 12-fold higher in individuals with two *APOE*4* alleles compared to

those with no *APOE*4* alleles.[11] Moreover, onset of symptoms occurs at a relatively younger age as compared with people having no *APOE*4* alleles or only one copy of *APOE*4* in their genotype.[11] The prevalence of individuals who carry two copies of the *APOE*4* alleles is only 2%, while the prevalence of those carrying one allele is 25%. The *APOE*4* allele is not diagnostic of AD, essential for disease presence, or indicative of future disease development. Additionally, the association between *APOE* genotype and AD differs based on ancestral background.[12]

Additional genetic explanatory factors continue to be investigated with a focus on differences in race and ethnicity. Genome-wide association studies (GWAS) have been done on large cohorts of healthy individuals and those with AD, which has led to the identification of more genetic variants. One with the highest post-GWAS research success is the ATP-binding cassette transporter A7, *ABCA7* gene.[13] Both *APOE* and *ABCA7* are involved in lipid metabolism and are the strongest heritable contributors for genetic risk.[14] Important research continues to explore the effects of genetic variations on cognitive function within diverse populations.

Environmental and Other Factors

A number of factors are associated with an increased risk of AD, including age, decreased reserve capacity of the brain (eg, reduced brain size, low educational level, reduced mental and physical activity), head injury, Down syndrome, depression, MCI, and risk factors for vascular disease (eg, hypercholesterolemia, hypertension, atherosclerosis, coronary heart disease, smoking, elevated homocysteine, obesity, metabolic syndrome, diabetes).[3,4,15] Whether these vascular risk factors are true causal risk factors for AD contributing to AD pathology, or whether they result in cerebrovascular pathology that, in turn, contributes to the symptoms of AD, remains to be established. The incidence of AD rises with increasing age, and AD may develop in individuals over the course of decades, suggesting that AD is a disease that likely develops throughout adulthood.[3] Of note, more females than males have AD.[3] While this may largely be a factor of females living longer than males, hypothetically, males who live to be older than 65 years may have better cardiovascular risk profiles than females of the same age; this is commonly referred to as "survival bias."[3] An analysis of the complex interactions between age, sex, vascular health, and AD is beyond the scope of this chapter.

PATHOPHYSIOLOGY

3 The signature lesions in AD include amyloid plaques and neurofibrillary tangles (NFTs) located in the cortical areas and medial temporal lobe structures of the brain.[1,15,16] Along with these lesions, degeneration of neurons and synapses as well as cortical atrophy occurs. It is unclear if or how these lesions are definitively implicated in the development of AD symptoms. This is particularly true as plaques and NFTs may also be present in other diseases, even in normal aging. Importantly, however, AD-affected subjects appear to have a higher burden of plaques and NFTs in their younger years compared to age-matched controls. Several mechanisms have been proposed to explain changes in the brain that result in symptoms of AD, including misfolding of proteins (Aβ aggregation and deposition leading to the formation of plaques and tangles), synaptic failure and depletion of neurotrophin and neurotransmitters, and mitochondrial dysfunction (oxidative stress, impaired insulin signaling in the brain, vascular injury, inflammatory processes, loss of calcium regulation, and defects in cholesterol metabolism).[1,10,16]

Amyloid Cascade Hypothesis

Cleavage of APP via β- and γ-secretase produces Aβ fragments that are 36 to 43 amino acids in length. Amyloid clearance pathways include degradation by enzymes such as neprilysin-1, phagocytosis by glial cells, or transportation into the vasculature. If not cleared, these soluble, monomeric Aβ fragments can aggregate. These aggregations can include soluble but toxic oligomers or protofibrils, or less soluble, larger, extracellular fibrils and plaques.[17,18] While less common than other Aβ peptides, $Aβ_{42}$ is prone to aggregation and plaque formation.[1,19] Amyloid can also aggregate in the perivascular space between neurons and vessels, as well as vascular smooth muscle and basement cell membranes, contributing to cerebrovascular damage.[17,18]

The amyloid cascade hypothesis states that there is an imbalance between the production and clearance of Aβ peptides resulting in their accumulation and aggregation, insoluble extracellular plaque formation, and ultimately the development of AD.[1,17,19] More recent versions of the amyloid cascade hypothesis assume that soluble oligomer and protofibril forms of Aβ that are not sequestered in plaques actually drive the disease by binding to cell surface receptors, metals, and cellular membranes.[1,17,19] Additionally, it is unknown whether the presence of Aβ in any of these forms is the primary pathology responsible for AD development, or whether these changes are a marker of an alternate pathology. If treatments that reduce Aβ production

or remove brain Aβ fail to arrest disease progression in those with early or prodromal disease, it would argue amyloidosis is not the primary pathology in most individuals with AD.

Neurofibrillary Tangles

At the same time Aβ was being identified in plaques, other researchers found that NFTs are common in the cells of the hippocampus and cerebral cortex (regions implicated in AD symptoms) in people with AD. These NFTs are composed of abnormally hyperphosphorylated tau protein. Tau protein provides structural support to microtubules, the cell's transportation, and skeletal support system.[4] When tau filaments undergo abnormal phosphorylation at a specific site, they cannot bind effectively to microtubules, and the microtubules collapse. Without an intact system of microtubules, the cell cannot function properly and eventually dies. Hypothetically, soluble forms of Aβ may trigger initial tau phosphorylation. In general, NFT density correlates with severity of dementia; however, NFTs are found in other dementing illnesses besides AD and may represent a common method by which various inciting factors culminate in cell death.[16,17,20]

Inflammatory Mediators

Inflammatory or immunologic paradigms are additional hypotheses relevant to AD neurodegeneration.[1] Inflammatory/immunologic hypotheses argue that although Aβ may have direct neurotoxicity, at least some of Aβ toxicity might actually be an indirect consequence of an immune response mediated by Aβ protofibril–induced microglia activation and astrocyte recruitment. This inflammatory response may represent an attempt to clear amyloid; however, it is also associated with release of cytokines, nitric oxide, other radical species, and complement factors that can both injure neurons and promote ongoing inflammation.[1] Indeed, levels of multiple cytokines and chemokines are elevated in AD brains, and certain proinflammatory gene polymorphisms are reported to be associated with AD.[1,21]

Cholinergic Hypothesis

Multiple neuronal pathways are destroyed in AD and neuronal damage can be seen in conjunction with plaque structures.[1,16] Widespread cell dysfunction or degeneration results in a variety of neurotransmitter deficits, with cholinergic abnormalities being among the most prominent.[1,10] Loss of cholinergic activity correlates with AD severity. In the late stage of AD, the number of cholinergic neurons is reduced, and there is loss of nicotinic receptors in the hippocampus and cortex. Presynaptic nicotinic receptors control the release of acetylcholine as well as other neurotransmitters important for memory and mood, including glutamate, serotonin, and norepinephrine.[1,10]

The discovery of vast cholinergic cell loss led to the development of a cholinergic hypothesis of AD which targeted cholinergic cell loss as the source of memory and cognitive impairment in AD. Consequently, increasing cholinergic function would improve symptoms of memory loss. This approach is flawed because cholinergic cell loss is a secondary consequence of AD pathology, not the disease-producing event, and cholinergic neurons are only one of many neuronal pathways destroyed in AD. Simple addition of acetylcholine cannot compensate for the loss of neurons, receptors, and other neurotransmitters lost during the course of the illness. Thus, cholinergic therapies are used to minimize or improve symptoms through augmentation of cholinergic neurotransmission at remaining synapses.

Other Neurotransmitter Abnormalities

Although the cholinergic system has received particular attention in AD pharmaceutical research, deficits also exist in other neuronal pathways. For example, serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus coeruleus are lost, while activity of dopamine-metabolizing monoamine oxidase type B is increased. In addition, abnormalities appear in glutamate pathways of the cortex and limbic structures, where a loss of neurons leads to a focus on excitotoxicity models as possible contributing factors to AD pathology.

Glutamate is the major excitatory neurotransmitter in the cortex and hippocampus. Many neuronal pathways essential to learning and memory use glutamate as a neurotransmitter, including the pyramidal neurons (a layer of neurons with long axons carrying information out of the cortex), hippocampus, and entorhinal cortex. Glutamate and other excitatory amino acid neurotransmitters have been implicated as potential neurotoxins in AD.[16] Dysregulated glutamate activity is thought to be one of the primary mediators of neuronal injury after stroke or acute brain injury. Although intimately involved in cell injury, the role of excitatory amino acids in AD is yet unclear; however, blockade of *N*-methyl-D-aspartate (NMDA) receptors decreases activity of glutamate in the synapse and may hypothetically lessen the degree of cellular injury in AD.

Apolipoprotein E

The fat-soluble transporter *APOE* is synthesized in the liver, central nervous system, and cerebrospinal fluid (CSF). It is responsible for transporting cholesterol in the blood and through the brain and interacts with Aβ in almost all pathways, including in its neuronal, glial, and vascular clearance. It is carried by low-density lipoprotein into neurons where it also binds to NFTs. The *APOE*4* allele, previously discussed under genetics, is associated with both modified clearance and increased deposition of Aβ in AD. It is also thought to act as an accelerating modulator in vascular dementia. The *APOE*4* allele is considered a strong risk factor for both EOAD and LOAD, whereas *APOE*2* is associated with a lower risk, and *APOE*3* a protective effect.[18,22]

Brain Vascular Disease and High Cholesterol

There is growing evidence of a causal association between cardiovascular disease and its risk factors and the incidence of AD. Cardiovascular risk factors that are also risk factors for dementia include hypertension, hypercholesterolemia, and diabetes.[23] For a given amount of AD pathology, vascular disease in the brain may compound the degree of cognitive impairment observed.[19] Vascular disease may accelerate amyloid deposition and reduce clearance of Aβ from the brain.[24] Presence of cardiovascular risk factors in midlife is strongly associated with development of AD in late life.[24] Midlife hypertension is adversely associated with AD, while late life hypertension may be inversely associated. Blood pressure decreases in the years leading up to clinical onset of dementia, conceivably because of reductions in physical activity and body weight.[24]

Mechanistically, the increased risk of AD seen among people with prediabetes and diabetes may be a result of microvascular damage or direct neurotoxicity related to increased glucose and insulin levels.[24] Disturbances in insulin-signaling pathways, both in the periphery and the brain, have been linked to AD. Insulin may also regulate the metabolism of Aβ and tau protein.[25]

Research has found multiple links between cholesterol and AD. Elevated cholesterol levels in brain neurons may alter membrane functioning and result in the cascade leading to plaque formation and AD.

Other Mechanisms

Other hypotheses proposed to explain AD pathogenesis include oxidative stress, mitochondrial dysfunction, and loss of estrogen. Each of these mechanisms may contribute to AD pathogenesis, but the extent of their contribution is uncertain. There is a growing body of evidence regarding the role of oxidative stress and the accumulation of free radicals in the brains of people with AD.[4] Some epidemiologic studies suggest vitamin E, and possibly the combination of vitamin E and vitamin C, may reduce AD risk, while others do not.[26] Mitochondrial dysfunction may result in disruption of energy metabolism in the neuron.[1,15] The role of estrogen in cognitive aging and dementia continues to be an active area of investigation. Despite convincing evidence that estrogens affect the brain in ways that would be expected to improve cognitive aging and reduce the risk of AD, the results of clinical studies have been largely disappointing.[27]

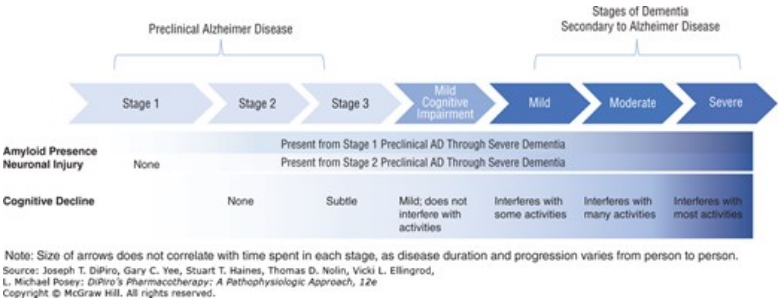
A single common mechanism for developing AD does not exist. Regardless of the etiology, however, the features remain the same: degeneration of neurons in higher brain areas; accumulation of NFTs and amyloid plaques; profound destruction of cholinergic pathways; and an insidious dementia, slowly progressive until death.

CLINICAL PRESENTATION

4 In the absence of abrupt changes in cognition or function, the onset of AD can be almost imperceptible. There are often pathologic changes related to AD long before symptoms emerge, and further deficits occur progressively over time, affecting multiple areas of cognition and function.[3,15] Figure 73-1 depicts the transition from preclinical AD to dementia of the Alzheimer type. Early disease may be characterized by changes in learning and memory, planning and organization, and mood. If these deficits do not impact patient function, the patient may be considered to have MCI. Approximately 15% of patients with MCI will develop dementia after 2 years.[3] Within 5 years, approximately one-third will develop dementia of the Alzheimer's type.[3] Patients with MCI may or may not experience further decline that impairs function and transition to dementia. These patients represent a critical juncture in evaluation, management, and potential mitigation of further cognitive decline.[3]

FIGURE 73-1

The continuum of Alzheimer disease: Progression of pathophysiology and clinical symptoms of AD. (*Data from References 28 and 29.*)



As pathology progresses, patients may experience further decline in these domains, as well as changes in personality, judgment, speech, and spatial orientation that begin to impact function. In the late stages of dementia, functional decline may be associated with gait changes, swallowing difficulties, and incontinence symptoms; behavioral changes may also result. For treatment and assessment purposes, it is helpful to divide AD symptoms into two basic categories: cognitive symptoms and neuropsychiatric (behavioral) symptoms. Cognitive symptoms are present throughout the illness, whereas behavioral symptoms are less predictable. Table 73-2 and Fig. 73-1 summarize the stages of AD.

TABLE 73-2

Stages of Alzheimer Disease

Mild (MMSE score 26–21)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems.
Moderate (MMSE score 20–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recall of recent events is severely impaired. May forget some details of past life events and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common.
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week.

MMSE, Mini-Mental State Examination.

Data from References 5 and 30.

CLINICAL PRESENTATION: Alzheimer Disease

General

- The patient may have vague memory complaints initially, or the patient's friends or family may report that the patient is "forgetful." Cognitive decline is typically gradual over the course of illness. Behavioral disturbances may be present in moderate stages. Loss of daily function such as dressing, bathing, and toileting is common in advanced stages.

Symptoms

Cognitive

- Memory loss (poor recall and losing items)
- Aphasia (circumlocution and anomia)
- Apraxia
- Agnosia
- Disorientation (impaired perception of time and unable to recognize familiar people)
- Impaired executive function

Neuropsychiatric

- Depression, psychotic symptoms (hallucinations and delusions)
- Behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness)

Functional

- Inability to care for self (dressing, bathing, toileting, and eating)

Diagnosis

According to the 2021 World Alzheimer Report, dementia is often underdetected, underdiagnosed, and subsequently undertreated and undermanaged.[31] Up to 75% of individuals seen in a primary care setting are not given an AD diagnosis.[32] Reasons for this include lack of awareness by patients or their family and friends that the early decline may be associated with AD, or limitations due to clinician awareness, training, and/or time.[32] Despite the phenomenon of underdiagnosis, the US Preventive Services Task Force concluded that there are insufficient data to recommend for or against routine cognitive screening in the absence of symptoms as the benefits may not outweigh the risks, as evidence does not suggest that screening impacts decision making.[32] However, screening for cognitive impairment is a required element of the Medicare Annual Wellness Visit.[33,34] Screening should always occur in the presence of symptoms recognized by the patient, family, or clinician. Discussing the diagnosis of dementia is potentially distressing for patients and their loved ones, especially during initial discussions. Most people, however, prefer to be told about a dementia diagnosis, as it allows them to appropriately plan and access necessary support and treatment services in the meantime.[5]

The Mini-Mental State Examination (MMSE) is a 30-point assessment tool for AD frequently cited in the literature and employed in practice; because of its copyrighted status; however, the MMSE must either be administered from memory or paid for by the user. Similarly, the Montreal Cognitive Assessment became proprietary in 2019, and users must now be trained and certified.[35] Alternatives include the Mini-Cog and the Saint Louis University Mental Status Exam.[36] Each of these tools varies in their characteristics, including sensitivity and specificity, for identifying an underlying dementia.

