The Alzheimer's Disease Clinical Spectrum

Diagnosis and Management

Alireza Atri, MD, PhD[a,b,c,*]

KEYWORDS

• Alzheimer's disease • Mild cognitive impairment • Cognitive • Treatment
• Donepezil • Memantine • Neuroimaging • Review

KEY POINTS

- Evaluation of older individuals with cognitive or behavioral symptoms, or functional decline, should use structured history and multidomain symptom-function reviews from the patient and a care partner or informant; a focused examination including a standardized cognitive instrument; and multitiered tests (laboratory tests, neuroimaging). In vivo biomarkers of Alzheimer's disease (AD), such as cerebrospinal fluid and PET, are also now clinically available.
- Level of impairment (mild cognitive impairment, dementia) and delineation of cognitive-behavioral syndrome, along with test results (that help exclude confounders and include AD) inform etiologic diagnosis, management of symptoms, and care plans.
- AD management is multifactorial. A first step involves a thorough review of medications and supplements to eliminate redundancies and potentially deleterious substances.
- Anti-AD pharmacotherapies approved by the US Food and Drug Administration (the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine; and the N-methyl-D-aspartate antagonist memantine) provide modest but meaningful benefits by mitigating symptoms, reducing clinical progression, and delaying disability.

Continued

Disclosure Statement: Dr. Atri has no equity, shares or salary from any pharma company and is not a member of any pharma speakers' bureau. He has received honoraria for consulting, educational lectures/programs/materials or advisory boards from AbbVie, Allergan, Alzheimer's Association, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, Lundbeck, Merck, Oxford University Press (medical book-related revenues), Sunovion, Suven, and Synexus. Dr. Atri's institution (Banner Health) has investigational observational study/trial related funding from Novartis. Dr. Atri's previous institution (California Pacific Medical Center) had contracts or received investigational clinical trial related funding from The American College of Radiology, AbbVie, Avid, Biogen, Lilly, Lundbeck, Merck, and vTV.

[a] Banner Sun Health Research Institute, Banner Health, 10515 W Santa Fe Drive, Sun City, AZ 85351, USA; [b] Department of Neurology, Brigham and Women's Hospital, 60 Fenwood Road, Boston, MA 02115, USA; [c] Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
* Banner Sun Health Research Institute, 10515 W Santa Fe Drive, Sun City, AZ 85351.
E-mail address: alireza.atri@bannerhealth.com

Med Clin N Am 103 (2019) 263–293
https://doi.org/10.1016/j.mcna.2018.10.009 **medical.theclinics.com**

Continued

- First-line treatment of behavioral problems is nonpharmacologic and involves identifying the trigger for the problem behavior. When identified, it is necessary to institute behavioral interventions, make environmental modifications, and to evaluate the impact of the interventions.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of cognitive impairment or dementia in individuals older than 65 years and, with rising longevity, a worldwide pandemic of mild cognitive impairment (MCI), AD, and AD-related dementia (ADRD) is anticipated.[1–5] AD is the sixth leading cause of death in the United States and the only top-10 cause still significantly increasing.[4] AD-related pathological changes often coexist with 1 or more other pathologies, particularly vascular-ischemic cerebral injury and diffuse Lewy body (DLB) disease.[1,6–9]

Timely detection, accurate diagnosis, and appropriate management of MCI, AD and ADRD are imperative.[4] Symptoms too often go undiagnosed, misattributed, or dismissed and ignored, which causes distressing, costly, and potentially harmful delays in receiving appropriate care.[1,4,5]

AD clinical (ADc) syndromes, Cognitive-Behavioral Syndromes (CBS) presumed to be due to AD, are heterogeneous, particularly in younger individuals (65 years of age or younger). MCI and dementia due to AD can be accurately diagnosed by a comprehensive evaluation that integrates pathologic AD biomarkers (cerebrospinal fluid [CSF] and amyloid PET). However, clinical use of AD CSF and PET biomarkers are not currently indicated in most symptomatic individuals to include or exclude AD pathology. These tests are reserved for atypical, rapidly progressive, or early-onset syndromes, or when comprehensive evaluation is inconclusive.[10,11] In relatively typical cases, an individualized approach to history, examination, and selected laboratory tests and neuroimaging (see later discussion) can provide a high-confidence diagnosis. No single biomarker, test, or score can provide the clinical diagnosis; this requires characterization of symptoms and level of impairment into a profile via a clinical evaluation.

Epidemiology, Risk Factors, Genetics, and Neuropathology

The prevalence of dementia, mostly attributed to AD or mixed AD, is increasing in the United States and globally.[4,5] By 2030, the number of Americans with dementia will increase by 35%[4,12] and will potentially triple by 2050.[13] **Table 1** shows the major risk factors for AD or dementia. AD or dementia prevalence approximately doubles every 5 years in individuals aged 65 to 85 years; from approximately 1% to 2% at 65 years, to more than 30% to 50% by age 85 years.[4] Of Americans of older than 60 years, 16% have MCI (6.7% prevalence for ages 60–64 years, 8.4% for 65–69 years, 10.1% for 70–74 years, 14.8% for 75–79 years, and 25.2% for 80–84 years), equating to 11.6 million individuals.

AD is a dual proteinopathy disease defined by a widespread but regionally specific pattern of intraparenchymal diffuse and neuritic ß-amyloid (Aß) plaques and intracytoplasmic (initially), then extracellular, neurofibrillary tangles with synaptic and neuronal loss and gliosis.[14–17] Neurofibrillary tangles consist of intracellular (then extracellular) deposits of hyperphosphorylated tau protein, a microtubule stabilizing protein. The AD pathway that leads to clinical stages of MCI or dementia starts decades before the