The only way to confirm a clinical diagnosis of AD is through direct examination of brain tissue at autopsy or biopsy. Several criteria have been used in clinical practice and research for the detection and diagnosis of dementia, including the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria,[37] the Agency for Healthcare Research and Quality guidelines,[38] the American Academy of Neurology guidelines,[39] the National Institute of Neurological Disorders and Stroke criteria,[40] and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria.[41] The *DSM-5* has subsumed the terminology dementia under major neurocognitive disorder; however, the term *dementia* is still often used in clinical practice.[37]

In 2011, revisions to the NINCDS-ADRDA criteria for the clinical diagnosis of AD were recommended by the National Institute on Aging (NIA) and the Alzheimer's Association (AA).[42] The new NIA-AA criteria view AD as a spectrum beginning with a preclinical phase progressing to increasingly severe clinical stages of AD, as depicted in Fig. 73-1. Three workgroups formulated diagnostic criteria for the dementia phase[43]; the symptomatic, predementia phase (MCI)[44]; and the asymptomatic, preclinical phase of AD.[45] The preclinical phase has been further broken down into three stages—stage 1 (asymptomatic cerebral amyloidosis), stage 2 (asymptomatic amyloidosis plus neurodegeneration), and stage 3 (amyloidosis plus neurodegeneration plus subtle cognitive/behavioral decline).[45] In 2018, the American Academy of Neurology updated their practice guideline for MCI.[45,46] Commonalities between guidance documents include the association of impairments in multiple cognitive domains and functional impairment with a clinical diagnosis of AD.

AD remains primarily a clinical diagnosis, but this will likely change as brain imaging, CSF testing, and other AD biomarkers supporting definitive diagnosis become increasingly available for routine clinical use. The patient's examination should suggest that cognitive decline from a previously higher baseline has occurred. The history should corroborate this finding and further indicate that cognitive decline has reached the point where changes in social or occupational functioning are present. It is possible to administer full neuropsychiatric testing—a battery of sophisticated exams that defines cognitive domain strengths and weaknesses and enables a neuroanatomic localization of the observed deficits. When approached in this way, neuropsychiatric testing can indicate a pattern of cognitive decline that is consistent with AD and assist with rendering a diagnosis that is as much a diagnosis of inclusion as it is of exclusion. Neuropsychiatric testing is considered optional but can prove quite useful for the diagnosis of AD, as well as differentiating types of cognitive impairment.

Objectively defining social or occupational dysfunction can prove tricky in the older patient who may be retired, lead a socially restricted lifestyle, or experience frailty. For such patients, the minimal requirement is to establish a negative impact on day-to-day life. Early on, this usually involves a change in instrumental activities of daily living (eg, handling finances and organizing medications) rather than basic activities of daily living (eg, hygiene and dressing). Some AD subspecialists use a detailed, standardized, semistructured interview of a nonpatient informant such as a caregiver as the most critical piece of the diagnostic evaluation.[47]

5 For people who meet criteria for dementia (whether the underlying cause is ultimately suspected to be AD or not), current recommendations from the American Academy of Neurology include a serologic evaluation that includes blood cell counts, serum electrolytes, liver function tests, a test of thyroid function, and a vitamin B_{12} level to rule out other causes of cognitive decline.[39] When circumstances suggest AD is not the leading entity on the differential diagnosis, other neurologic tests such as CSF analysis or electroencephalogram can occasionally be justified.

Guidelines recommend that structural imaging (noncontrast-enhanced computed tomography [or CT] or magnetic resonance imaging [MRI]) be performed in the evaluation of people with suspected dementia.[48] These tests may identify structural abnormalities consistent with AD or other pathology, such as brain atrophy, vascular damage, or tumors. Efforts to define the role of other AD diagnostic tests are ongoing.

Use of preclinical indicators typically reserved for the research setting, such as functional imaging, CSF biomarkers, and genetic tests, may become increasingly important with the emergence of potentially disease-modifying agents. Positron emission tomography, or PET, scanning may be used to identify a pattern of neurodegeneration consistent with AD. Such neurodegeneration may be evidenced by reduced uptake of a glucose tracer, indicating hypometabolism, or by modified uptake of an amyloid- or tau-specific tracer, indicating the presence of CNS pathology.[49] Radiologic tracers specific to amyloid plaques (Pittsburgh compound B [PiB], florbetapir F18, florbetaben F18, and flutemetamol F18) often used in research may be used to identify individuals with early disease; however, without widespread access, clinical utility is limited. Additionally, the diagnostic accuracy of PET scanning alone still lags behind that of the clinical examination and history.[45] The presence of amyloid and tau within the CSF may also be utilized to identify patients with early stages of AD, but similar access and interpretation barriers exist.[50] Likewise, *APOE* genotyping is not clinically

recommended now, as presence of an *APOE*4* allele alone does not cause AD.[51] While *APOE* genotyping by itself is insufficient to make a diagnosis of AD, demonstrating an *APOE*4* allele in a suspected patient increases the specificity of the diagnosis. Unless the person developed dementia before the age of 60 years and also had a parent who developed AD before the age of 60 years, *PSEN1*, *PSEN2*, or APP genotyping is usually not indicated. Unclear benefits, potential harms, and ethical concerns limit testing for genetic causes of dementia as a part of routine diagnosis and should only be completed with informed consent following genetic counseling.[51]

Mild Cognitive Impairment

Aging is associated with changes in cognitive function. Importantly, MCI constitutes a syndromic designation that categorizes people with cognitive complaints insufficient to warrant a dementia diagnosis. The NIA-AA criteria specifically address the diagnosis of MCI.[44,46,52] Approximately 15% of patients with MCI will develop dementia after 2 years.[3,52] While clinicians may be seeing the initial manifestation of a progressive, degenerative dementia that will eventually meet AD diagnostic criteria, not everyone meeting MCI criteria will develop AD.[44,46] When a diagnosis of MCI is made, routine cognitive screening should be done to monitor for further cognitive loss.

TREATMENT

Desired Outcome

6 Approved and investigative pharmacologic therapies have generally failed to demonstrate a reduced risk of progression to dementia, including when used in early MCI.[46,53] As such, the primary goal of treatment in AD is to symptomatically treat cognitive difficulties and preserve patient function for as long as possible. Secondary goals include managing psychiatric and behavioral sequelae. Current AD treatments do not seem to prolong life, cure AD, or halt or reverse the pathophysiologic processes of the disorder.[47]

General Approach to Treatment

Prior to initiating treatment for AD, a thorough medication review should be completed, as many medications can contribute to cognitive impairment in vulnerable individuals, but certain classes are more commonly implicated. Benzodiazepines and other sedative hypnotics, anticholinergics, and antipsychotics have been associated with cognitive impairment.[54] In addition, H_2-receptor antagonists, corticosteroids, and opioids like meperidine have been implicated in cases of delirium or acute cognitive change.[54] Because medication use is a reversible cause of cognitive symptomatology, medication review and management are essential.

Clinical trials demonstrate modest benefits of early and continuous treatment with cholinesterase inhibitors with the addition of memantine in moderate-to-severe disease.[55] Following this approach, along with a symptomatic approach to address behavioral symptoms as they arise, allows for maximal maintenance of cognition and activities of daily living. Considering the Food and Drug Administration (FDA) evaluation of potentially disease-modifying immunotherapies for use in MCI and early AD, it remains to be seen how the place in therapy of cholinesterase inhibitors and/or memantine will change, if at all. Patient and family education at the time of diagnosis, including discussion of the course of illness, realistic expectations of treatment, and the importance of legal and financial planning are essential to appropriate treatment.

Dosing recommendations for patients with renal or hepatic dysfunction or low body weight are detailed in Table 73-3. It is important to consider that most people with AD are older adults and therefore may be taking multiple medications for other acute and chronic health conditions.[56] The benefits of medication therapy for AD and other comorbid medical conditions must be weighed against each medication's time-to-benefit and potential for adverse events.

TABLE 73-3

Dosing of Medications Used for Cognitive Symptoms

Medication	Brand Name	Initial Dose	Usual Range	Specific Populations	Other

Cholinesterase Inhibitors					
Donepezil	Aricept, Aricept ODT, Adlarity transdermal	5 mg daily in the evening (oral)[a] 5-10 mg/day (transdermal patch) applied weekly	5-10 mg daily in mild-to-moderate AD 10-23 mg daily in moderate-to-severe AD	No dosage adjustments recommended	Available as: tablet, ODT, oral solution, transdermal patch Can be taken with or without food Incidence of GI adverse effects (including weight loss) are higher with 23 mg daily dose Therapy interruptions require retitration of dose Store transdermal patch in fridge
Rivastigmine	Exelon, Exelon Patch	1.5 mg twice daily (capsule, oral solution) 4.6 mg/day (transdermal patch)	3-6 mg twice daily (capsule, oral solution) 9.5-13.3 mg/day (transdermal patch)	Capsule, oral solution: Renal impairment, hepatic impairment, or low body weight (<50 kg [<110 lb]): may be able to only tolerate lower doses Transdermal patch: Mild-to-moderate hepatic impairment or low body weight: consider maximum daily dose of 4.6 mg every 24 hours	Available as: capsule, oral solution, transdermal patch Therapy interruptions require retitration of dose Take with meals Also indicated for mild-to-moderate dementia associated with Parkinson disease Use of multiple transdermal patches at the same time is associated with hospitalization and death
Galantamine	Razadyne, Razadyne ER	4 mg twice daily (tablet, oral solution) 8 mg daily in the morning (extended-release capsule)	8-12 mg twice a day (tablet, oral solution) 16-24 mg daily (extended-release capsule)	Moderate renal or hepatic impairment: maximum daily dose of 16 mg Severe renal or hepatic impairment: not recommended	Available as: tablet, oral solution, extended-release capsule Recommended to take with meals
***N*-methyl-D-aspartate (NMDA) Receptor Antagonist**					
Memantine	Namenda, Namenda XR	5 mg daily (tablet, oral solution) 7 mg daily (extended-release capsule)	10 mg twice daily (tablet, oral solution) 28 mg daily (extended-release capsule)	Severe renal impairment: recommended maintenance dose of 5 mg twice daily (tablet, oral solution) or 14 mg daily (extended-release capsule) Severe hepatic impairment: administer with caution	Available as: tablet, oral solution, extended-release capsuleTherapy interruptions require retitration of dose Can be taken with or without food Can open capsule and sprinkle contents on applesauce for ease of administration
Cholinesterase Inhibitor + NMDA Receptor Antagonist					
Memantine + Donepezil	Namzaric	7 mg/10 mg daily (if patient is stabilized on donepezil and not	28 mg/10 mg daily	Severe renal impairment: 14 mg/10 mg daily	Available as: memantine extended-release and donepezil capsule Can be taken with or without food

		currently on memantine) 28 mg/10 mg daily (if patient is stabilized on memantine and donepezil)			Can open capsule and sprinkle contents on applesauce for ease of administration
Anti-amyloid Monoclonal Antibody					
Aducanumab-avwa	Aduhelm	1 mg/kg intravenous solution	Titrated up to 10 mg/kg intravenous once every 4 weeks	No dosage adjustments recommended	Available as 170 mg/1.7 mL and 300 mg/3 mL single-dose vials Must be diluted in 100 mL of 0.9% NaCl and administered over ~1 hour
Lecanemab-irmb	Leqembi	10 mg/kg intravenous solution	10 mg/kg intravenous once every 2 weeks	Has not been studied; no dosage adjustments recommended	Available as 200 mg/2mL and 500 mg/5 mL single-dose vials Must be diluted in 250 mL of 0.9% NaCl and administered over ~1 hour

[a]In cases of insomnia or vivid dreams, may dose in the morning. ODT, orally disintegrating tablet. ER and XR, extended release; NaCl, sodium chloride; GI, gastrointestinal.

Data from References 57–66.

Nonpharmacologic Therapy

7 Evidence has been insufficient to warrant the routine use of non-pharmacologic interventions to prevent or delay the development of dementia or AD. There has been promising evidence; however, that promotion of a healthy lifestyle in mid-life may help modify potential risk factors for LOAD.[67–71] A 2018 meta-analysis found exercise training may delay cognitive decline in persons at risk for AD.[71] Specifically the World Health Organization (WHO) recommends weekly moderate-intensity aerobic exercise (at least 150 minutes) to help preserve functioning and reduce risk.[71]

AD has a profound effect on both the patient and family. Use of nonpharmacologic interventions is the current primary strategy for management of AD, and medications should be used in the context of multimodal interventions. Neuropsychiatric symptoms (also referred to as behavioral and psychological symptoms of dementia [BPSD]) are among the most challenging and distressing symptoms of the disease and may be the determining factor in a family's decision to seek institutional care. Symptoms such as sleep disturbances, wandering, urinary incontinence, agitation, and aggression in patients with dementia are best managed using behavioral interventions rather than medications whenever possible.[55,72]

Upon initial diagnosis, the patient and caregiver should be educated on the course of illness, prognosis, available treatments, legal decisions, and quality of life issues. Caregiving strategies, including stress-management techniques and support group options, should also be discussed. Caregiver education and support programs improve caregiver skill, knowledge, confidence, and quality of life, and even delay time to nursing home placement for their loved one.[73,74] Table 73-4 lists basic principles of care for people with AD.

TABLE 73-4

Basic Principles of Care for the Person with Alzheimer Disease

1. Consider vision, hearing, or other sensory impairments
2. Find optimal level of autonomy and adjust expectations for patient performance over time
3. Avoid confrontation. Remain calm, firm, and supportive if the patient becomes upset. Validate their feelings
4. Maintain a consistent, structured environment with stimulation level appropriate for the individual patient
5. Provide frequent reminders, explanations, and orientation cues; employ guiding, demonstration, and reinforcement
6. Reduce choices, keep requests and demands of the patient simple, and avoid complex tasks that lead to frustration
7. Bring sudden declines in function and the emergence of new symptoms to professional attention
8. Redirect to an enjoyable activity

Data from References 2, 51, 75, and 76.

The general approach to nonpharmacologic strategies for BPSD is to identify the symptom, determine causative factors, and adapt the caregiving environment to remedy the situation.[3] Environmental triggers may include noise, glare, and too much background distraction, including television. Personal discomfort may also trigger behaviors, so it is important to monitor for pain, hunger, thirst, constipation, full bladder, fatigue, infections, skin irritation, personal care, comfortable temperature, fears, and frustrations.[72,74,76] Medical comorbidity is a major source of functional and cognitive impairment in people with AD, so general health maintenance is necessary.[3] Interventions should redirect the patient's attention rather than be confrontational and should specifically address known triggers. Creating a calm environment and removing stressors and triggers is key. Other nonpharmacologic approaches include exercise, light therapy, music therapy, reminiscence therapy, aroma therapy, relaxation techniques, validation therapy, massage and touch therapy, and multisensory stimulation.[74,76] Caregivers should be referred to support services for assistance in developing nonpharmacologic strategies for managing difficult behaviors.