Table 1
Risk factors for Alzheimer's disease and dementia

Modifiable (in Early Life and Midlife Ages 45–65 y, or Later Life Ages >65 y)	Nonmodifiable
Vascular risks	Age
Diabetes (later life)	Gender (female more than male; ~1.5 relative risk [RR][13,133])
Hypertension (midlife)	Family history (first-degree or second-degree relative or multiple generations; RR 2–6)
Dyslipidemia (midlife)	Race (African American and Hispanic individuals are at 1.5–2-fold RR compared with white individuals due to a combination of genetic, health disparity, and socioeconomic factors[38])
Metabolic syndrome and obesity (midlife)	Down syndrome
Smoking tobacco (later life)	Apolipoprotein (APOE)-ε4 allele carriers (individuals who carry one or two APOE-ε4 alleles of the APOE gene have a 3-fold and 8–10-fold RR, respectively, compared to homozygous APOE-ε3 allele carriers)
Low physical activity (later life)	Cerebral amyloidosis (positive biomarker of the AD pathologic process[a])
Cerebral hypoperfusion, cerebrovascular injury or stroke	
Depression (later life)	
Severe head trauma or traumatic brain injury	
Hearing loss (midlife)	
Low cognitive reserve (early life and potentially midlife). Cognitive reserve is "the brain's capacity to maintain cognitive function despite neurologic damage or disease"[1]. (Low Cognitive reserve, thought to be due to low educational, professional or social attainment, or low intelligence, carries ~1.5–2 RR)[132]	

[a] Is currently a nonmodifiable risk factor but primary and secondary prevention trials using amyloid-modifying drugs are in progress and early results support that cerebral amyloid plaque burden can be lowered; whether this would then translate to lowering risk of progression to MCI or dementia, potentially making this be a modifiable risk factor, is to be determined.

onset of symptoms.[2] The new AD biological framework and the model of pathologic AD biomarkers from Jack and colleagues[18] conceptualize a progressive sequence of measurable biochemical, neurophysiological, and neuroanatomical alterations that can be detected years before psychometrically and clinically noticeable deterioration in cognition, behavior, and function. Typical AD neuropathology starts and spreads in a consistent pattern. Pathologic tangle findings correlate best with symptoms. In the dementia stages of AD, many patients have cortical or cortico-subcortical microhemorrhages due to cerebral amyloid angiopathy-related vasculopathy and leakage[19]; hemosiderin microdeposition from microhemorrhages are seen on gradient-echo or susceptibility-weighted MRI sequences in 15% to 20% of patients.[20]

The genetics and cause of AD are complex and incompletely understood.[2,21] AD-risk attributable to genetic factors is estimated at 70%. Familial autosomal dominant AD is rare (<1%), usually manifests in early-onset AD (onset age <65 years; <4% of AD), and is caused by mutations in presenilin 1, amyloid precursor protein, or presenilin 2.[21] In the most common form of AD, sporadic late-onset AD, many genetic variations contribute to increase or lower risk; greater than 20 have been identified (AlzGene Database; www.alzgene.org).[22] The major risk or susceptibility gene in sporadic AD involves apolipoprotein-E (APOE). APOE-ε4 alleles are associated with accelerated Aß-deposition and earlier onset and higher risk of developing AD symptoms.[21,23]

The cause of AD remains controversial and is incompletely understood.[24–26] Prevailing models posit a central role of accumulation of synaptic neurotoxic forms of Aß to induce inflammatory and microglial cascades, broad ionic and neurotransmitter abnormalities, mitochondrial dysfunction, oxidative stress, and hyperphosphorylation of the microtubule stabilizing protein tau and formation of tangles.[26–31]

Tau-mediated processes cause further synaptic and neuronal dysfunction and destruction, leading to cortical dysfunction. Other models posit microvascular injury, tipping the balance in favor of toxic Aß accumulation.[25]

SYMPTOMS

Clinical Features

There can be large heterogeneity in ADc syndromes; particularly regarding development and progression of symptoms and clinical decline. Clinical criteria recognize atypical presentations, or atypical AD, as variants. The 2011 National Institute on Aging and Alzheimer's Association (NIA-AA) criteria for AD recognizes nonamnestic AD presentations that include language, visuospatial, and executive dysfunction features.[32]

At the MCI level of impairment, when daily function and behavior are not significantly affected, the most typical presentations of AD are amnestic (single or multidomain amnestic-MCI). Amnestic-MCI is greater than 90% associated with underlying AD pathology. MCI significantly increases risk of annual progression to dementia (relative risk [RR] 6–8). MCI with negative biomarkers versus 1 or more AD pathology biomarkers (ie, AD pattern in CSF, high amyloid load in amyloid PET) or biomarkers of neurodegeneration (eg, AD pattern on structural MRI or fluorodeoxyglucose [FDG]-PET; high CSF tau and phospho-tau levels) has a 2 to 3 relative risk of progression to dementia (8% vs 17%–22% per year[33]).

Clinical Characteristics of Alzheimer's Disease: Symptoms and Signs

Individuals with very mild or mild AD dementia manifest variable but significant changes and/or mild-to-moderate impairments in multiple cognitive, functional, and behavioral domains. Patterns of change may overlap but are not part of normal cognitive aging, as manifested by differential aging and AD effects on cognitive networks.[34] In normal aging, individuals typically retain longstanding personalities and interests, including their levels of initiative, motivation, sociability, empathy, affect, and behavior. AD changes are not synonymous with old age (**Box 1**).

In retrospect, some of the earliest symptoms manifest years before receiving a clinical diagnosis of dementia, including changes in mood, anxiety, and sleep. Heightened anxiety, depressive symptoms, apathy, and withdrawal are highly prevalent in preclinical or early stages of AD.[35–37] Progression to later-stage symptoms, such as impaired judgment, disorientation, and confusion; major behavioral changes, such as aggression and agitation; and neuropsychiatric symptoms, such as delusions and hallucinations, can go unrecognized and undertreated until diagnosis. Recognition of the 10 early warning symptoms or signs[38] (**Table 2**) and appropriate evaluation is the first step of effective care.

DIAGNOSIS

The first pillar in appropriate care is accurate and timely diagnosis. AD dementia remains a clinical diagnosis. Of individuals age 70 years or older, 20% to 40% without cognitive impairment have biomarker or autopsy evidence of AD pathology[2]; therefore, pathologic AD findings are not sufficient for symptoms.

The 3 major clinical criteria for the AD spectrum are the revised 2011 NIA-AA criteria,[32,39] the International Working Group (Dubois and colleagues[39,40]) 2010 revised new lexicon criteria, and the *Diagnostic and Statistical Manual of Mental Disorders*, *5th edition* criteria.[41] The new 2018 NIA-AA research framework dissociates AD symptoms or phenotypes from the pathologic process. It defines AD, for research purposes, purely in terms of a biopathologic construct with the AD biomarkers of

Box 1
Cognitive changes across the lifespan: decline in fluid intelligence in early adulthood and preservation and increase in crystalized intelligence until late life

- Aspects of cognitive decline begin in early adulthood but there are large interindividual differences in rates of decline
- Cognitive domains decline differently
- Effects on fluid intelligence
  - Performance on measures of fluid intelligence, such as speed of mental processing; working memory; recall and retention of verbal and visual information (learning and memory), in particular visuospatial memory; and reasoning begin to decline in many individuals from age 20 to 30 years.[134,135]
  - These cognitive changes can affect creativity, abstract reasoning, and novel problem-solving abilities.
  - These changes can affect lower speed and efficiency in acquiring and remembering new information; translating into a lower learning rate and slower retrieval of information and memories.
- Effects on crystalized intelligence
  - With age, accumulation of greater experience and knowledge can allow for better performance on measures of crystallized intelligence.
  - Better crystalized intelligence can manifest in improved (compared with ages 20–30 years) or stable performance from age 50 to 70 years on tests of specific procedures (eg, acquired skills), semantic knowledge (eg, facts about the world), reading, and vocabulary.[134,135]
- These cognitive abilities still rely on successful retrieval of stored procedures and information; loss of information storage is not considered a normal part of cognitive aging.

amyloid, tau, and neurodegeneration (ATN) criteria, which aids in defining the disease stages.[2]

Box 2 shows the 2011 NIA-AA all-cause dementia definition; dementia-level impairment requires cognitive or behavioral symptoms "of sufficient magnitude to interfere with usual work or daily function." MCI diagnosis is a matter of "clinical judgment made by a skilled clinician" regarding the presence of cognitive impairment without "significant interference in the ability to function at work or in usual daily activities," and must be individualized to the patient in the context of the patient's particular circumstances and premorbid level of function and performance as appreciated through clinical interview with the patient and informant.[32]

Box 3 shows the 2011 NIA-AA criteria for AD dementia, categorized as

1. Probable AD dementia
2. Possible AD dementia
3. Probable or possible AD dementia with evidence of the AD pathophysiologic process.

The third category was intended for research purposes and is recently replaced by the new research framework, ATN classification, of the AD biopathologic spectrum.[2] A diagnosis of possible AD dementia is made if the individual has either an atypical course or an etiologically mixed presentation.

Evaluation of Alzheimer's Disease: History, Examination, Cognitive Assessment, and Tests

According to recent preliminarily announced multidisciplinary US national guidelines, the *Alzheimer's Association Best Clinical Practice Guidelines for the*

Table 2
Comparison of behaviors associated with normal aging and symptoms and behaviors that may be observed in cognitive-behavioral impairment in Alzheimer's disease

	Normal Aging (Occasional and Inconsistent Behaviors)	Behaviors and Symptoms in AD (Persistent and Progressively More Frequent Symptoms and Behaviors)
Memory	Minor lapses of information retrieval with later recall (eg, forgetting an appointment or names and remembering later) Recall slightly slower	Memory loss, especially for recently learned information Forgetting important dates and appointments Repetitive questioning for same answer in a short time frame Increasing reliance on memory aids for tasks that they used to do themselves
Planning or problem-solving	Develops a plan, follows recipes, occasional error when balancing checkbook, may find an error later	Difficulty with developing a plan Difficulty following a plan or using a familiar recipe Difficulty working with numbers or paying bills Difficulty starting, focusing, or completing on a project
Familiar task completion	Occasionally need help to record a television show or to use a device or application	Trouble using appliances and devices Confusion or trouble driving to a familiar location Trouble remembering rules of a favorite game Trouble managing a budget
Recognition of time or place	Occasionally confused about date but remember it later	Forget exact location, address, nearby streets, or the route taken to get there Often confused about dates, day of the week, or time; may confuse season in later stages Trouble processing future events; mostly only aware of immediate events Difficulty remembering or confusing the correct timeline of events; may up mix events and people
Comprehension of visual images and spatial relationships	Vision changes related to cataracts, myopia, less acuity; may affect driving at night and glare	Visual processing problems, such as difficulty reading, determining color or contrast, judging distance, recognizing familiar objects, or seeing full picture or surroundings May become disoriented; not knowing the location or how they arrived there Driving more difficult even in daylight due to lower ability to estimate distance and speed of oncoming traffic

(*continued on next page*)

Table 2
(continued)

	Normal Aging (Occasional and Inconsistent Behaviors)	Behaviors and Symptoms in AD (Persistent and Progressively More Frequent Symptoms and Behaviors)
Communication, use and recall of words and names during talking and writing	Occasional trouble finding word, name, or phrase	Difficulty joining or following a conversation Struggling with vocabulary; often puts words together to describe a word Forgetting meaning of some words Using the wrong or imprecise words Becoming less fluent, starting to stutter, getting stuck during speech or have broken speech.
Ability to retrace steps	May misplace an item but usually able to retrace steps to find the item	Frequently misplacing personal items May leave things in odd places and unable to retrace steps to find them
Judgment and interpersonal interactions	Making an occasional bad decision Being occasionally irritable or less interactive	Decline in sound judgment, may include money, finances, personal interactions and actions Engaging in more risky, inappropriate, or unusual behavior More vulnerable to being taken advantage of by unscrupulous telemarketers and fraud Less attention to grooming and hygiene
Work or social activities	Usually enjoy and participate in family and social events but sometimes need a break	May avoid social interactions because they sense a change in their behavior Attend and engage less or abandon or lose interest in previous hobbies, projects, sports, and social activities May not remember how to perform hobby or complete projects
Mood and personality	Experiencing mild anxiety or sadness in reaction to life events and stressors May prefer using a routine to do things	May become anxious, depressed, less motivated, fearful, suspicious, or having labile affect Can be easily upset when in out of comfort zone scenario Overreacting; often frustrated when cannot remember or do things or blaming others Becoming impulsive or insensitive through words or actions.

Data from Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement 2013;9(2):208–45; and Schott JM. The neurology of aging: what is normal? Pract Neurol 2017;17(3):172–82.