The caregiver must be prepared to face the changes in life that will occur, and acceptance rarely comes easily. Denial on the part of the patient and rationalization on the part of the family are common. The clinician should encourage the family to address legal and financial matters and designate a durable power of attorney for execution of financial and medical decisions once the patient can no longer make those decisions or is deemed incompetent. The caregiver will need to identify resources to provide respite services as they will need time for rest, relaxation, and the conduct of personal business. Eventually, they will need to face critical and difficult questions with respect to institutionalization. Local and national resources, such as the Alzheimer's Association, can provide detailed information regarding support services. Table 73-5 lists this and other referral sources for caregivers. Education, communication, and planning are key nonpharmacologic components of caring for a person with AD. Preparation in the early stages of illness may lessen some caregiver stress as the disease progresses.

TABLE 73-5

Resources for Caregivers of Persons with Alzheimer Disease

The following organizations provide educational literature and information on diagnosis, treatment, social support, and ongoing research in Alzheimer disease:

- US Administration for Community Living, National Family Caregiver Support Program http://acl.gov/programs/support-caregivers/national-family-caregiver-support-program
- National Institute on Aging (NIA) Alzheimer's Disease Education & Referral Center (ADEAR) http://www.nia.nih.gov/health/about-adear-center
- Alzheimer's Association (AA) http://www.alz.org
- Alzforum http://www.alzforum.org
- Caregiver Action Network http://caregiveraction.org
- Family Caregiver Alliance http://www.caregiver.org

Pharmacologic Therapy

Pharmacotherapy for Cognitive Symptoms

Table 73-6 presents pharmacologic treatment recommendations for managing cognitive symptoms in AD. Current guidelines recommend initiation of cholinesterase inhibitors for AD with no preference for a specific agent.[55,77] Galantamine and oral rivastigmine are FDA-approved in mild-to-moderate AD. Donepezil and transdermal rivastigmine are FDA-approved in mild, moderate, and severe disease. Despite inconclusive evidence for early intervention, cholinesterase inhibitors are commonly prescribed off-label prior to formal diagnosis of AD. Memantine is indicated for moderate-to-severe AD, as current evidence does not support its use in earlier disease stages.[55,77] Additional benefit may be achieved when memantine is added to cholinesterase inhibitor therapy in moderate-to-severe AD; however, the data is conflicting.[55,77] There is no evidence supporting combination therapy of more than one cholinesterase inhibitor. Cholinesterase inhibitors have not demonstrated efficacy for use in MCI.[46,53] At present, anti-amyloid monoclonal antibodies are the only drug class indicated for use in patients with MCI due to AD.[61,62]

TABLE 73-6

Pharmacologic Treatment Options for Cognitive Symptoms in Alzheimer Disease

- In MCI due to AD, consider therapy with an anti-amyloid mAb (aducanumab, lecanemab), then titrate to recommended maintenance dose as tolerated
- In mild-to-moderate AD, consider therapy with a cholinesterase inhibitor (donepezil, rivastigmine, or galantamine) or anti-amyloid mAb (aducanumab, lecanemab) then titrate to recommended maintenance dose as tolerated
- In moderate-to-severe AD, consider adding antiglutamatergic therapy (memantine), then titrate to recommended maintenance dose as tolerated; alternatively, consider memantine or cholinesterase inhibitor therapy alone
- Behavioral symptoms may require additional pharmacologic approaches

Data from Reference 74.

Cholinesterase Inhibitors

In the early 1980s, researchers began to examine means to enhance cholinergic activity in people with AD by inhibiting the hydrolysis of acetylcholine through reversible cholinesterase inhibition. Tacrine was the first such medication to be examined in a systematic fashion and is no longer available in the US market, having been replaced by safer, more tolerable cholinesterase inhibitors. The newer cholinesterase inhibitors

donepezil, rivastigmine, and galantamine show similar modest symptomatic improvements in cognitive, global, and functional outcomes in people with mild-to-moderate AD, and duration of benefit varies from 3 to 24 months.[78,79] One open-label extension study of galantamine showed benefit beyond the 24-month mark.[80]

The mechanism of action differs slightly between medications in this class.[81] Donepezil specifically and reversibly inhibits acetylcholinesterase. Rivastigmine is a pseudo-irreversible inhibitor of both butyrylcholinesterase (an "overflow" enzyme to acetylcholinesterase) and acetylcholinesterase. Galantamine is a selective, competitive, reversible acetylcholinesterase inhibitor that also enhances the action of acetylcholine on nicotinic receptors. The clinical relevance of these differences is unknown.

Choice of cholinesterase inhibitor therapy for an individual patient is based primarily on ease of use, patient preference, cost, and safety issues, such as potential for interactions. Pharmacokinetic properties should also be considered, as rivastigmine and galantamine have short half-lives (1.5 and 7 hours, respectively) compared to donepezil (70 hours). If rivastigmine or galantamine treatment is interrupted for several days or longer, the patient should be restarted at the lowest dose and titrated up to the current dose. This is true for all formulations of cholinesterase inhibitors, including the rivastigmine transdermal patch.[57–59] Dosing strategies for cholinesterase inhibitors and memantine are summarized in Table 73-3.

Adverse medication reactions and corresponding monitoring parameters are described in Table 73-7. Cholinesterase inhibitors have similar, pro-cholinergic adverse reaction profiles, and are generally well tolerated. The most frequent adverse reactions associated with these agents are mild-to-moderate gastrointestinal (GI) symptoms (eg, nausea, vomiting, and diarrhea) that may impact appetite and weight.[82] Gradual dose titration over several weeks to months can improve tolerability.[36] Use of extended-release or transdermal dosage form may reduce GI adverse effects. Caution should be used to ensure the previous patch has been removed, prior to placing a new patch, as reports of cholinergic overdose with rivastigmine transdermal has been reported.[83] Alternatives to the immediate-release dosage form are available (e.g., extended release or transdermal) for patients who have complex dosing regimens, tolerability issues, or difficulty swallowing, though cost may be an issue. Bradycardia has been noted to be a potentially dose-limiting adverse effect for the class and use is contraindicated in patients with a heart rate below 50 beats per minute. When this is a concern, consideration should be given to reducing other heart rate–limiting medications (eg, beta-blockers) where appropriate. In patients who report pro-cholinergic increases in urinary frequency, concurrent use of anticholinergic medications with cholinesterase inhibitors should be avoided and nonpharmacologic interventions employed, if possible.[84] Patients and caregivers should be cautioned against abrupt discontinuation of cholinesterase inhibitor therapy, as this can lead to worsening cognition and behavior in some people with AD.[85] Cholinesterase inhibitors may have some potential to cause seizures; however, they may also be related to AD.[57–59]

TABLE 73-7

Monitoring Medication Therapy for Cognitive Symptoms

Medication	Adverse Medication Reaction	Monitoring Parameter	Comments
Cholinesterase inhibitors	Dizziness, syncope, bradycardia, atrial arrhythmias, sinoatrial and atrioventricular block, myocardial infarction	Report of dizziness or falls, pulse, blood pressure, and postural blood pressure change	Dizziness is usually mild, transient, and not related to cardiovascular problems Routine pulse checks at baseline, monthly during dose titration, and every 6 months thereafter
	Nausea, vomiting, diarrhea, anorexia, weight loss	Weight and GI complaints	Take with food to decrease GI upset Usually transient, dose-related GI adverse effects seen with medication initiation, dose titration, or medication switch Frail patients or those with low body weight may be more likely to experience GI adverse effects

			and significant weight loss, particularly when rivastigmine is prescribed or when titrating to donepezil 23 mg GI adverse effects less prominent with transdermal vs oral rivastigmine
	Peptic ulcer disease, GI bleeding	Signs or symptoms of active or occult GI bleeding	Of particular concern for patients at increased risk of developing ulcers, such as those with a history of ulcer disease or concurrently taking NSAIDs
	Insomnia, vivid/abnormal dreams, nightmares	Complaints of sleep disturbances, daytime drowsiness	Donepezil can be taken in the morning to decrease risk of sleep disturbances
Galantamine	Serious skin reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis)	Appearance of skin rash	Discontinue galantamine at first sign of skin rash, unless clearly not medication-related If signs/symptoms are suggestive of a serious reaction, consider alternative treatment and do not rechallenge
Rivastigmine	Allergic dermatitis	Application site reaction spread beyond patch size, evidence of a more intense local reaction (increasing erythema, edema, papules, vesicles), and persistence of symptoms for more than 48 hours after patch removal	Discontinue rivastigmine if evidence of disseminated allergic dermatitis appears Patients sensitized by exposure to the transdermal patch may not be able to take rivastigmine by mouth either; allergy testing and close medical supervision recommended
Memantine	Headache, confusion, dizziness, hallucinations	Report of dizziness or falls, hallucinations	Confusion may be observed during dose titration and is usually transient
	Constipation	GI complaints	Memantine may mitigate GI adverse effects associated with cholinesterase inhibitor therapy
Aducanumab	Amyloid-related imaging abnormalities (ARIA)	MRI at baseline, and prior to 7th and 12th infusions or if a patient experiences symptoms suggestive of ARIA to identify brain edema, microhemorrhage, superficial siderosis Symptoms of headache, confusion, dizziness, visual disturbances, and nausea	Vigilance for ARIA and focal neurologic changes are recommended during the first 8 doses, especially during dose titration
	Hypersensitivity reactions	Angioedema and urticaria (rare)	Discontinue infusion at first sign of hypersensitivity reaction
Lecanemab	ARIA	MRI at baseline (within past 12 months), and prior to 5th, 7th and 14th infusions or if a patient experiences symptoms suggestive of ARIA to identify brain edema, microhemorrhage, superficial siderosis ARIA symptoms include headache, confusion, visual changes, dizziness, nausea, gait difficulty; rarely seizures	Vigilance for ARIA and focal neurologic changes are recommended during the first 7 doses (14 weeks)

	Infusion-related reactions	Fever, flu-like symptoms, nausea, vomiting, hypo- and hypertension, oxygen desaturation	Majority occurred with the first infusion Manage by reducing the infusion rate or discontinue Consider prophylaxis with antihistamines, NSAIDs, acetaminophen or corticosteroids prior to future infusions

ARIA, amyloid-related imaging abnormalities; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from References 55, 57–59, 63, 64, and 66, 86.

The use of high-dose donepezil (23 mg) may be associated with an improvement in cognitive measures; however, some may consider this clinically insignificant.[86] Additionally, this dose is associated with a threefold increased risk of GI effects and a near doubling in the rate of treatment withdrawal, leading to it not being routinely prescribed in clinical practice.

Depending on individual patient response, tolerability, and preference, switching to an alternate dosage form or alternative cholinesterase inhibitor may be necessary during the course of AD treatment. Manufacturer recommendations for this practice are specified in the prescribing information, but the optimal procedure for switching between agents remains uncertain. When switching from one cholinesterase inhibitor to another due to intolerance, a washout period is recommended. Length of the washout period may vary based on pharmacokinetics and time to adverse reaction resolution.[87] Some patients who fail to respond to donepezil, rivastigmine, or galantamine may respond when switched to a different medication with some clinicians preferring an overnight switch to minimize the potential for clinical deterioration.[87] Importantly, loss of benefit over time may not be an appropriate reason to switch cholinesterase inhibitors, as the progressive nature of AD is likely to become more noticeable over time.[87] Indeed, initiation of memantine may be a more appropriate next step as patients progress in their disease course.[51]

In natural disease progression studies, scores on the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-cog) worsen (increase) by an average of five or fewer points over 1 year in mild dementia and 7 to 11 points annually in moderate dementia. Based on these findings, the consensus is that a four-point change in the ADAS-cog (a scale that ranges from 0-70) represents a clinically significant change.[55] Therefore, if a pharmacotherapeutic agent improves (decreases) the ADAS-cog score by four points, one could think of this as having delayed progression of disease symptoms by 6 months. The usefulness of the ADAS-cog in clinical practice is limited because of the administration time. Therefore, it is much more practical to assess changes in disease severity using the MMSE or other assessment tools. An untreated person with AD has an average decline of two to four points in MMSE score per year. Successful treatment would reflect a decline of less than two points a year. It is reasonable to change to a different cholinesterase inhibitor if the decline in MMSE score is greater than two to four points after 1 year with the initial agent.[87]

Antiglutamatergic Therapy

Memantine is the only NMDA receptor antagonist available for AD. Glutamate is an excitatory neurotransmitter in the brain implicated in long-term potentiation, a neuronal mechanism important for learning and memory.[51] Blocking NMDA receptors can mitigate excitotoxic neurotoxicity and potentially provide neuroprotection (as has been suggested in animal models); however, there is no clinical evidence to indicate that memantine confers neuroprotection in AD.[88]

Memantine is indicated for use in moderate-to-severe AD.[63] Its use has been studied in people with moderate and severe AD as monotherapy and in combination with donepezil with favorable results on cognition and function.[77] To date, studies of memantine alone and in combination with cholinesterase inhibitors in mild AD have provided insufficient evidence to support an indication for mild AD.[77]

In tablet or oral solution form, memantine should be initiated at 5 mg once a day and titrated weekly in 5 mg intervals to the target maintenance dose of 10 mg twice daily. The extended-release capsule form of memantine is to be initiated at 7 mg daily and titrated weekly up to a maximum of 28 mg daily. Dose titration is achieved in 7 mg intervals with at least 1 week between dose adjustments. Dosing of 5 mg twice daily (tablet and oral solution) or 14 mg daily (extended-release capsule) is recommended in patients with severe renal impairment (creatinine clearance of 5-29 mL/min [0.08-0.49 mL/s]).[63,64]

Memantine has been well tolerated in randomized clinical trials (RCTs). Common adverse events include headache, constipation, confusion, and dizziness. Post-marketing cases of treatment emergent agitation have been reported as well. It has 100% bioavailability regardless of administration with or without food and protein binding is relatively low (45%). Memantine is not metabolized by the liver, does not inhibit cytochrome P450 activity, and is primarily excreted unchanged in the urine with a half-life of 60 to 80 hours.[63,64]

Role of Combination Therapy

Combination therapy with memantine added to a cholinesterase inhibitor is generally prescribed for people with moderate-to-severe AD, as the medication classes have different mechanisms of action. This practice slows cognitive and functional decline to a significant degree compared to cholinesterase inhibitor monotherapy or no treatment.[89] One trial randomized people with moderate-to-severe AD already receiving stable donepezil treatment to either memantine or placebo. At the end of 6 months, participants randomized to receive memantine and donepezil had significantly better outcomes in measures of cognition, function, behavior, and global status than those continued on donepezil monotherapy. This group also had a lower rate of discontinuation due to adverse events.[90] Based on data from this study and others, memantine may have a role in mitigating GI adverse events associated with cholinesterase inhibitors.

In 2014, a combination product containing memantine extended-release and donepezil was approved by the FDA for moderate-to-severe AD in patients already stabilized on memantine and donepezil.[65] As medication effectiveness was based on bioequivalence with the two active ingredients, the package insert separately lists the most common adverse effects of each and not in combination. This product comes in four fixed dose strengths, and dosage reduction is recommended in the case of severe renal impairment. No dosage adjustments are needed in patients with mild or moderate renal or hepatic impairment and it has not been studied in patients with severe hepatic impairment.