Evaluation of Neurodegenerative Cognitive Behavioral Syndromes, Alzheimer's disease and Dementias in the United States,[42] the clinician's approach to the evaluation and disclosure process in suspected AD or ADRD should involve triggering an evaluation in individuals when there is a symptom or concern regarding cognitive, behavioral, or functional decline; involving the patient and a care partner or

Box 2
2011 National Institute on Aging and Alzheimer's Association core clinical criteria for all-cause dementia

Dementia: cognitive or behavioral (neuropsychiatric) symptoms are present that

1. Interfere with the ability to function at work or at usual activities
2. Represent a decline from previous levels of functioning and performing
3. Are not explained by delirium or major psychiatric disorder
4. Cognitive impairment is detected and diagnosed through a combination of
   a. History-taking from the patient and a knowledgeable informant
   b. An objective cognitive assessment, either a bedside mental status examination or neuropsychological testing (neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis)
5. The cognitive or behavioral impairment involves a minimum of 2 of the following domains
   a. Impaired ability to acquire and remember new information
      Symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route
   b. Impaired reasoning and handling of complex tasks, poor judgment
      Symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities
   c. Impaired visuospatial abilities
      Symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements or orient clothing to the body
   d. Impaired language functions (speaking, reading, writing)
      Symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors
   e. Changes in personality, behavior, or comportment
      Symptoms include: uncharacteristic mood fluctuations, such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors

From 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):265; with permission.

informant; and using a 3-step diagnostic formulation process. This process includes (1) identifying and classifying the overall level of impairment (eg, MCI, mild neurocognitive disorder, dementia, or major neurocognitive disorder); (2) defining the CBS; and (3) establishing likely cause or causes (diseases or conditions causing the CBS) using a multitiered, structured, and individualized testing approach (eg, assessments, laboratory tests and neuroimaging).

Diminished cognitive capacity can adversely affect the ability of patients to manage their medications and follow medical recommendations. Clinicians should retain a high index-of-suspicion for cognitive, functional, or behavioral changes and warning signs in older patients (see **Table 2**). Subclinical cognitive impairment or dementia should be considered as a cause or contributor in older patients with escalating decompensation of an otherwise well-managed and stable chronic medical condition (eg, diabetes, hypertension, congestive heart failure); new onset of confusion; delirium (in the context of medical illness, medications, or surgery);

Box 3
2011 National Institute on Aging and Alzheimer's Association core clinical criteria for probable Alzheimer's disease dementia

A diagnosis of probable AD dementia can be made when the patient
1. Meets criteria for dementia (see Box 2)
2. Has the following characteristics
   a. Insidious onset
      Symptoms have a gradual onset over months to years, not sudden over hours or days
   b. Clear-cut history of worsening of cognition by report or observation
   c. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories
      i. Amnestic presentation: most common syndromic presentation of AD dementia; deficits should include impairment in learning and recall of recently learned information; should also be evidence of cognitive dysfunction in at least 1 other cognitive domain (see article discussion)
      ii. Nonamnestic presentations
         1. Language presentation: the most prominent deficits are in word-finding; deficits in other cognitive domains should be present
         2. Visuospatial presentation: the most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia; deficits in other cognitive domains should be present
         3. Executive dysfunction: the most prominent deficits are impaired reasoning, judgment, and problem-solving; deficits in other cognitive domains should be present
3. The diagnosis of probable AD dementia should not be applied when there is evidence of
   a. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden
   b. Core features of dementia with Lewy bodies other than dementia itself
   c. Prominent features of behavioral variant frontotemporal dementia
   d. Prominent features of semantic variant primary progressive aphasia or nonfluent or agrammatic variant primary progressive aphasia
   e. Evidence for another concurrent, active neurologic disease, or a nonneurological medical comorbidity or use of medication that could have a substantial effect on cognition

From 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):265–6; with permission.

weight-loss; failure-to-thrive; anxiety; social withdrawal or apathy; depressive and behavioral symptoms (eg, agitation, personality changes, hoarding, delusions); symptoms of presyncope or syncope, transient ischemic attack, or chronic dizziness; and unsteadiness or falls of unclear cause or thought to be related to medications or dehydration.

The history should be obtained from the individual, as well as a knowledgeable care partner or informant. In addition to cognitive symptoms and warning signs (see **Table 2**), assessments of cognition, function, and behavior should be personalized and interpreted within the context of the individual's psychosocial background, level of education or intelligence, function and attainment, primary language, ethnicity, and culture. The AD-8 screening instrument provides a practical symptoms questionnaire for changes in thinking and memory that can be a red flag for ADc syndromes.[43]

History of Present Illness

Presenting symptoms, as well as the most salient symptoms, complaints, and problems, and how the patients has progressed, should be assessed. Helpful questions include

1. When was the last time the patient's thinking was normal?
2. In retrospect, what was the first major change that was noticed?
3. What is now the most prominent symptom or change?
4. What is the most bothersome symptom, problem, or behavior?
5. How have these symptoms progressed?

It is important to delineate both the course (eg, generally linear decline vs clearly stepwise decline) and the pace (eg, very slow initially but more rapid in the last 6 months) of the progression of symptoms or problems, including any major fluctuations or full or partial recovery.

Other important questions include whether there are any

1. Major fluctuations in symptoms on a day-to-day (or hour-to-hour) basis
2. Unusual associated features (eg, falls, weakness, tremor, parkinsonism, personality changes, or odd behaviors)
3. Temporal associations with symptoms onset or worsening (eg, a stepwise decline after a major illness or surgery; happening mostly at night or when the patient is tired).

For example, rapid onset and deterioration (hours and days) is most consistent with an overlying encephalopathy or delirium, whereas a more subacute onset and progression (over weeks and months) is a greater indication of an overlying indolent or chronic infection, metabolic disorder, mass lesion, medication side-effect, sequelae of vascular insults and infarcts, or hydrocephalus. Any of these may overlie and decompensate vulnerabilities in individuals with undetected CBS. AD or ADRD have insidious onset and slow progression over many months and years but can be unmasked in the context of delirium or other cognitive stressors.

Table 3 summarizes components of a comprehensive review of cognition, daily function, behavior, or neuropsychiatric symptoms; other pertinent neurologic and general reviews of systems; salient past medical history (focus on cerebrovascular and hypoxic-ischemic risk factors); medications and supplements (Beers criteria lists those avoided in older individuals, including anticholinergics and sedative-hypnotics[44]); educational, work, and social history; hobbies and health-related behaviors (particularly alcohol intake, sleep and exercise); and potential safety concerns.

Approach to Multitiered Testing: Laboratory Studies

Table 4 outlines a multitiered and individualized approach to testing. Studies help exclude common comorbid conditions in older individuals that can contribute to cognitive impairment in susceptible individuals and that can be treated. It is highly unlikely for a hormonal or vitamin deficiency, or a metabolic, infectious, autoimmune, toxic, neoplastic, or paraneoplastic condition, to mimic the clinical phenotype of typical late-onset AD dementia. Although many of these comorbid conditions can cause decompensation of cognitive-behavioral function in susceptible individuals with subclinical or unrecognized mild impairments or dementia, they are not a primary cause of dementing syndromes. A judicious and stepwise approach to tests that prioritizes more common and treatable conditions, and less invasive and more

Table 3
Elements of history and multidomain symptom-function reviews in evaluation of cognitive-behavioral syndrome due to Alzheimer's disease or Alzheimer's disease–related dementia

Review of cognitive, functional, and neuropsychiatric domains	Cognition	Changes or difficulty with memory, orientation, language, attention, executive functions, judgment, reasoning, problem-solving, visuospatial functions, insight
	Function or ADLs	Instrumental ADLs: keeping appointments and checkbook; making payments and managing finances; shopping; handling money; engaging in hobbies; driving, commuting, and traveling; preparing meals and cooking; using tools, electronics, and appliances; doing laundry, cleaning, and housekeeping; making household repairs; managing medications
		Basic ADLs: dressing, eating, bathing, grooming, feeding, mobility, toileting, continence
	Behavior and neuropsychiatric	Presence, frequency, and severity of personality changes; neuropsychiatric symptoms and problem behaviors; false beliefs and delusions; hallucinations; apathy and indifference; anxiety, irritability, and lability; dysphoria and depression; inappropriate elation or euphoria; agitation and aggression; disinhibition and impulsivity; aberrant or repetitive motor behaviors, disrupted sleep and aberrant nighttime behaviors; changes in eating habits and tastes; aberrant oral intake
Review of systems	Neurologic	New headaches, weakness, incoordination, numbness, dysesthesia
	Parkinsonism	Dysarthria, tremor, poverty of movements, imbalance, difficulty walking or shuffling gait, falls, abnormal movements, stiffness, weakness, dysphagia (choking or coughing with food or drink)
	General	Appetite, weight, continence, vision, hearing
	Sleep	Nature and quality of sleep, time to bed and awake, time falling asleep, number of times awake or up and why, difficulty falling or staying asleep, early morning wakening, snoring, restlessness, kicking, acting out dreams, sleep walking, daytime somnolence or naps
Salient past medical history	Cardiovascular and cerebrovascular; hypoxic-ischemic	Transient ischemic attack, stroke, hypertension, dyslipidemia, diabetes, arrhythmias, coronary artery or vascular disease, myocardial infarction, congestive heart failure, cardiac or vascular procedures, smoking, obstructive sleep apnea, snoring, severe lung disease
	Neurologic	Seizures or epilepsy, concussion or traumatic brain injury (including duration of loss of consciousness and any sequelae), meningoencephalitis, delirium, encephalopathy
	Psychiatric, and mental health	Mood disorder, depression, anxiety, electroconvulsive therapy, alcohol or substance abuse
	Other general and medical	Hormonal disorders, thyroid disease or deficiency, vitamin deficiency (particularly vitamin B12 deficiency), immunosuppression, malignancy, exposure to environmental toxic substances
	Development and school	Prenatal and birth history, developmental milestones, learning, attentional or cognitive problems, school performance (need to repeat grade or receive extra academic support or special education programs)

(*continued on next page*)

Table 3
(*continued*)

Medications and supplements	Medications	With special attention to anticholinergic and sedative-hypnotic and narcotic medications; particularly avoid those on the updated Beers criteria in older individuals due to potential cognitive side-effects[44]
	Supplements	Ask for a full list and components
Educational, social and work history	Educational and work	Achievement, performance, and the nature of education and occupation to inform past level of function, cognitive reserve, and problem trends
	Social	Social history regarding interpersonal relationships and support networks
Hobbies, community activities and health-related habits	Hobbies	Nature, level, and changes in engagement, activity, and performance of hobbies
	Exercise	Nature or type, frequency, duration, and intensity of exercise; amount of daily activity
	Alcohol and substance intake	Past and current level of alcohol intake (quantify); history of problem drinking; use of other substances, past or current
Family history	Family members diagnosed or suspected to have AD, dementia, or senility; other neurologic and psychiatric diagnoses; age of onset, nature, and progression of symptoms; age at death; pathologic confirmation	
Review of safety and well-being	Access, use, and monitoring of medications, driving (including changes, accidents, scrapes, tickets), power tools, firearms, stove, or cooking; wandering potential	
Caregiver burden and distress	Assess level of stress, care burden, mood disorder, anxiety, burnout; can be formally quantified using structured instrument[136]	

Table 4
Multitiered testing in cognitive-behavioral syndromes: a tiered approach to laboratory and ancillary studies in etiologic evaluation of mild cognitive impairment and dementia syndromes

Tier	Type	What	When or Who or How	Why or Comments
1	Serum	Thyroid stimulating hormone, vitamin B12, homocysteine, complete blood count with differential, complete metabolic panel (including calcium, magnesium, liver function tests), erythrocyte sedimentation rate, C-reactive protein	Always or almost always and routinely done as foundational dementia assessment laboratory tests and imaging All individuals All or almost all tests	Broad and relatively inexpensive tests for common conditions in older individuals that can contribute to cognitive and behavioral impairments
	Imaging	Brain MRI without gadolinium; if unavailable or contraindicated, obtain noncontrast head computed tomography (CT)		Brain MRI (or CT), assessing: atrophy patterns (hippocampal and cortical atrophy in temporal and lateral parietal lobes are consistent with AD); infarcts, leukoaraiosis, and microhemorrhages; nondegenerative conditions (eg, hydrocephalus, mass lesions)
2	Serum	ANA, HgbA1c, lipid profile, folate, ammonia, lead, Lyme antibody, RPR, HIV, SPEP, methylmalonic acid (MMA), PT, PTT	Sometimes Some individuals as-needed based on individual characteristics (epidemiology; clinical risk profile from history, examination, or laboratory tests or studies) Some or few tests	—
	Imaging	Chest plain film or radiograph		
	Other	Sleep study: for obstructive sleep apnea or REM sleep disorder		