Anti-amyloid Monoclonal Antibody

Disease-modifying immunotherapies have long been of interest in pharmacotherapy development; however, both active and passive immunotherapies against amyloid have historically failed to modify disease course. Additionally, they have resulted in serious adverse events, including brain edema and meningitis, thought to be related to transient increases in vascular amyloid secondary to the clearance and removal of vascular amyloid resulting in cerebral edema or microhemorrhage.[18,19,91,92] Hypothetically, agent selectivity and early disease course intervention may optimize success and mitigate such adverse events. The available and investigational agents vary in their mechanism (active vs passive), amyloid target (eg, more pathological oligomeric vs potentially protective monomeric amyloid, soluble vs insoluble amyloid, amyloid amino acid residue) and binding conformations.[91–95] Although active immunotherapies remain in development, passive immunotherapies have been a large part of the pipeline owing to their ability to provide a more predictable and controlled response.

Four humanized, immunoglobulin G1 monoclonal antibodies have been designated as AD breakthrough therapies by the FDA (ie, aducanumab, lecanemab, donanemab, and gantenerumab), where preliminary evidence indicates substantial improvement over existing therapies on significant endpoints.[96–99] One of these agents, aducanumab, was the first agent controversially approved under this accelerated pathway for use in MCI due to AD and mild AD. Three clinical trials evaluated the safety and efficacy of aducanumab in this population. While all three trials had reductions in biomarker-indicated pathology such as presence of amyloid or tau in a dose and time-dependent manner, two trials were ended early for presumed clinical futility. A later re-analysis of the data found a significant reduction in cognitive, functional, and behavioral decline in only one trial. Under the accelerated pathway, continued approval of aducanumab is likely to be contingent upon verification of clinical benefit in confirmatory trials underway.[96,97] Lecanemab was subsequently approved under the same accelerated pathway following completion of a phase III trial that reduced markers of amyloid and reduced cognitive and functional decline at 18 months.[100–102] It is anticipated that lecanemab will file for traditional FDA approval. Phase III trials of donanemab and gantenerumab have not yet been published, but it is anticipated donanemamb will file for accelerated approval.

Anti-amyloid antibodies bind to and remove various forms of amyloid in the brain. Aducanumab and lecanemab bind to soluble amyloid aggregates in the brain, including oligomer, protofibril, and fibril formations. Donanemab preferentially binds to insoluble amyoids plaques it is hypothesized that differences in amyloid selectivity may be related to efficacy and adverse medication effects.[103,104] It is also thought that the removal of amyloid has potential disease-modifying implications, whether from direct or indirect actions in the disease process.

Each of the FDA-approved anti-amyloid antibody preparations are administered via intravenous infusion, but vary in their dilution, administration, and schedules. Aducanumab is administered every 4 weeks and titrated to a maintenance dose of 10 mg/kg to reduce the likelihood of CNS adverse effects. Lecanemab is administered as 10mg/kg every 2 weeks and does not require titration.[105] These agents are broken down via endogenous pathways and as such are not expected to require dosage adjustments in renal or hepatic impairment. Aducanumab's half-life is approximately 25 days and it reaches steady-state before the fifth dose.[61,62] Lecanemab's half-life is approximately 5-7 days and it reaches steady-state around 6 weeks.[105]

In addition to infusion-related reactions such as urticaria and angioedema, the agents may cause cerebral edema and microhemorrhage. Such CNS-related adverse effects may result in further cognitive decline, focal neurologic changes, and a theoretical increase in risk of intracranial hemorrhage.[61,62] Carriers of *APOE*4* may be at greater risk for these CNS effects owing to a greater burden of vascular amyloid.[106] Screening for baseline cerebrovascular risk and frequent imaging can mitigate these CNS-related effects. Patients at risk for CNS adverse events include those taking anticoagulants and those with underlying cerebrovascular disease. Baseline and monitoring MRI should be conducted to identify patients at risk for these adverse effects, and the development of amyloid-related imaging abnormalities (ARIA) that evidence cerebral edema (ARIA-e) and microhemorrhage (ARIA-h) (see Table 73-7) with treatment. Occurance may warrant medication suspension or discontinuation. Patients should also be monitored for the development of focal neurologic symptoms and have an additional MRI conducted if symptoms warrant. Patients with uncontrolled seizure disorder should be excluded from treatment due to the risk of focal neurologic adverse events.[61,62]

The potential degree and duration of clinical benefit of anti-amyloid antibodies remains largely unclear. The unknown durability of effect and adverse effect profile, combined with the possible decline in self-management capacity to meet the administration and monitoring requirements, render their place in therapy questionable. It is largely unknown what impact therapeutic discontinuation will have on overall progression. In addition, there are access gaps related to reimbursement for medication and ancillary services, as well as the health system resources needed to safely administer and monitor medication use.[107,108] As a result, the Institute for Clinical and Economic review has rated the comparable cost effectiveness of aducanumab as "insufficient" to demonstrate a net health benefit for patients with MCI due to AD or mild AD.[107]

Effect of Current Treatments on Neurodegenerative Processes

AD is a progressive disorder and affected individuals typically experience some degree of cognitive decline and histologic change for years (if not decades) before a diagnosis is made. Therefore, the ideal treatment will be one that not only reverses symptoms by enhancing cognitive function (a symptomatic treatment) but also arrests the neurodegeneration-relevant molecular processes that underlie cognitive decline (a disease-modifying treatment).

Clinical trials for AD prompt consideration of whether positive outcomes suggest either a symptomatic or disease-modifying effect. Any rapid performance improvement in cognitive ability, activities of daily living, or behavioral end points is indicative of a symptomatic effect. All cholinesterase inhibitor agents and memantine demonstrate this pattern, and anti-amyloid antibodies suggests a similar effect. Arrest of decline or a sustained reduction in the slope of decline would argue the presence of a disease-modifying effect; however, it has not been possible to unequivocally demonstrate this in trials of the approved treatments. Long-duration, double-blind, placebo-controlled trials to evaluate whether available agents have disease-modifying effects are difficult to perform, because doing so would require continuing a placebo arm over an extended period, well beyond demonstration of symptomatic benefit. Also, subject attrition over an extended study would complicate both intent-to-treat and observed case analyses.

With cholinesterase inhibitors and memantine, pivotal placebo-controlled trials were followed by open-label extension studies, lasting as long as 5 years. As part of these studies, decline in the treatment group was compared with "projected" placebo groups based on continued follow-up of the placebo groups included in the 6-month randomized phase of the efficacy study, as well as natural history cohorts from the pre-cholinesterase inhibitor therapy era. Although analyses of this sort conclude that, for up to at least 5 years, people receiving treatment exceed their projected nontreatment cognitive performance, no convincing evidence of a disease-modifying effect emerges.[109–112]

Barriers to Clinical Effectiveness Research

Disagreement exists about how best to determine effectiveness of AD treatments. Selection of qualitative vs quantitative assessment may bias a clinician's impression of response as subtle changes are often detected only by psychometric testing. As no standard has been suggested to define the effectiveness of AD medications, great variation exists between clinicians, and the duration of treatment. Realistic expectations for success may include

slowed decline in behavioral, functional, and cognitive abilities and delayed long-term care placement.[113] An initial dramatic improvement in symptoms is unlikely but may be reported by a minority of patients or their caregivers.

Unfortunately, clinical trials have failed to provide answers to key questions in treating people with AD and challenges associated with population heterogeneity and difficulties inherent to the diagnosis, make interpretation of therapeutic response difficult.[114] For example, individuals given a diagnosis for AD often lack the hallmark pathologies (ie, amyloid plaques and NFTs) on postmortem examination. Similarly, clinical trials of potentially disease modifying agents have failed to produce reliable results, indicating that disease stage and preclinical diagnosis may be of increasing importance. Additionally, because of overlap between AD and other dementing illness, trials including those diagnosed with AD may in fact include patients with a heterogenous, mixed profile of dementia. Further, as individuals who fail to display the clinical symptoms of the disease may still be developing the underlying pathologies, there may be contamination of control groups. Each of these factors may present a challenge to the internal validity of clinical trials.

Guidance in extrapolating data related to changes in cognition is needed so a reasonable duration of clinical treatment with pharmacotherapy can be determined. One concern is that those who respond to treatment may lose the benefits of that treatment once the medication is stopped.[115] Gaps in treatment have been linked with worse cognitive outcomes in clinical trial extension studies; however, there is no increased risk of institutionalization or death associated with gaps in cholinesterase inhibitor therapy.[116,117] Regardless, dosing regimens should be simplified and patient and caregiver preferences considered in an effort to improve medication adherence and persistence.

Management of Brain Vascular Health

9 Guidelines for the care of people with AD support the management of vascular brain disease and its associated risk factors as part of treatment.[51] There is a link between AD and cardiovascular disease, including heart failure, atrial fibrillation, and coronary artery disease, and a growing body of evidence that brain vascular disease plays a role in the progression of dementia.[21] Management of brain vascular disease includes monitoring blood pressure, glucose, and cholesterol, and initiation of appropriate interventions.[118–120]

The WHO and Alzheimer's Disease International encourage primary prevention through public health campaigns targeting smoking, underactivity, midlife obesity, midlife hypertension, and diabetes.[121] Adherence to the Mediterranean Diet, Dietary Approaches to Stop Hypertension (DASH) diet, or combination Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet may reduce the risk of cognitive impairment or decline.[24,122] Physical activity is an important component of vascular brain health and is associated with a reduced risk of cognitive impairment.[24,71,123] However, most positive trial findings have been from cognitively healthy older adults.[24,122] While appropriate management of vascular disease risk factors may reduce the risk for developing AD, insufficient evidence exists to draw definitive conclusions on the association between risk factor modification and risk of AD.[24,118]

Other Potential Treatment Approaches

Estrogen

Estrogen replacement has been studied extensively for the treatment and prevention for AD with most, but not all, retrospective epidemiologic studies showing a lower incidence of AD with estrogen replacement therapy after menopause. Prospective clinical trials have not supported the use of estrogen as a treatment for cognitive decline, and longer trials tend to suggest harm. The evidence does not support the use of estrogen to treat or prevent dementia.[27] Although phytoestrogens found in soy-containing foods and soy-derived dietary supplements have been suggested for the treatment or prevention of dementia, there are no clinical trials supporting such use.[27]

Anti-inflammatory Agents

Retrospective epidemiologic studies suggest a protective effect against AD in patients who have taken nonsteroidal anti-inflammatory drugs (NSAIDs); however, the benefits of anti-inflammatory agents have been less compelling in prospective clinical studies. In fact, there is no significant cognitive benefit in persons with AD treated with NSAIDs, aspirin, or steroids.[124] Due to lack of compelling data and a significant incidence of adverse effects, particularly gastritis and the possibility of GI bleeds, these agents are not recommended for general use in the treatment or prevention of AD.[124]

Lipid-Lowering Agents

Four RCTs of statin therapy, given to older individuals at risk for vascular disease, indicated no significant benefit of statin therapy for probable or possible AD.[125] Cognitive impairment has been recognized as a rare adverse event associated with statin therapy.[126] More research is needed to understand the complex relationship between cholesterol, statin therapy, and cognitive functioning but for now, these agents should be reserved for patients who have other indications for their use.

Dietary Supplements

Many nutraceuticals, herbal products, medical foods, and other dietary supplements have been promoted for the prevention and treatment of AD, and available evidence has been reviewed.[127–129] While a detailed discussion of their use is beyond the scope of this chapter, the more commonly used supplements are as follows.

Vitamin E Supplementation

Based on pathophysiologic theories involving oxidative stress and the accumulation of free radicals in AD, significant interest has evolved regarding the use of antioxidants in the treatment of AD. Two RCTs have evaluated the effects of vitamin E supplementation (1,000 IU twice daily) in people with AD. The first studied people with moderate AD for 2 years and had a significant delay in the time to institutionalization in the treatment group compared to placebo.[130] The second studied the efficacy of α-tocopherol, memantine, or their combination in people with mild-to-moderate AD taking an acetylcholinesterase inhibitor (mean follow-up time of 2.3 years) and showed a reduced annual rate of decline in activities of daily living in those treated with vitamin E, but no cognitive benefits were seen.[131] No significant adverse effects were reported between treatment groups in either study; however, according to a meta-analysis high-dose vitamin E increases mortality.[132] In addition, vitamin E had no benefit in people with MCI in the progression to AD,[133] or in preventing dementia in asymptomatic older males.[134] Considering these findings, there is insufficient evidence to recommend vitamin E supplementation for the treatment or prevention of AD.[135]

Vitamin B Supplementation

Elevated serum homocysteine is associated with cognitive decline and supplementation with B vitamins (folic acid along with B_{12} and/or B_6) has been explored to reduce homocysteine levels in older adults with dementia. Clinical trials consistently demonstrate reduced homocysteine levels in the intervention groups receiving vitamin B supplementation, but without significant difference in MMSE scores between control and intervention groups. In other words, reduced homocysteine levels have not translated into improved cognitive outcomes for people with AD thus far.[136]

Ginkgo biloba

Ginkgo biloba for the prevention and treatment of AD has been extensively studied given its potential to increase blood flow, decrease blood viscosity, antagonize platelet-activating factor receptors, increase anoxia tolerance, inhibit monoamine oxidase, and serve as an antioxidant. Active ingredients in *Ginkgo biloba* include flavonoids, *Ginkgo* flavone glycosides, and bioflavonoids. Most studies reporting benefit in people with cognitive impairment or dementia have studied a standardized extract, EGb 761, in doses of 240 mg/day for 22 to 26 weeks.[137] The clinical significance of the modest benefits detected is unclear, and direct comparisons to cholinesterase inhibitors or memantine are lacking. A large trial of *Ginkgo biloba* 120 mg twice a day did not reduce the overall incidence rate of either dementia or AD in older adults with normal cognition or MCI.[138] In another large trial the long-term use of *Ginkgo biloba* extract did not reduce the risk of progression to AD among older adults suffering from memory complaints compared with placebo.[139] Adverse medication effects reported from EGb 761 studies were typically mild, including nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, and weakness. Because EGb also has a potent antiplatelet effect, it should be avoided by individuals taking anticoagulant or antiplatelet therapies and should be used cautiously in patients taking NSAIDs.[137,140]

Apoaequorin

Prevagen® (apoaequorin) has been postulated to impact cognition by modulating calcium homeostasis and secondary messaging; however, the

manufacturer data has not been peer reviewed and only focuses on single domains of cognition. Additionally, a simulation of the gastric environment found that 90% of this compound is broken down within 30 seconds. As the compound is large in size, it is not clear whether there is a mechanism for absorption or ability to cross the blood brain barrier.[141]

Medical Foods

Several medical foods have been studied for the treatment of MCI or AD, but there is little evidence of benefit to date. Medical foods constitute a unique category that consists of ingestible entities intended for the treatment of diseases that have "specific nutritional requirements" and for which the medical food may manipulate disease-relevant pathophysiology. Medical foods are intended to be used under the supervision of a physician. The most commonly used for people with mild-to-moderate AD are Axona, Souvenaid®, and CerefolinNAC®.[142]

Axona (caprylidene) is a mixture of medium-chain fatty acids, consisting primarily of the C8 fatty acid caprylic acid.[143] Caprylidene is converted by the liver to a ketone body, β-hydroxybutyrate, which crosses the blood–brain barrier and can be used as an alternative fuel to glucose in the brain. Support for caprylidene efficacy in AD comes from a single clinical trial in which subjects randomized to 40 mg/day of caprylidene for 45 days performed relatively better on the ADAS-cog than did subjects randomized to a placebo; however, this benefit was entirely driven by subjects without the *APOE*4* allele.[144] In general, adverse effects were mild, with GI-related effects being the most common. Coconut oil is a source of caprylic acid but may not contain sufficient quantities to meet the needs of a person with AD; however, it continues to be used by some patients as a less expensive alternative to caprylidene.[143]

Souvenaid is a mixture of omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids), uridine monophosphate, phospholipids, B complex vitamins (B_6, B_{12}, and folate), choline, vitamin E, and selenium.[145] A systematic review and meta-analysis of three RCTs comparing Souvenaid to placebo found no significant differences in cognition, function, or behavior, although one study showed improvement in verbal recall in people with mild AD in the Souvenaid treatment group.[145] No serious adverse events were reported in the clinical studies.

CerefolinNAC® contains vitamin B_{12}, L-methylfolate, and N-acetylcysteine, and its use targets the association of hyperhomocysteinemia with MCI and progression to dementia. A small prospective case-control study of people with AD and hyperhomocysteinemia suggested longer CerefolinNAC® treatment duration, milder baseline severity, and greater magnitude of homocysteine reduction from baseline were all significant predictors of slowed cognitive decline, when compared to AD subjects with normal homocysteine levels not receiving CerefolinNAC®.[146] Randomized controlled trials are needed to confirm these findings; however, to date, there is insufficient evidence to recommend medical foods for the treatment of AD.

Omega-3 Fatty Acids

Arguments that omega-3 fatty acids found in fish oil, such as docosahexaenoic acid and eicosapentaenoic acid, could benefit individuals with AD have existed for some years. A recent Cochrane review found no evidence of significant adverse effects, but also no benefit on cognition, function, dementia severity, or quality of life in people with AD.[147] There is insufficient evidence now to recommend omega-3 fatty acids for the treatment of AD.

Medications and Treatment Strategies in Development

New medication development is focused on disease-modifying and prevention strategies and has fallen broadly into several categories: treatments designed to reduce levels of brain Aβ or manipulate its configuration, treatments targeting tau protein, anti-inflammatory approaches (eg, cytokines, microglial cells), and therapies targeting glutaminergic and cholinergic response (eg, sigma receptors, AMPA-kines). Interest in targeting early, prodromal AD has also risen. The NIA-AA Research Framework provides guidance for biomarker testing to capture such early disease which relies on assessment of three criteria: (1) presence of neurodegeneration, (2) presence of amyloid, or (3) presence of tau in the brain using specific imaging of CSF sampling techniques.[46,148,149]

Although many potential new medications have advanced to early clinical studies, no new agents had entered the market since 2004, until the approval of aducanumab and now lecanemab. While progress has been made in developing novel biomarkers and improving RCT designs, results remain disappointing.[25,61,62,98,99] One reason for the failure of so many AD therapies may be that current strategies do not target the pathways that ultimately result in AD. Another reason may be that medications are being initiated when the disease has already progressed too far to be reversed.[25] Focus on

the amyloid hypothesis of AD, and to a lesser extent on tau, may have led to discounting other treatment approaches. AD is likely a multifactorial condition, which suggests that a single approach will not prevent or treat AD in all patients. Some of the potential targets of interest going forward include dysfunction of neuronal networks, inflammation, infectious agents such as herpes virus or prions, accumulation of neurotoxic proteins related to sleep deprivation and blood–brain barrier dysfunction, mitochondrial dysfunction, environmental factors, and conditions affecting brain vascular health including diabetes, obesity, hypertension, and hypercholesterolemia.[25] There is also a great deal of attention to identify AD biomarkers and recommendations are likely to evolve over time as we better understand the underlying disease pathophysiology and predictors of patient response. Regardless, now there are no specific recommendations regarding the choice of medication, dosing regimen, or treatment duration for cognitive agents (ie, cholinesterase inhibitors and memantine) based on genotype or other biomarkers.

Given the exponentially increasing number of individuals and families facing the diagnosis of AD, government leaders of G7 countries have strategized to drive innovation and improve the quality of life for people affected by AD, by establishing a goal to find a cure or disease-modifying therapy by 2025.[150] This effort resulted in more research directed toward achieving this goal. Furthermore, the National Institutes of Health, FDA, pharmaceutical companies, and nonprofit organizations joined together to form the "Accelerating Medicines Partnership" to create networks, share data, and manage RCTs.[151]

Pharmacotherapy of Neuropsychiatric Symptoms

Most patients with AD manifest neuropsychiatric symptoms (also referred to as BPSD) at some point in the illness.[152–154] These symptoms can be roughly divided into four categories: (1) psychotic; (2) hyperactive (eg, inappropriate or disruptive behavior); (3) affective (eg, depression); and (4) apathy.[152,153] Effective management of BPSD is important because symptoms are distressing to both the patient and caregiver, necessitate increased caregiver supervision and patience. Escalating and challenging BPSD is a leading reason for nursing home placement.

10 Strategies for treatment of BPSD should include nonpharmacologic interventions first, followed by pharmacologic interventions when necessary. Behaviors, such as agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, may be caused by medications, medical illness (eg, pain, constipation, dehydration, infection), environmental precipitants, physical/verbal abuse, or unmet physical and psychological needs. Correcting possible underlying causes before initiating medication therapy is critical.[154,155] The need for medications may arise when neuropsychiatric symptoms are of sufficient severity to cause significant distress to the patient or caregiver, interfere with function or cause disability, impede delivery of necessary care, or pose a danger to self or others and have not responded to nonpharmacologic interventions.[55,121,154–156] The balance between potential risks and expected benefits of the intended medication must be acceptable to the patient or surrogate decision maker. Medications should be used cautiously, with adequate monitoring for effectiveness and adverse events.

Despite the high prevalence of neuropsychiatric symptoms in AD, relatively little research has been conducted, and no medication is approved by the FDA for the treatment of BPSD; however, clinical trials are ongoing.[149] Considering limited clinical data, treatment is primarily empiric, with adverse effect profiles used as a guide in selecting the appropriate treatment. For instance, psychotropic medications with anticholinergic effects should be avoided because they may worsen cognition and interfere with cholinesterase inhibitor therapy.

General guidelines governing pharmacologic therapy for BPSD can be summarized as follows: reserve for situations where nonpharmacologic therapies failed, use reduced doses, monitor closely, titrate dosage slowly, minimize duration of therapy, attempt tapers, and document carefully. Treatment should be considered temporary.[155] Caregivers may have unrealistic expectations regarding the effects of these medications, and the anticipated benefits and risks should be clearly explained. Disruptive behaviors and delusions wax and wane with disease progression, and some behaviors (eg, wandering, hoarding, screaming, repetitive behaviors) lack evidence of a medication response.[157] Attempts to slowly taper and discontinue medication should be undertaken regularly in minimally symptomatic patients, as behaviors often fluctuate, changing in character and intensity over time, and the medication may no longer be providing a benefit.[154,155]

Cholinesterase Inhibitors and Memantine

Cholinesterase inhibitors and memantine may be beneficial in both managing BPSD and reducing their incidence.[153] While cholinesterase inhibitors may improve apathy, depression, tension, and irritability in mild-to-moderate dementia, they do not appear to significantly reduce acute agitation.[153] Memantine may show modest benefit for mitigating agitation, aggression, delusions, and hallucinations; however, recent trials of memantine

specifically evaluating its effect on treating agitation in people with AD found no benefit.[153] These benefits should be considered along with cognitive benefits in treatment decisions and weighed against their adverse effects. Long-term effects on behavior have not been demonstrated and further research is needed.

Antidepressants

Antidepressants may be prescribed for BPSD to help manage depression, anxiety, apathy, as well as agitation and aggression. Depressive symptoms and anxiety are common in people with AD. Apathy is seen in 48% to 92% of individuals with dementia, and clinically significant depression occurs in approximately 32% with mild dementia, 23% with moderate disease, and 18% in the severe stage of the dementia.[158] Results of trials studying the efficacy of antidepressants in treating depression in people with AD are conflicting,[154] and improvement among participants receiving placebo is also common. In practice, treatment with selective serotonin reuptake inhibitors (SSRIs) is initiated most commonly in people with AD, based on adverse effect profile, risk of interactions, and evidence of efficacy.[154] Among the SSRIs, the best evidence exists for sertraline and citalopram.[75,154] Serotonergic function may also play a role in some of the other BPSD of AD, such as agitation, and some studies support the use of SSRIs in managing these behaviors, even in the absence of depression.[154] Clinical trials are needed to compare the efficacy of SSRIs to second-generation antipsychotics (SGAs). Tricyclic antidepressants should generally be avoided because of their anticholinergic activity.[153] Chapter 88 has a more complete discussion of treatment of depression.

Antipsychotics

Antipsychotics are used in the management of neuropsychiatric symptoms in AD despite efforts by the Centers for Medicare and Medicaid Services and other groups to reduce their use in nursing homes.[159] Brexpiprazole has gained FDA approval for management of agitation associated with dementia secondary to AD. Prior to that antipsychotics were used off-label for management of BPSD in AD. There is modestly convincing evidence that certain SGAs provide some benefit for particular neuropsychiatric symptoms with the most studied being aripiprazole, risperidone, olanzapine, and quetiapine. More than 20 RCTs have evaluated SGAs for BPSD, with more than 5,000 patients participating and treatment durations of 6 to 26 weeks for most trials.[160] A meta-analysis of 16 trials demonstrated the efficacy of aripiprazole, risperidone, olanzapine, and quetiapine over placebo; however, they were associated with a higher risk of adverse medication reactions. The investigators concluded the increased risk of adverse reactions and mortality may offset the benefit. An outpatient RCT of 421 people with AD and psychosis, aggression, or agitation randomized to receive olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks found no significant differences among treatments in time to treatment discontinuation or improvement based on the Clinical Global Impression–Change (CGI-C) response. The investigators concluded that adverse medication reactions may offset the therapeutic advantages of SGAs for treatment of psychosis, aggression, or agitation in people with AD.[161]

Adverse medication reactions are common with first-generation antipsychotics (FGAs) and SGAs in people with AD and include somnolence, extrapyramidal symptoms, abnormal gait, cerebrovascular events, and increased risk of death.[160,162] Compared to SGAs, FGAs are associated with more severe extrapyramidal effects and hypotension. In 2005, the FDA mandated the addition of a boxed warning to all SGAs due to increased risk of mortality in older adults with dementia-related psychosis; this warning was expanded in 2008 to include all FGAs as well.[163] Mortality was mostly cardiovascular (eg, sudden death, heart failure) or infectious (eg, pneumonia) in nature. Given their risk of sedation, EPS, anticholinergic effects, and hypotension, antipsychotics can also contribute to falls. In 2011, the Office of Inspector General released a report which described that the majority (83%) of SGA prescription claims were for nursing home residents without FDA-approved indications.[162] In 2012, the Centers for Medicare and Medicaid Services launched the National Partnership to Improve Dementia Care in Nursing Homes to improve quality of care for nursing home residents with dementia. Although the percentage of residents receiving antipsychotic therapy has since decreased, from 23.9% in 2011 to 14.5% in 2020, about one in six people living in nursing homes are receiving antipsychotic medications.[159,164]

There is a modest expectation of treatment benefit and a potential for significant harm associated with antipsychotic use in people with AD. Individual risk and benefit must be considered and discussed with family and caregivers when initiating therapy. Prescribing of antipsychotics in AD should be restricted to patients with severe symptoms not responding to other measures, and treatment should be tapered as early as possible.[155,156] Doses should be initiated at one-third to one-half of the usual adult starting dose (or with smallest available tablet strength), and target doses are much lower than those for other indications.[155] The recommended starting dose of brexpiprazole is 0.5mg daily, titrated weekly to a recommended dose of 2mg daily. The dose should not exceed 3mg daily. Brexpiprazole does require lower doses with strong CYP2D6 and 3A4 inhibitors.[165] The American

Psychiatric Association (APA) guidelines recommend tapering and discontinuing the antipsychotic after 4 weeks at an adequate dose if no clinical benefit is seen. If benefit is seen, an attempt to taper should be made 4 months after initiation, to reduce risk of harm as original need for the medication may change.[155] A meta-analysis of RCTs of antipsychotic discontinuation showed no significant increase in BPSD severity upon discontinuation compared to the continuation group.[166] For patients continued on antipsychotics, monitor for tardive dyskinesia and metabolic effects. Chapter 87, "Schizophrenia" includes a more detailed discussion of antipsychotic monitoring.

Miscellaneous Therapies

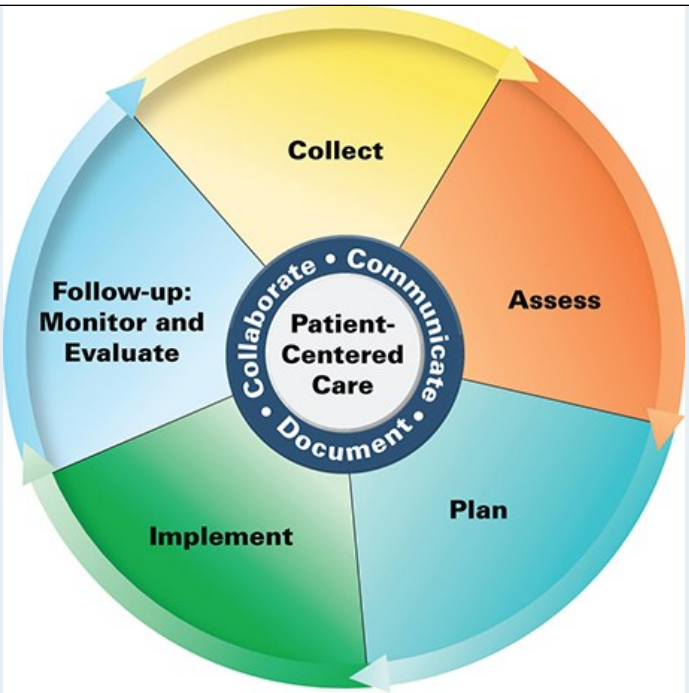
Because antipsychotic and antidepressant therapies have only modest efficacy and pose the potential for undesirable adverse effects, medications traditionally used to treat disruptive behaviors and aggression in other psychiatric and neurologic disorders have been suggested as potential alternatives. These alternatives include benzodiazepines and antiseizure medications.[154]

Benzodiazepines have been used to treat anxiety, agitation, and aggression, but the benefit is unclear especially given the risk of sedation, falls, impaired cognition, respiratory depression, and paradoxical disinhibition.[153] Evidence for their use in BPSD is lacking. Antiseizure medications used as "mood stabilizers" such as carbamazepine, lamotrigine, gabapentin, and pregabalin may have some benefit but evidence is limited or conflicting.[167] Adverse effects and interactions of carbamazepine often outweigh benefits. Valproic acid is no longer recommended as a result of an association of mood stabilizers with severe adverse reactions in patients with BPSD.[152,153] In general sedative hypnotics including benzodiazepines and benzodiazepine receptor agonists (eg, zolpidem) should be avoided as the risk of harm (eg, sedation, falls) outweighs the benefit.[54] Melatonin and ramelteon have been used for circadian rhythm disturbances. More recently, suvorexant, an orexin antagonist, was studied for insomnia in patients with mild-to-moderate AD showing improvement in total sleep time and wake after sleep onset. Somnolence and falls occurred in the suvorexant treated groups.[168]

Neuropsychiatric symptoms are often the most difficult aspect of AD for the caregiver. When nonpharmacologic approaches fail, selected antipsychotics and antidepressants may be useful for effective management of behavioral, psychotic, and depressive symptoms, thereby easing caregiver burden and allowing the patient to spend additional time at home. All too often, however, nonpharmacologic measures are not implemented appropriately, and medication overuse is an ongoing problem. Adverse events remain an important concern in this population as well.