(*continued on next page*)

Table 4
(continued)

Tier	Type	What	When or Who or How	Why or Comments
3–4	Serum, CSF, imaging, biopsy, genetics	Thyroid peroxidase antibodies (TPO), antithyroglobulin antibodies (TGA), AD CSF biomarker panel (AB_{42}, tau, phospho-tau) with calculation of amyloid-tau index; EEG; brain FDG-PET (or SPECT) scan, brain amyloid-PET scan, APOE-4 allele, testing for AD deterministic gene mutations	Very occasionally or rarely Very few individuals: some individuals with atypical clinical profiles, early-onset, or rapid progression Highly sparingly or very few tests	Most should be done by a specialist or in consultation with specialist[45] Assessment of early onset AD can include analysis of specific *in vivo* AD biomarkers such as CSF AD pattern and/or brain amyloid-PET, and, under special circumstances, testing for APOE-4 allele, and deterministic AD gene mutations[a]

Abbreviations: Ab, antibody; ANA, antinuclear antibody; EEG, electroencephalogram; HgbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; PT, prothrombin time; PTT, partial thromboplastin time; REM, rapid eye movement; RPR, rapid plasma reagin; SPEP, serum protein electrophoresis.

[a] When there are 2 or more generational histories of AD or dementia syndrome suggestive of autosomal pattern or early-onset; testing for deterministic AD mutations should be done in consultation with genetic counseling.

cost-effective tests, is recommended in evaluating progressive profiles that are not atypical or rapidly progressive.

Tier-1 dementia assessment laboratory tests should be obtained in all or almost all patients evaluated for suspected CBS. Tier-1 laboratory tests are low cost, widely available, and relatively high-yield as a broad screen for common comorbid conditions that can contribute to symptoms or decompensate an underlying CBS in a susceptible individual. None of these conditions primarily cause dementia. For example, thyroid and vitamin B_{12} deficiencies are common in older adults and can cause neurologic or neuropsychiatric symptoms and decompensation. Hyperhomocysteinemia is associated with functional B_{12} deficiency, vascular damage, and cardiac or cerebrovascular risk. Other conditions informed by tier-1 laboratory tests include dehydration (eg, blood urea nitrogen-to-creatinine ratio >20:1), hyponatremia or hypernatremia, hypomagnesemia, hypercalcemia (and hypocalcemia), hypoglycemia or hyperglycemia, anemia, uremia, and hepatic dysfunction. Erythrocyte sedimentation rate and C-reactive protein broadly screen for systemic indolent or insidious inflammatory or autoimmune infectious and neoplastic processes (eg, undetected lung, liver, or colon cancer).

Structural brain imaging, preferably with MRI, is a tier-1 test in suspected AD or ADRD (if unavailable or contraindicated, use a noncontrast head computed tomography [CT] scan). Hippocampal and cortical atrophy in temporal and parietal regions on MRI or CT support an AD-related neurodegenerative pattern; however, absence of this pattern does not exclude pathologic AD. MRI or CT can also provide evidence for leukoaraiosis (white matter burden); vascular cognitive impairment (VCI) or dementia (injury); mixed AD or VCI; and, rarely, for conditions that are not neurodegenerative and are treatable that may cause the CBS (eg, a large frontal meningioma). It can also dictate a substantial change in management; for example, in individuals with copious microhemorrhages placed on blood thinners or those with a mass lesion.

Tier 2 tests can be ordered in some individuals with a low-threshold reason based on particular clinical and epidemiologic profiles, findings on examination, or other test results.

In individuals presenting with symptoms of early-onset, highly atypical, or rapidly progressive dementia, in which the cause remains in doubt by a dementia specialist, more comprehensive testing can be pursued (tier 3–4). This may include spinal fluid testing and/or amyloid brain PET for AD profile (ie, low CSF $A\beta_{42}$, high tau and phospho-tau with an amyloid-tau index of less than 1.0, excessive and widespread binding of an amyloid PET agent in the brain) and exclusion of other less common cognitive or behavior-impairing conditions.[3,45]

FDG-PET or single-photon emission CT (SPECT), and MRI or CT, do not directly measure AD-related pathology but suggest neurodegeneration and can support that AD is causative or contributory. Bilateral parietal and temporal hypometabolism on FDG-PET or SPECT is useful to distinguish AD versus *frontotemporal degeneration* in individuals with behavioral or dysexecutive CBS in whom cause is in doubt. Presence of pathologic AD does not exclude other pathologies causing or contributing to the patient's CBS; for example, 70% to 80% of individuals with DLB are also amyloid-positive on PET.[46] In 2016, Atri[47] reviewed neuroimaging in CBS, AD, or ADRD.

Office-Based Brief Cognitive Testing

Office-based brief cognitive testing should include administration of at least 1 standardized and validated brief instrument for detection of cognitive impairment or dementia, such as MoCA, GPCOG, Blessed Dementia Information-Memory-Concentration scale (BDS-IMC), MMSE, SLUMS, Mini-Cog, and MIS (these tests were compared by Cordell and colleagues[48]). Further tests should be individually adapted and performance should be interpreted in the context of the individual's symptoms, history, demographics, and expected level of performance. The MoCA is a good initial choice for detection; it takes approximately 8 to 12 minutes to administer, has good psychometric properties, acceptable sensitivity to detection of mild impairment, and is available in several forms and languages. The BDS-IMC is useful for tracking progression because it accommodates performance across a broad range of dementia stages, from mild to severe; in contrast, performance on the MoCA often reaches floor values in moderate to severe stages of AD dementia.

Formal Neuropsychological Evaluation

Formal neuropsychological evaluation is useful when higher confidence is needed regarding delineation of the level of impairment and characterization of the CBS; especially when the initial evaluation is borderline or has discrepancies, and when there are unusual clinical profiles, extremes of age or education, and English as a secondary language. It also assists in determining possible contribution of a mood disorder, the patient's capacity, differential diagnosis (DDx), individualized care planning, and recommendation of compensatory strategies to leverage cognitive strengths and avoid limitations.