PATIENT CARE PROCESS

Patient Care Process for Alzheimer Disease



Collect

- Patient characteristics (eg, age, sex, race)
- Patient history (eg, past medical, family, and social history)
- Collateral information from family, friends, and caregivers
- Current medications including medications that may cause or worsen cognitive, neuropsychiatric, and/or functional symptoms (see list of common offending agents, in “Assess”)
- Assessments for cognitive, neuropsychiatric, and functional symptoms; for example:
  - Mini-Mental State Examination or Montreal Cognitive Assessment (cognition)
  - Neuropsychiatric Inventory (behavioral disturbances)
  - Bristol Activities of Daily Living Scale (function)
- Laboratory data
  - Comprehensive metabolic panel, including electrolytes, glucose, and liver function tests
  - Complete blood cell count
  - Serum B_{12}, homocysteine, and/or methylmalonic acid testing
  - Thyroid function tests
  - Rapid plasma reagin and human immunodeficiency virus testing
  - Urinalysis and/or chest x-ray
- Other Diagnostic Tests

- CT or MRI scans

Assess

- Risk factors for AD (eg, age, family history, low education level, smoking)
- Cognitive symptoms (eg, memory loss, aphasia, apraxia, agnosia, disorientation, impaired executive function)
- Neuropsychiatric symptoms (eg, depression, psychotic symptoms, behavioral disturbances)
- Functional symptoms (eg, inability to care for self), including patient's ability to manage and self-administer their own medications
- Medications that may cause or worsen cognitive, neuropsychiatric, and/or functional symptoms; for example:
  - Benzodiazepines and other sedative hypnotics
  - Anticholinergics
  - Opioid analgesics
  - Antipsychotics
  - Antiseizure medications
  - Skeletal muscle relaxants
- Labs, diseases, or syndromes that may cause or worsen cognitive, neuropsychiatric, and/or functional symptoms; for example:
  - Alcohol or substance use
  - Depression
  - B_{12} or folate deficiency
  - Hyperhomocysteinemia
  - Hypothyroidism and hyperthyroidism
  - Electrolyte disturbances (eg, hyponatremia)
  - Glucose abnormalities (eg, hypoglycemia)
  - Infectious processes (eg, tertiary syphilis, human immunodeficiency virus, urinary tract infection)
  - Complete blood count to rule out anemia or infection
  - Vision, hearing, or other sensory impairments
  - Other common types of dementia in late life (see Table 73-1)
- Stages of AD (see Table 73-2 and Fig. 73-1)
- Appropriateness of current living situation (eg, independent living, assisted living, nursing home)
- Appropriateness and effectiveness of current medication regimen

Plan*

- Tailored lifestyle modifications (eg, diet, physical activity) for management of brain vascular health
- Medication therapy regimen for cognitive symptoms (if appropriate) including specific medication(s), dose, route, frequency, and intended duration; specify the continuation and discontinuation of existing therapies (see Tables 73-3 and 73-6)
- Monitoring parameters including efficacy, safety (medication-specific potential adverse reactions), and time frame (see Table 73-7)
- Patient, family, and caregiver education (eg, risks vs benefits of treatment, expected outcomes, medication therapy selection)
- Referrals to other health professionals (eg, social work, psychology, occupational therapy) when appropriate

Implement*

- Provide patient, family, and caregiver education regarding all elements of treatment plan
- Provide caregiver access to local and national resources (see Table 73-5)
- Provide family and caregiver education regarding basic principles of care for the patient with AD (see Table 73-4)
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Presence of adverse effects related to medications for cognitive symptoms
- Disease progression, including incidence or worsening of neuropsychiatric symptoms of dementia in accordance with standard assessment tools (see list of commonly used assessments, in “Collect”)
- Patient adherence to treatment plan using multiple sources of information
- Patient, family, and caregiver expectations

****Collaborate with patients, caregivers, and other healthcare professionals.***

EVALUATION OF THERAPEUTIC OUTCOMES

An evaluation of therapeutic outcomes in the person with AD begins with a thorough assessment at baseline and a clear definition of therapeutic goals. Cognitive status, functional performance, mood, and behavior all need to be evaluated before initiation of medication therapy. The clinician should interview both the patient and the caregiver to assess response to medication therapy. In evaluating response to cognitive agents, the clinician should ask questions about the patient’s ability to perform daily functional tasks, mood and behavior, and memory and orientation. Objective assessments (eg, MMSE for cognition, Bristol Activities of Daily Living Scale for function, Neuropsychiatric Inventory for behavioral disturbances) can be used to quantify changes over time.[169]

Because target neuropsychiatric symptoms of dementia may manifest differently, a detailed list of target symptoms should be documented in the pharmacotherapy plan to aid in monitoring. These could include, for example, “striking at spouse because patient believes they are an impostor” or “verbal threats and refusal to allow clothes to be changed,” as opposed to documenting vague symptoms, such as “aggression” or “delusions.” To make an accurate assessment of depression, multiple symptoms (eg, sleep, appetite, activity, interest levels) need to be considered in addition to the patient’s stated mood. As noted above, the failure of pharmacologic modalities to impact these target symptoms should result in discontinuation. If responses are seen, tapering and subsequent monitoring for recurrence should be undertaken.

The patient should be observed carefully for potential adverse effects of medication therapy, including the specific adverse effect and how it is being assessed. Consensus on the frequency of monitoring is lacking, but patients should generally be monitored for adverse events within 2 to 4 weeks of initiation of therapy, for therapeutic effect in 8 to 12 weeks, and at least every 3 to 6 months thereafter.[170] The effects of cognitive agents will not necessarily be obvious, and a treatment period of several months to a year may be necessary before it can be determined whether therapy is beneficial.

Cognitive effects of the medication are often noticed only as a plateauing during treatment or as deterioration following medication discontinuation. In general, cognitive agents should be continued if the patient is demonstrating no change in clinical status. If there is doubt, the medication can be slowly tapered and discontinued, and the patient monitored off the medication for 4 to 6 weeks to determine the need for continued therapy. Medication deprescribing for people with AD is aided by the availability of deprescribing guidelines and algorithms for antipsychotics, cholinesterase inhibitors, and memantine.[171] The question of when, if ever, to stop medication therapy for AD remains controversial. Treatment benefits are not always evident, and fear of deterioration can lead to patients being prescribed medication therapy for AD from the time of their diagnosis until death. Some clinicians recommend withdrawing medication therapy if the patient significantly deteriorates in cognition or function, while others wait until the patient has lost all cognitive and functional abilities. Tolerability, cost, and patient and family preferences factor heavily into medication therapy discontinuation decisions. If cholinesterase inhibitors are discontinued and cognition worsens or behavioral issues emerge, the medications can be reinitiated.

CONCLUSION

Ultimately, AD, as with other dementias, is a complex condition to evaluate and manage. Clinicians are encouraged to work interprofessionally and collaborate closely with patients and their families to minimize stigma, identify therapeutic goals, and address concerns as they arise.

ABBREVIATIONS

AA	Alzheimer's Association
Aβ	β-Amyloid peptide
AD	Alzheimer disease
ADAS-cog	Alzheimer's Disease Assessment Scale—Cognitive Subscale
ADRDA	Alzheimer's Disease and Related Disorders Association
AHRQ	Agency for Healthcare Research and Quality
APOE	apolipoprotein E
APP	amyloid precursor protein
ARIA	amyloid-related imaging abnormalities
BPSD	behavioral and psychological symptoms of dementia
CGI-C	Clinical Global Impression–Change
CSF	cerebrospinal fluid
CT	computed tomography
DASH	Dietary Approaches to Stop Hypertension
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
EOAD	early onset Alzheimer disease

FDA	Food and Drug Administration
FGA	first-generation antipsychotics
GI	gastrointestinal
LOAD	late onset Alzheimer disease
MCI	mild cognitive impairment
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NFT	neurofibrillary tangle
NIA	National Institute on Aging
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
PET	positron emission tomography
PSEN	presenilin genes
RCT	randomized clinical trial
SGA	second-generation antipsychotic
SSRI	selective serotonin reuptake inhibitor

REFERENCES

1. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: An update. *Pharmacol Rep.* 2015;67(2):195–203. [PubMed: 25712639]

2. U.S. Department of Health and Human Services. National Plan to Address Alzheimer's Disease. Available at https://aspe.hhs.gov/collaborations-committees-advisory-groups/napa/napa-documents/napa-national-plans. Last accessed August 25, 2022.

3. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2021;17(3):327–406. [PubMed: 33756057]

4. Jiang T, Yu JT, Tian Y, Tan L. Epidemiology and etiology of Alzheimer's disease: From genetic to non-genetic factors. *Curr Alzheimer Res.* 2013;10(8):852–867. [PubMed: 23919770]

5. Robinson L, Tang E, Taylor J-P. Dementia: Timely diagnosis and early intervention. *BMJ.* 2015;350:h3029. [PubMed: 26079686]

6. Bertram L, Tanzi RE. The genetics of Alzheimer's disease. *Prog Mol Biol Transl Sci.* 2012;107:79–100. [PubMed: 22482448]

7. Macleod R, Hillert E-K, Cameron RT, Baillie GS. The role and therapeutic targeting of α-, β- and γ-secretase in Alzheimer's disease. *Future Sci OA.* 2015;1(3):FS011.

8. Vilatela MEA, López-López M, Yescas-Gómez P. Genetics of Alzheimer's disease. *Arch Med Res.* 2012;43(8):622–631. [PubMed: 23142261]

9. Kelleher RJ III, Shen J. Presenilin-1 mutations and Alzheimer's disease. *Proc Natl Acad Sci U S A.* 2017;114(4):629–631. [PubMed: 28082723]

10. Hampel H, Mesulam M-M, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain.* 2018;141(7):1917–1933. [PubMed: 29850777]

11. Michaelson DM. APOE ε4: The most prevalent yet understudied risk factor for Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):861–868. [PubMed: 25217293]

12. Hohman TJ, Cooke-Bailey JN, Reitz C, et al. Global and local ancestry in African-Americans: Implications for Alzheimer's disease risk. *Alzheimers Dement*. 2016;12(3):233–243. doi: 10.1016/j.jalz.2015.02.012.

13. De Roeck A, Van Broeckhoven C, Sleegers K. The role of ABCA7 in Alzheimer's disease: Evidence from genomics, transcriptomics and methylomics. *Acta Neuropathol.* 2019;138(2):201–220. doi: 10.1007/s00401-019-01994-1.

14. Reitz C, Jun G, Naj A, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ϵ4, and the risk of late-onset Alzheimer disease in African Americans. *JAMA.* 2013;309(14):1483–1492. doi: 10.1001/jama.2013.2973.

15. Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. *J Am Board Fam Med.* 2012;25(3):367–382. [PubMed: 22570400]

16. Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron.* 2014;82(4):756–771. [PubMed: 24853936]

17. Chen GF, Xu TH, Yan Y, et al. Amyloid beta: Structure, biology and structure-based therapeutic development. *Acta Pharmacol Sin.* 2017;38(9):1205–1235. doi: 10.1038/aps.2017.28.

18. Long JM, Holtzman DM. Alzheimer disease: An update on pathobiology and treatment strategies. *Cell*. 2019;179(2):312–339. doi: 10.1016/j.cell.2019.09.001.

19. Prins ND. Immunotherapy against amyloid-β in Alzheimer's disease: An overview. In: Ingelsson M, Lannfelt L, eds. *Immunotherapy and Biomarkers in Neurodegenerative Disorders Methods in Pharmacology and Toxicology*. New York, NY: Humana Press; 2016;3–17.

20. Takeda S. Progression of Alzheimer's disease, tau propagation, and its modifiable risk factors. *Neurosci Res.* 2019;141:36–42. doi: 10.1016/j.neures.2018.08.005.

21. Tublin JM, Adelstein JM, del Monte F, et al. Getting to the heart of Alzheimer's disease. *Circ Res.* 2019;124(1):142–149. [PubMed: 30605407]

22. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: Causes and treatment. *Molecules*. 2020;25(24):5789. doi: 10.3390/molecules25245789.

23. O'Brien JT, Markus HS. Vascular risk factors and Alzheimer's disease. *BMC Med.* 2014;12:218. [PubMed: 25385509]

24. de Bruijn RFAG, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med.* 2014;12:130. [PubMed: 25385322]

25. Mullane K, Williams M. Alzheimer's disease (AD) therapeutics – 1: Repeated clinical failures continue to question the amyloid hypothesis of AD and the current understanding of AD causality. *Biochem Pharmacol.* 2018;158:359–375. [PubMed: 30273553]

26. Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of nutrients, dietary supplements and vitamins on cognition: A systematic review and meta-analysis of randomized controlled trials. *Can Geriatr J.* 2015;18(4):231–245. [PubMed: 26740832]

27. Henderson VW. Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after menopause. *J Steroid Biochem Mol Biol.* 2014;142:99–106. [PubMed: 23727128]

28. 2021 Alzheimer's Disease Facts and Figures, Special Report: Race, Ethnicity and Alzheimer's in America. Alzheimer's Association. Available at: https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf. Accessed February 22, 2022.

29. Lazarczyk MJ, Bouras C, Hot PR, et al. Preclinical Alzheimer disease: Identification of cases at risk among cognitively intact older individuals. *BMC Medicine*. 2012;10:127. [PubMed: 23098093]

30. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189–198. [PubMed: 1202204]

31. Gauthier S, Rosa-Neto P, Morais J, Webster C. *World Alzheimer Report 2018*. London, England: Alzheimer's Disease International. Available at: https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf. Last accessed August 25, 2022.

32. Moyer VA. Screening for cognitive impairment in older adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2014;160(11):791–797. [PubMed: 24663815]

33. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in a primary care setting. *Alzheimers Dement*. 2013;9(2):141–150. [PubMed: 23265826]

34. Colburn JL, Nothelle S. The Medicare annual wellness visit. *Clin Geriatr Med.* 2018;34(1):1–10. doi: 10.1016/j.cger.2017.09.001.

35. MoCA Cognitive Assessment. Available at: mocatest.org. Accessed November 9, 2021.

36. Rabins PV, Blass DM. In the clinic. Dementia. *Ann Intern Med.* 2014;161(3):ITC1–ITC16. [PubMed: 25089871]

37. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* 5th ed. Washington, DC: American Psychiatric Association; 2013.

38. Agency for Health Care Policy and Research. *Diagnosis and Treatment of Clinical Alzheimer's-Type Dementia: As Systematic Review*. Rockville, MD: Agency for Health Care Policy and Research; 2020. [PubMed:] [[XSLOpenURL/]]

39. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: Diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1143–1153. [PubMed: 11342678]

40. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250–260. [PubMed: 8094895]

41. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939–944. [PubMed: 6610841]

42. Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):257–262. [PubMed: 21514247]

43. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National

Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263–269. [PubMed: 21514250]

44. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270–279. [PubMed: 21514249]

45. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280–292. [PubMed: 21514248]

46. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(3):126–135. [PubMed: 29282327]

47. Fillenbaum GG, Peterson B, Morris JC. Estimating the validity of the clinical Dementia Rating Scale: The CERAD experience. Consortium to Establish a Registry for Alzheimer's Disease. *Aging (Milano).* 1996;8(6):379–385. [PubMed: 9061124]

48. Harper L, Barkhof F, Scheltens P, et al. An algorithmic approach to structural imaging in dementia. *J Neurol Neurosurg Psychiatry*. 2014;85(6):692–698. [PubMed: 24133287]

49. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535–562. [PubMed: 29653606]

50. Horgan D, Nobili F, Teunissen C, et al. Biomarker testing: Piercing the fog of Alzheimer's and related dementia. *Biomed Hub*. 2020;5(3):19–40. doi: 10.1159/000511233.

51. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390(10113):2673–2734. [PubMed: 28735855]

52. Geda YE. Mild cognitive impairment in older adults. *Curr Psychiatry Rep.* 2012;14(4):320–327. [PubMed: 22773365]

53. Matsunaga S, Fujishiro H, Takechi H. Efficacy and safety of cholinesterase inhibitors for mild cognitive impairment: A systematic review and meta-analysis. *J Alzheimers Dis.* 2019;71(2):513–523. doi: 10.3233/JAD-190546.

54. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;(4):674–694.

55. Sadowsky CH, Galvin JE. Guidelines for the management of cognitive and behavioral problems in dementia. *J Am Board Fam Med.* 2012;25(3):350–366. doi: 10.3122/jabfm.2012.03.100183.

56. Parsons C. Polypharmacy and inappropriate medication use in patients with dementia: An under-researched problem. *Ther Adv Drug Saf.* 2017;8(1):31–46. [PubMed: 28203365]

57. Razadyne (galantamine hydrobromide). Titusville, NJ: Janssen Pharmaceuticals; 2021. Package insert.

58. *Exelon (rivastigmine tartrate).* East Hanover, NJ: Novartis Pharmaceuticals; 2021. Package insert.

59. *Exelon Patch (rivastigmine transdermal system).* East Hanover, NJ: Novartis Pharmaceuticals; 2021. Package insert.

60. *Aricept (donepezil hydrochloride).* Woodcliff Lake, NJ: Eisai; 2018. Package insert.

61. Aducanumab (*Aduhelm*) for Alzheimer's disease. *Med Lett Drugs Ther.* 2021;63(1628):105–106. [PubMed: 34543258]

62. Aducanumab-avwa (*Aduhelm*). Cambridge, MA: Biogen and Eisai; 2021. Package insert.

63. *Namenda (memantine hydrochloride).* Madison, NJ: Allergan, Inc.; 2019. Package insert.

64. *Namenda XR (memantine hydrochloride).* Madison, NJ: Allergan, Inc.; 2019. Package insert.

65. Namzaric capsules (memantine hydrochloride extended release and donepezil hydrochloride). Madison, NJ: Allergan, Inc.; 2019. Package insert.

66. Leqembi(lecanemab-irmb) Eisai, Nutley, NJ 2023 package insert

67. Ed. Downey A, Stroud C, Landis S, Leshner AI. *Preventing Cognitive Decline and Dementia: A Way Forward*. Washington, DC: National Academy of Sciences; 2017.

68. Deckers K, van Boxtel MP, Schiepers OJ, et al. Target risk factors for dementia prevention: A systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry*. 2015;30(3):234–246. 10.1002/gps.4245 [PubMed: 25504093] .

69. Vos SJB, van Boxtel MPJ, Schiepers OJG, et al. Modifiable risk factors for prevention of dementia in midlife, late life and the oldest-old: Validation of the LIBRA Index. *J Alzheimers Dis.* 2017;58(2):537–547. doi: 10.3233/JAD-161208.

70. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* 2020;396(10248):413–446. doi: 10.1016/S0140-6736(20)30367-6.

71. Panza GA, Taylor BA, MacDonald HV, et al. Can exercise improve cognitive symptoms of Alzheimer's disease? *J Am Geriatr Soc.* 2018;66(3):487–495. doi: 10.1111/jgs.15241.

72. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. *JAMA.* 2012;308(19):2020–2029. [PubMed: 23168825]

73. Mittelman MS, Bartels SJ. Translating research into practice: Case study of a community-based dementia caregiver intervention. *Health Aff (Millwood).* 2014;33(4):587–595. [PubMed: 24711319]

74. Caspar S, Davis ED, Douziech A, et al. Nonpharmacological management of behavioral and psychological symptoms of dementia: What works, in what circumstances, and why? *Innov Aging*. 2018;2(1):igy001. doi: 10.1093/geroni/igy001.

75. Alzheimer's Association. Challenging Behaviors. Available at: http://www.alz.org/national/documents/statements_antipsychotics.pdf. Last accessed November 9, 2021.

76. Catic AG. Nonpharmacologic management of behavioral and psychological symptoms of dementia in long-term care residents. *Ann Long-Term Care*. 2015;23(11):23–30.

77. Rabins PV, Rovner BW, Rummans T, et al. GuidelineWatch (October 2014): Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. Available at: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf. Last accessed August 29, 2022.

78. Birks JS, Grimley Evans J. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev.* 2015;9:CD001191. [PubMed: 26393402]

79. Buckley JS, Salpeter SR. A risk-benefit assessment of dementia medications: Systematic review of the evidence. *Drugs Aging*. 2015;32(6):453–467. [PubMed: 25941104]

80. Raskind MA, Peskind ER, Truyen L, et al. The cognitive benefits of galantamine are sustained for at least 36 months: A long-term extension trial. *Arch Neurol.* 2004;61(2):252–256. [PubMed: 14967774]

81. Masters CL, Bateman R, Blennow K, et al. Alzheimer's disease. *Nat Rev Dis Primers*. 2015;1:15056. [PubMed: 27188934]

82. Lin JS, O'Connor E, Rossom RC, et al. *Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force*. Rockville, MD: Agency for Healthcare Research and Quality; 2013. [PubMed:] [[XSLOpenURL/]]

83. Jönsson AK, Lövborg H, Hägg S A fatal outcome after unintentional overdosing of rivastigmine patches. Curr Drug Saf 2012;7(1):30–2. 10.2174/157488612800492717
[PubMed: 22663954] .

84. Triantafylidis LK, Clemons JS, Peron EP, et al. Brain over bladder: A systematic review of dual cholinesterase inhibitor and urinary anticholinergic use. *Drugs and Aging*. 2018;35(1):27–41. [PubMed: 29350336]

85. Bidzan L, Bidzan M. Withdrawal syndrome after donepezil cessation in a patient with dementia. *Neurol Sci.* 2012;33(6):1459–1461. [PubMed: 22249402]

86. Schwartz LM, Woloshin S. How the FDA forgot the evidence: The case of donepezil 23 mg. *BMJ.* 2012;344:e1086. [PubMed: 22442352]

87. Massoud F, Desmarais JE, Gauthier S. Switching cholinesterase inhibitors in older adults with dementia. *Int Psychogeriatr.* 2011;23(3):372–378. [PubMed: 21044399]

88. Fonseca-Santos B, Gremião MPD, Chorilli M. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease. *Int J Nanomedicine*. 2015;10:4981–5003. [PubMed: 26345528]

89. Deardorff WJ, Feen E, Grossberg GT. The use of cholinesterase inhibitors across all stages of Alzheimer's disease. *Drugs Aging*. 2015;32(7):537–547. [PubMed: 26033268]

90. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: A randomized controlled trial. *JAMA.* 2004;291(3):317–324. [PubMed: 14734594]

91. Barrera-Ocampo A, Lopera F. Amyloid-beta immunotherapy: The hope for Alzheimer disease? *Colomb Med (Cali).* 2016;47(4):203–212. [PubMed: 28293044]

92. Suzuki K, Iwata A, Iwatsubo T. The past, present, and future of disease-modifying therapies for Alzheimer's disease. *Proc Jpn Acad Ser B Phys Biol Sci.* 2017;93(10):757–771. doi: 10.2183/pjab.93.048.

93. Sumner IL, Edwards RA, Asuni AA, et al. Antibody engineering for optimized immunotherapy in Alzheimer's disease. *Front Neurosci.* 2018;12:254–254. doi: 10.3389/fnins.2018.00254.

94. Zhao J, Nussinov R, Ma B. Mechanisms of recognition of amyloid-β (Aβ) monomer, oligomer, and fibril by homologous antibodies. *J Biol Chem.* 2017;292(44):18325–18343. doi: 10.1074/jbc.M117.801514.

95. Vander Zanden CM, Chi EY. Passive immunotherapies targeting amyloid beta and tau oligomers in Alzheimer's disease. *J Pharm Sci.* 2020;109(1):68–73. doi: 10.1016/j.xphs.2019.10.024.

96. Schneider L. A resurrection of aducanumab for Alzheimer's disease. *Lancet Neurol.* 2020;19(2):111–112. doi: 10.1016/S1474-4422(19)30480-6.

97. Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. *Alzheimers Dement*. 2021;17(4):696–701. doi: 10.1002/alz.12213.

98. Ernst J. FDA grants two antibodies breakthrough therapy designation for Alzheimer's disease. Healio. June 24, 2021. Available at: https://www.healio.com/news/neurology/20210624/fda-grants-lecanemab-breakthrough-therapy-designation-for-treatment-of-alzheimers-disease. Accessed November 11, 2021.

99. Inacio P. FDA grants breakthrough therapy designation to gantenerumab. Alzheimer's News Today. October 12, 2021. Available at: https://alzheimersnewstoday.com/2021/10/12/gantenerumab-alzheimers-named-fda-breakthrough-therapy/. Accessed November 11, 2021.

100. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023;388(1):9–21. 10.1056/NEJMoa2212948 [PubMed: 36449413] .

101. https://www.alzheimer-europe.org/news/roche-announces-results-graduate-phase-iii-trials-gantenerumab

102. https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional

103. Zhao J, Nussinov R, Ma B Mechanisms of recognition of amyloid-β (Aβ) monomer, oligomer, and fibril by homologous antibodies. J Biol Chem 2017;292(44):18325–18343. 10.1074/jbc.M117.801514 [PubMed: 28924036] .

104. Vander Zanden CM, Chi EY Passive Immunotherapies Targeting Amyloid Beta and Tau Oligomers in Alzheimer's Disease. J Pharm Sci 2020;109(1):68–73. 10.1016/j.xphs.2019.10.024 [PubMed: 31647950] .

105. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s000lbl.pdf

106. Pankiewicz JE, Sadowski MJ. APOE genotype and Alzheimer's immunotherapy. *Oncotarget*. 2017;8(25):39941–39942. doi: 10.18632/oncotarget.17990.

107. Lin GA, Whittington MD, Synnott PG, et al. Aducanumab for Alzheimer's disease: Effectiveness and Value. Institute for Clinical and Economic Review. August 5, 2021. Available at: https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf. Accessed October 25, 2021.

108. Canevelli M, Rossi PD, Astrone P, et al. "Real world" eligibility for aducanumab. *J Am Geriatr Soc.* 2021;69(10):2995–2998. doi: 10.1111/jgs.17390.

109. Rogers SL, Doody RS, Pratt RD, Ieni JR. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: Final analysis of a US multicentre open-label study. *Eur Neuropsychopharmacol.* 2000;10(3):195–203. [PubMed: 10793322]

110. Farlow MR, Lilly ML, ENA713 B352 Study Group. Rivastigmine: An open-label, observational study of safety and effectiveness in treating patients with Alzheimer's disease for up to 5 years. *BMC Geriatr.* 2005;5:3. [PubMed: 15659242]

111. Reisberg B, Doody R, Stöffler A, et al. A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch Neurol.* 2006;63(1):49–54. [PubMed: 16401736]

112. Doody RS, Geldmacher DS, Gordon B, et al. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol.* 2001;58(3):427–433. [PubMed: 11255446]

113. Howard R, McShane R, Lindesay J, et al. Nursing home placement in the donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO-AD) trial: Secondary and post-hoc analyses. *Lancet Neurol.* 2015;14(12):1171–1181. [PubMed: 26515660]

114. Ryan J, Fransquet P, Wrigglesworth J, Lacaze P. Phenotypic heterogeneity in dementia: A challenge for epidemiology and biomarker studies. *Front Public Health.* 2018;6:181. [PubMed: 29971228]

115. Rainer M, Mucke HA, Krüger-Rainer C, et al. Cognitive relapse after discontinuation of drug therapy in Alzheimer's disease: Cholinesterase

inhibitors versus nootropics. *J Neural Transm.* 2001;108(11):1327–1333.

116. Gaudig M, Richarz U, Han J, et al. Effects of galantamine in Alzheimer's disease: Double-blind withdrawal studies evaluating sustained versus interrupted treatment. *Curr Alzheimer Res.* 2011;8(7):771–780. [PubMed: 21707533]

117. Pariente A, Fourrier-Réglat A, Bazin F, et al. Effect of treatment gaps in elderly patients with dementia treated with cholinesterase inhibitors. *Neurology*. 2012;78(13):957–963. [PubMed: 22422894]

118. Dichgans M, Leys D. Vascular cognitive impairment. *Circ Res.* 2017;120(3):573–591. [PubMed: 28154105]

119. Mongkhon P, Naser AY, Fanning L, et al. Oral anticoagulants and risk of dementia: A systematic review and meta-analysis of observational studies and randomized controlled trials. *Neurosci Biobehav Rev.* 2019;96:1–9. [PubMed: 30391408]

120. Zonneveld TP, Richard E, Vergouwen MDI, et al. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. *Cochrane Database Syst Rev.* 2018;7:CD007858. [PubMed: 30024023]

121. World Health Organization and Alzheimer's Disease International. Dementia: A Public Health Priority. Geneva, Switzerland: World Health Organization. Available at: http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pdf. Last accessed August 29, 2022.

122. Anstey KJ, Eramudugolla R, Hosking DE, et al. Bridging the translation gap: From dementia risk assessment to advice on risk reduction. *J Prev Alzheimer's Dis.* 2015;2(3):189–198.

123. Jeremy Y, Maaike A, Jennifer R, Naji T. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev.* 2015;4:CD005381.

124. Jaturapatporn D, Isaac MG, McCleery J, Tabet N. Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease. *Cochrane Database Syst Rev.* 2012;2:CD006378.

125. McGuinness B, Craig D, Bullock R, et al. Statins for the treatment of dementia. *Cochrane Database Syst Rev.* 2014;7:CD007514.

126. Schultz BG, Patten DK, Berlau DJ. The role of statins in both cognitive impairment and protection against dementia: A tale of two mechanisms. *Transl Neurodegener.* 2018;7:1–11. [PubMed: 29387348]

127. Butler M, Nelson VA, Davila H, et al. Over-the-counter supplement interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia. *Ann Intern Med.* 2018;168(1):52–62. [PubMed: 29255909]

128. Spence J, Chintapenta M, Kwon HI, Blaszczyk AT. A brief review of three common supplements used in Alzheimer's disease. *Consult Pharm.* 2017;32(7):412–414. [PubMed: 28701253]

129. Libro R, Giacoppo S, Rajan TS, et al. Natural phytochemicals in the treatment and prevention of dementia: An overview. *Molecules*. 2016;21(4):518. [PubMed: 27110749]

130. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med.* 1997;336(17):1216–1222. [PubMed: 9110909]

131. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. *J Am Med Assoc.* 2014;311(1):33–44.

132. Miller ER, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med.* 2005;142(1):37–46. [PubMed: 15537682]

133. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med.* 2005;352(23):2379–2388. [PubMed: 15829527]

134. Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of antioxidant supplement use and dementia in the prevention of Alzheimer's disease by vitamin E and selenium trial (PREADViSE). *JAMA Neurol.* 2017;74(5):567–573. [PubMed: 28319243]

135. Farina N, Llewellyn D, Isaac MGEKN, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst Rev.* 2017;4:CD002854. [PubMed: 28418065]

136. Zhang DM, Ye JX, Mu JS, Cui XP. Efficacy of vitamin B supplementation on cognition in elderly patients with cognitive-related diseases: A systematic review and meta-analysis. *J Geriatr Psychiatry Neurol.* 2017;30(1):50–59. [PubMed: 28248558]

137. Yuan Q, Wang CW, Shi J, Lin ZX. Effects of Ginkgo biloba on dementia: An overview of systematic reviews. *J Ethnopharmacol.* 2017;195:1–9. [PubMed: 27940086]

138. DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: A randomized controlled trial. *JAMA.* 2008;300(19):2253–2262. [PubMed: 19017911]

139. Vellas B, Coley N, Ousset PJ, et al. Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): A randomised placebo-controlled trial. *Lancet Neurol.* 2012;11(10):851–859. [PubMed: 22959217]

140. Stoddard GJ, Archer M, Shane-McWhorter L, et al. Ginkgo and warfarin interaction in a large Veterans Administration population. *AMIA Annu Symp Proc.* 2015;2015:1174–1183. [PubMed: 26958257]

141. Apoaequorin (Prevagen) Natural Medicines database. Apoaequorin [monograph]. Available at: http://naturalmedicines.therapeuticresearch.com.