DIFFERENTIAL DIAGNOSIS

Table 5 provides the DDx of ADc syndromes. Symptoms do not necessarily present or progress in a uniform pattern, and mixed AD syndromes and pathologies are common. Co-existent AD and vascular-ischemic pathology (causing the clinical spectrum of VCI, which includes dementia), and AD with DLB pathology (causing AD-DLB

Table 5
Differential diagnosis of Alzheimer's disease clinical syndromes and Parkinson's plus sensorimotor cognitive-behavioral syndromes

ADc Syndrome	ADc Syndrome Characteristic	DDx
Amnestic ADc	Difficulty with learning and remembering new information	AD and mixed AD (AD + VCI, AD + DLB > AD + VCI + DLB) >> Pure DLB, Hippocampal sclerosis dementia, Argyrophilic grain disease, pure VCI, TDP-43 Pathology and Primary Age-Related Tauopathy Of note: Korsakoff syndrome, TBI, sequelae of HSV encephalitis are readily distinguished by history
Language variant ADc (presenting as primary progressive aphasia (PPA) syndrome)	Variable difficulty with different aspects of language, such as word-finding or hesitancy, fluency, syntax or grammar, writing, reading, comprehension, word-meaning, and naming	Logopenic variant PPA (word-finding): AD > FTD (4R tau > 3R tau or Pick disease) Nonfluent or agrammatic variant PPA (pronunciation or syntax): FTD (4R tau > TDP-43) > AD Semantic variant PPA (word meaning and naming): FTD (TDP-43>>3R tau or Pick disease) >> AD
Visuospatial variant ADc (presenting as posterior cortical atrophy syndrome)	Difficulty with visuospatial cognition and visuoperception, including processing, integration, interpretation, identification	AD > DLB and mixed AD + DLB >> CJD
Behavioral or dysexecutive variant AD	Changes in behavior and personality and/or executive functions, judgment, reasoning, problem-solving	FTD (TDP-43 > Pick disease or 3R tau) >> AD, VCI, DLB, PDD, PSP, AD mixed pathologies, CTE
Mixed Cognitive-Behavioral Syndrome with motor or sensorimotor presentations; Parkinsons-Plus syndromes	Parkinsonism; and/or sensorimotor perception difficulties; and/or apraxia and neglect	Parkinsons-Plus Syndrome: DLB > AD/VCI mixed pathologies, PDD > PSP, MSA Corticobasal Syndrome: CBD > AD, PSP

Relative prevalence of pathology accounting for the observed Cognitive-Behavioral Syndrome: > denotes relatively more prevalent than; >> denotes relatively much more prevalent than.

ADc syndromes are defined by the nature of the cognitive-behavioral domain primarily, prominently, and progressively affected.

Abbreviations: CBD, corticobasal degeneration; CJD, Creutzfeldt-Jakob disease; CTE, chronic traumatic encephalopathy; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MSA, multiple systems atrophy; PDD, Parkinson's disease dementia; PSP, progressive supranuclear palsy; TBI, traumatic brain injury.

variants), are prevalent in older individuals.[9,49,50] The DDx of atypical or variant ADc syndromes is broad and depends on the particular CBS characterized by the most prominent presenting domain of impairment. Prion diseases are very rare but Creutzfeldt-Jakob disease is on the DDx of atypical ADc syndromes when there is rapid onset and progression of symptoms (over weeks to months).

TREATMENT OF ALZHEIMER'S DISEASE

Management of AD requires shared goal setting and a triadic partnership between the clinician, patient, and care partners; it is also dynamic, multifactorial, and multidisciplinary. AD management involves (1) early recognition and diagnosis of symptoms, combined with a proactive customized care plan for the patient–caregiver dyad because without accurate diagnosis and appropriate disclosure no care can be provided; (2) nonpharmacologic interventions and behavioral approaches; (3) appropriate pharmacology; and (4) dynamic and pragmatic care plan adjustment according to changes in the patient–caregiver dyad's goals, capacity, condition, and resources, which facilitates continued therapeutic alliance, adherence, and patient and caregiver well-being and safety. Caregivers provide the glue for the therapeutic legs of the care plan.

The current AD treatment paradigm is multifaceted management of symptoms and reduction of long-term clinical decline. First and foremost, management should involve truthful and compassionate disclosure of the diagnosis, according to the patient–caregiver dyad's wants and capacities, along with tailored psychoeducation regarding the syndrome, level of impairment, the disease name and stage, expected course, management options and expectations, and life and care planning needs. Nonpharmacologic or behavioral approaches should be recommended based on the patient–caregiver dyad's priorities, strengths, limitations, resources, and environment. After this foundation is formed, a stage-appropriate pharmacologic treatment plan can be instituted. Long-term management of AD dementia requires proactive planning and flexibility to modify care plans according to changes in the condition and resources of the patient–caregiver dyad.

MANAGEMENT OF ALZHEIMER'S DISEASE DEMENTIA

Nonpharmacologic Management: Behavioral Interventions and Coping Strategies

Nonpharmacologic interventions and behavioral strategies should be used as the first-line option to ameliorate neuropsychiatric symptoms (eg, agitation, apathy, delusions, and disinhibition) and problem behaviors (eg, resistance to care, caregiver shadowing, hoarding, and obsessive-compulsive behaviors) in AD dementia.[51,52] Problem behaviors are distressing to patients and caregivers and, left untreated, exact a devastating toll and lead to poor outcomes.[53,54] During the course of their illness, as many as 85% to 90% of patients will experience neuropsychiatric symptoms or problem behaviors, such as noncognitive behavioral symptoms and behavioral and psychological symptoms of dementia (BPSD), which are associated with more rapid decline, earlier institutionalization, higher distress, worse quality of life, and greater health care utilization and costs.[53,54] Treatment of BPSD using pharmacology alone has low treatment benefit effect sizes (Cohen's $d \leq 0.2$) and, in some cases (eg, antipsychotics), is associated with substantial side-effects and short-term and long-term risks for morbidity and mortality.[55]

Early and ongoing BPSD screening, root-cause analysis, intervention, monitoring, and care plan modification are important components of comprehensive AD dementia care; they can facilitate prevention and treatment efficacy by eliminating triggers and directing treatments to the root cause, not just at the symptoms.