142. Food and Drug Administration. Frequently Asked Questions About Medical Foods; Second Edition. Available at: https://www.fda.gov/files/food/published/Guidance-for-Industry--Frequently-Asked-Questions-About-Medical-Foods--Second-Edition-%28PDF%29.pdf. Last accessed August 29, 2022.

143. Chintapenta M, Spence J, Kwon HI, Blaszczyk AT. A brief review of caprylidene (Axona) and coconut oil as alternative fuels in the fight against Alzheimer's disease. *Consult Pharm.* 2017;32(12):748–751. [PubMed: 29467067]

144. Henderson ST, Vogel JL, Barr LJ, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: A randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond).* 2009;6:31. [PubMed: 19664276]

145. Onakpoya IJ, Heneghan CJ. The efficacy of supplementation with the novel medical food, Souvenaid, in patients with Alzheimer's disease: A systematic review and meta-analysis of randomized clinical trials. *Nutr Neurosci.* 2017;20(4):119–227. [PubMed: 25290491]

146. Hara J, Shankle WR, Barrentine LW, Curole MV. Novel therapy of hyperhomocysteinemia in mild cognitive impairment, Alzheimer's disease, and other dementing disorders. *J Nutr Heal Aging*. 2016;20(8):825–834.

147. Phillips P. Omega 3 fatty acids for the treatment of dementia: A Cochrane review summary. *Int J Nurs Stud.* 2017;67:83–84. [PubMed: 27884389]

148. Petersen RC, Aisen P, Boeve BF, et al. Mild cognitive impairment due to Alzheimer disease in the community. *Ann Neurol.* 2013;74(2):199–208. doi: 10.1002/ana.23931.

149. US National Library of Medicine. Available at: Clinicaltrials.gov.

150. Pickett J, Bird C, Ballard C, et al. A roadmap to advance dementia research in prevention, diagnosis, intervention, and care by 2025. *Int J Geriatr Psychiatry*. 2018;33(7):900–906. [PubMed: 29468724]

151. National Institutes of Health. Alzheimer's Disease. Available at: http://www.nih.gov/research-training/accelerating-medicines-partnership-amp/alzheimers-disease. Last accessed August 29, 2022.

152. Masopust J, Protopopová D, Vališ M, et al. Treatment of behavioral and psychological symptoms of dementias with psychopharmaceuticals: A review. *Neuropsychiatr Dis Treat.* 2018;14:1211–1220. [PubMed: 29785112]

153. Tible OP, Riese F, Savaskan E, von Gunten A. Best practice in the management of behavioural and psychological symptoms of dementia. *Ther Adv Neurol Disord.* 2017;10(8):297–309. [PubMed: 28781611]

154. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ.* 2015;350:h369. [PubMed: 25731881]

155. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *Am J Psychiatry*. 2016;173(5):543–546. [PubMed: 27133416]

156. Ngo J, Holroyd-Leduc JM. Systematic review of recent dementia practice guidelines. *Age Ageing*. 2015;44(1):25–33. [PubMed: 25341676]

157. Cohen-Mansfield J, Jensen B, Resnick B, Norris M. Knowledge of and attitudes toward nonpharmacological interventions for treatment of behavior symptoms associated with dementia: A comparison of physicians, psychologists, and nurse practitioners. *Gerontologist*. 2012;52(1):34–45. [PubMed: 22075773]

158. Desai AK, Schwartz L, Grossberg GT. Behavioral disturbance in dementia. *Curr Psychiatry Rep.* 2012;14(4):298–309. [PubMed: 22644311]

159. Crystal S, Jarrín OF, Rosenthal M, et al. National partnership to improve dementia care in nursing homes campaign: State and facility strategies, impact, and antipsychotic reduction outcomes. *Innovation in Aging*. 2020;4(3):1–13. doi: 10.1093/geroni/igaa018.

160. Ma H, Huang Y, Cong Z, et al. The efficacy and safety of atypical antipsychotics for the treatment of dementia: A meta-analysis of randomized placebo-controlled trials. *J Alzheimers Dis.* 2014;42(3):915–937. [PubMed: 25024323]

161. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med.* 2006;355(15):1525–1538. [PubMed: 17035647]

162. Levinson DR. Medicare atypical antipsychotic drug claims for elderly nursing home residents. Available at: http://oig.hhs.gov/oei/reports/oei-07-08-00150.pdf. Last accessed August 29, 2022.

163. Food and Drug Administration Information for Healthcare Professionals: Conventional Antipsychotics. Available at: https://wayback.archive-it.org/7993/20170722190727/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm. Last accessed August 29, 2022.

164. Centers for Medicare & Medicaid Services. National Partnership to Improve Dementia Care in Nursing Homes: Antipsychotic Medication Use Data Report (April 2021). Available at: https://www.cms.gov/files/document/antipsychotic-medication-use-data-report-2020q4-updated-07302021.pdf. Last accessed August 29, 2022.

165. Rexulti (brexpiprazole). Otsuka Tokyo, Japan 5/2023 package insert

166. Pan YJ, Wu CS, Gau SS, et al. Antipsychotic discontinuation in patients with dementia: A systematic review and meta-analysis of published randomized controlled studies. *Dement Geriatr Cogn Disord.* 2014;37(3-4):125–140. [PubMed: 24157687]

167. Supasitthumrong T, Bolea-Alamanac BM, Asmer S, et al. Gabapentin and pregabalin to treat aggressivity in dementia: A systematic review and illustrative case report. *Br J Clin Pharmacol.* 2019;(4):690–703.

168. Belsomra (suvorexant). Whitehouse Station, NJ. Merck Sharp and Dohme Corp. 2021. Package insert.

169. Sheehan B. Assessment scales in dementia. *Ther Adv Neurol Disord.* 2012;5(6):349–358. [PubMed: 23139705]

170. Kim LD, Factora RM. Alzheimer dementia: Starting, stopping drug therapy. *Cleve Clin J Med.* 2018;85(3):209–214. [PubMed: 29522388]

171. Deprescribing.org. Available at: http://deprescribing.org/resources/deprescribing-guidelines-algorithms/. Accessed September 3, 2021. Deprescribing Guidelines and Algorithms.

SELF-ASSESSMENT QUESTIONS

1. Which of the following is the most common form of dementia among older adults?
   A. Lewy body dementia
   B. Vascular dementia
   C. Alzheimer disease
   D. Organic brain syndrome
2. Genetic susceptibility to late-onset AD is primarily linked to which of the following?
   A. Apolipoprotein E4 genotype
   B. Presenilin gene mutations
   C. Amyloid precursor protein mutations
   D. Apolipoprotein E2 genotype
3. Which of the following statements is TRUE regarding the pathophysiology of AD?
   A. AD is caused by amyloid plaques.
   B. AD is caused by neurofibrillary tangles.
   C. AD is caused by inflammatory brain processes.
   D. The cause of AD is not completely understood.
4. When initiating pharmacologic treatment for a patient with a new diagnosis of AD, which of the following would be the safest and most effective option?
   A. Vitamin E
   B. Donepezil
   C. *Ginkgo biloba*
   D. Memantine
5. Which cholinesterase inhibitor inhibits both butyrylcholinesterase and acetylcholinesterase?
   A. Donepezil

B. Galantamine

C. Memantine

D. Rivastigmine

6. What is the route of administration of aducanumab?

A. Oral

B. Intravenous

C. Transdermal

D. Intramuscular

7. Which of the following interventions is considered first-line therapy for behavioral and psychological symptoms of dementia?

A. Sertraline

B. Quetiapine

C. Carbamazepine

D. Multisensory stimulation

Please use the following case for Questions 8-10:

An 87-year-old patient was diagnosed with AD and vascular dementia 2 years ago. At that time, donepezil 5 mg daily was started and continued at that dose. The patient denies any difficulty tolerating the medication and also takes warfarin and metoprolol for atrial fibrillation and lisinopril for hypertension. The patient's spouse notes that the patient's memory has declined significantly over the last several months.

8. Which of the following statements is TRUE regarding this patient's donepezil therapy?

A. Patient is receiving an appropriate maintenance dose of donepezil.

B. Patient has not been titrated to the target maintenance dose of donepezil.

C. Donepezil is not an appropriate therapy for a patient in this stage of AD.

D. Donepezil should be avoided in this patient due to vascular dementia and atrial fibrillation.

9. The patient's spouse confides in you that they plan to the start patient on a supplement for brain health that contains *Ginkgo biloba*. What would be the most appropriate advice to offer to the patient's spouse regarding *Ginkgo biloba*?

A. *Ginkgo biloba* is an appropriate therapy because it is more effective than donepezil.

B. *Ginkgo biloba* should be avoided because of its potential to worsen cognitive outcomes.

C. *Ginkgo biloba* should be avoided because of its potential drug interaction with warfarin.

D. *Ginkgo biloba* is appropriate because it is effective for treating both AD and atrial fibrillation.

10. Which of the following is an appropriate recommendation for the patient's spouse regarding management of this patient's cardiovascular disease?

A. Hypertension control is no longer necessary.

B. The risks of continuing warfarin outweigh the potential benefits.

C. Clopidogrel and aspirin should be added to patient's drug regimen to improve vascular health.

D. Treating hypertension and atrial fibrillation is recommended to optimize brain vascular health.

Please use the following case for Questions 11 and 12:

An 84-year-old patient was diagnosed with AD 4 years ago. Symptoms first became apparent to family about 1 year before the diagnosis was made. Current Mini-Mental State Examination (MMSE) score is 14. The patient is unable to perform most activities of daily living and does not recognize caregivers on some days.

11. Which of the following medications/medication combinations has NOT been shown to be effective therapy for this patient's stage of AD?

A. Aducanumab 10mg/kg every 4 weeks

B. Donepezil 10 mg nightly at bedtime

C. Memantine 10 mg twice daily

D. Donepezil 10 mg nightly at bedtime + memantine 5 mg twice daily

12. The patient's spouse asks about using Tylenol PM to help the patient fall asleep. What would you recommend?

A. Tylenol PM is preferred over prescription sedative hypnotics to treat insomnia in patients with AD.

B. Tylenol PM is preferred for both pain and insomnia because it may enhance the effects of cholinesterase inhibitors in patients with AD.

C. Tylenol PM should be avoided because of the pharmacokinetic drug interaction between diphenhydramine and memantine.

D. Tylenol PM should be avoided because diphenhydramine may worsen cognitive function.

13. A 77-year-old patient was diagnosed with AD 2 months ago with an MMSE score of 22 at diagnosis. At that time, donepezil was started at 5 mg nightly at bedtime. Would it be considered appropriate to add memantine to the medication regimen now?

A. Yes, patient has moderate AD.

B. Yes, patient is unlikely to respond to donepezil.

C. No, patient has mild AD.

D. No, memantine should never be added to cholinesterase inhibitor therapy.

14. Of the following, which is the most common adverse medication reaction of donepezil?

A. Elevated blood pressure

B. Tachycardia

C. Agitation

D. Diarrhea

15. Which of the following counseling points would be appropriate to discuss with a newly diagnosed patient and their family in regard to expectations of AD therapy?

A. Combination therapy with a cholinesterase inhibitor plus memantine usually halts the progression of AD.

B. Risks of adverse mediation reactions outweigh the benefits in mild AD.

C. Time to reach significant functional decline may be delayed by medication therapy but AD will continue to progress.

D. Memory noticeably improves for most patients with AD when therapy is first initiated.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** The majority (60%-80%) of dementia cases are AD. See "Epidemiology" section for more information.
2. **A.** Apolipoprotein E (*APOE*)*4 is the main genetic risk factor associated with for late-onset AD. See "Etiology" section (Etiology and Genetics) for more information.
3. **D.** A multitude of genetic, environmental, and possibly additional unknown variables contribute to development of AD. See the "Etiology" and "Pathophysiology" sections for more information.
4. **B.** Of the options listed, donepezil has the most safety and efficacy data to support its use. See "Treatment" section for more information about cholinesterase inhibitors, memantine, and dietary supplements.
5. **D.** Rivastigmine inhibits both butyrylcholinesterase and acetylcholinesterase. See "Treatment" section (Cholinesterase Inhibitors) for more information.
6. **D.** The route of administration of aducanumab is intravenous. This information can be found in Table 73-3.
7. **D.** Nonpharmacologic interventions are first line for neuropsychiatric symptoms of dementia. See "Treatment" section (Pharmacotherapy of Neuropsychiatric Symptoms) for more information.
8. **B.** The patient has been treated with donepezil 5 mg daily for 2 years. As they are not experiencing any bothersome adverse medication effects and have no known contraindications to increasing the dose, it would be appropriate to trial donepezil 10 mg daily. Since they are on metoprolol, monitoring for bradycardia should be included in your monitoring plan. Dosing information and monitoring parameters can be found in Tables 73-3 and 73-7.
9. **C.** The risks of using *Ginkgo biloba* outweighs the benefits in this patient. While heavily studied, convincing data to support the utility of Ginkgo biloba in AD is lacking. Moreover, in this case, *Ginkgo biloba* may potentiate the bleeding risk associated with warfarin. See "Treatment" section (*Ginkgo biloba*) for more information.
10. **D.** Vascular health plays a significant role in vascular dementia and AD. As such, the patient's diagnosis of dementia does not negate their need for ongoing management of cardiovascular disease. See "Pathophysiology" section (Brain Vascular Disease and High Cholesterol) and "Treatment" section (Management of Brain Vascular Health) for more information.
11. **A.** There is no data to support effectiveness of using aducanumab in moderate AD. See "Treatment" section for more information.
12. **D.** Tylenol PM contains both acetaminophen and diphenhydramine, the latter of which is strongly anticholinergic. Anticholinergic medications are known to contribute to cognitive impairment and, as such, should be avoided in this patient. See "Clinical Presentation" section (Diagnosis) for more information.
13. **C.** As the patient is newly diagnosed with mild AD and is still taking the lowest possible dose of donepezil, adding memantine does not seem necessary now. It would be reasonable, however, to consider increasing the donepezil dose to 10 mg daily if the patient is tolerating the drug well. As the patient's AD progresses, it may become necessary to increase the donepezil dose and/or add memantine. Dosing information can be found in Table 73-3.
14. **D.** Of the adverse medication reactions listed, diarrhea is most likely to be associated with donepezil. As cholinesterase inhibitors are procholinergic, patients may experience diarrhea and urinary incontinence. Cholinesterase inhibitors are associated with bradycardia, not tachycardia. Adverse drug event information can be found in Table 73-7.

15. **C.** It is important to be realistically optimistic with patients and their care partners, especially in the early stages of dementia. At present, there is no treatment option available to halt the progression of AD; however, some patients respond well to drug therapy, and large studies have shown the potential for medication use to delay functional decline and institutionalization. See "Treatment" section (Pharmacotherapy for Cognitive Symptoms) for more information.