Psychoeducation should include caregiver education on the biopsychosocial substrates behind BPSD (eg, loss of behavioral and coping reserve, compromise of top-down control from fronto-striatal networks, regression to childhood capacities and behaviors in a progression-regression model of dementia), and

strategies to avoid behavioral triggers and better communicate and care for the patient. It is important for caregivers to appreciate that overall poor and problem behaviors by the demented individual are not intentional (eg, to be mean, ornery, or vindictive) but are due to disease, brain injury or damage, and diminished capacities. This is nobody's fault; it is just part of the illness. Environmental modification, maintaining consistency, and simple routines can also be very helpful.[56,57]

Pharmacologic Management

Eliminating deleterious medications

The initial step in the pharmacologic management of AD consists of eliminating redundant and potentially deleterious medications. For example, diphenhydramine, often taken as an over-the-counter drug combination with acetaminophen for sleep and pain relief; other sedative-hypnotics; and medications for anxiety (eg, benzodiazepines) or urinary incontinence (antimuscarinic) are relatively contraindicated in elderly and cognitively vulnerable persons.[44,58]

Identification and treatment of comorbid conditions that decompensate dementia

Treating these conditions can affect better cognition, function, and behavior in patients with AD. In many, the symptoms and signs of decompensation can be subtle and chronic and do not manifest as acute delirium or encephalopathy. The delirium-dementia link has been reviewed in the literature.[59,60] Tier 1 to 2 CBS or dementia assessment laboratory tests or studies (see **Table 4**) can help identify common conditions that exacerbate symptoms, including dehydration, electrolyte and metabolic derangements, anemia, cardiac or cerebral ischemia, hypoxia, thyroid and vitamin deficiencies (eg, vitamin B_{12} deficiency), and infections (eg, urinary tract infections, pneumonia). Other conditions, such as pain from arthritis, constipation, hunger, thirst, or fatigue, are also common in AD, particularly in later stages when patients cannot appropriately recognize or communicate their symptoms. These can lead to BPSD, particularly anxiety, irritability, agitation, aggression, or sleep-wake disturbances.

Antipsychotics: use with extreme caution under strict specific circumstances

Antipsychotics carry a US Food and Drug Administration (FDA) black-box warning in dementia; they must be used with extreme caution, ongoing monitoring, and only when strict conditions are met.[55,56] Short-term and long-term antipsychotic use is associated with substantial risk of cognitive decline, morbidity (eg, parkinsonism, falls, pneumonia, or cardiovascular and cerebrovascular events), and mortality. Their use is reserved as a last resort for severe refractory behavioral disturbances without an identifiable and treatable cause (eg, severe aggression, agitation, or psychosis not due to delirium, pain, or infection) or when a serious risk of immediate harm or safety exists that cannot be otherwise ameliorated.[55,56] Risperidone is European Medicines Agency approved in Europe for short-term, 12-week, use in dementia when there is refractory severe agitation or psychosis. After a careful evaluation by a dementia specialist, cautious use of antipsychotics should be limited to the lowest effective dosages for short durations. Continued use requires ongoing monitoring, assessment of risk-benefit, and continued consent from the family or care providers regarding goals of treatment and trade-offs.

Approved anti-Alzheimer disease medications: cholinesterase inhibitors and memantine

Cholinesterase inhibitors (ChEIs) (donepezil, galantamine, rivastigmine) and the N-methyl-D-aspartate (NMDA)-antagonist, memantine, are the only FDA-approved

treatments for AD dementia and are recommended broadly in consensus guidelines and practice parameters.[1,52,61,62] ChEIs and memantine also have complementary mechanisms of action, potentially additive effects, and demonstrate acceptable tolerability and safety profiles.[63] A recent systematic review and meta-analysis by Tricco and colleagues[64] included 110 studies and 23,432 subjects supports efficacy, effectiveness, and safety. A pharmacologic foundation of anti-AD therapies, whether with a ChEI or memantine monotherapy, or, ultimately, combined together as add-on dual combination therapy, most often as memantine added on to stable background ChEI treatment, have demonstrated benefits in the short-term and long-term to reduce decline in cognition and function, retard the emergence and impact of neuropsychiatric symptoms, and to delay nursing home placement without prolongation of time to death.[64,65] Viewed from the social perspective, anti-AD pharmacotherapy (donepezil, memantine, galantamine, rivastigmine) can reduce the economic burden of the illness, even in later stages of illness.[66]

Short-term responses to anti-AD medications vary between individuals. Aggregate data suggest that during the initial 6 to 12 months of treatment, performance on measures of cognition, activities of dialing living (ADL), behavioral symptoms, or global clinical impression of change may significantly improve in a minority (10%–30%), plateau in nearly half (30%–50%), or continue to deteriorate in about a third (20%–40%) of treated patients. Discontinuation of ChEI treatment is, on aggregate, harmful. Patients taken off, or those inconsistently taking, anti-AD medications progress more rapidly than those who continue treatments, particularly ChEIs. Unless otherwise indicated, clinicians should avoid discontinuation trials of ChEIs to see if there is worsening. Even temporary discontinuation is associated with irreversible declines and greater risk of nursing home placement.[67–72]

Sustained treatments provide a modest expectation of short-term stabilization or improvement, and longer-term slowing of clinical decline. As the disease progresses, over several months to years, patients who may initially show improvement or stability, will eventually decline. It is important for clinicians to communicate practical issues associated with pharmacologic treatment, including rationale, need for monitoring, and expectations. In the long run, current treatments of AD dementia mitigate decline but do not prevent it. From a public health and economics perspective, therapies that minimize caregiver burden and delay nursing home entry translate into significant benefits related to worker productivity and health care savings.[66,73–75]

Cholinesterase inhibitors

ChEIs facilitate central cholinergic activity by reducing the physiologic breakdown of acetylcholine (ACh) by the enzyme acetylcholinesterase (AChE) in the synaptic cleft. No high-quality data support significant group-level efficacy differences between the 3 ChEIs generically available in the United States. Donepezil and rivastigmine are FDA-approved and labeled for mild, moderate, and severe AD dementia; galantamine has approval for mild and moderate AD.

Cholinesterase inhibitors safety and tolerability With slow titration in appropriate individuals, ChEIs are generally tolerated well and have an acceptable adverse effect profile.[64] The most common adverse effects, including nausea, vomiting, anorexia, flatulence, loose stools, diarrhea, salivation, and abdominal cramping, are related to peripheral cholinomimetic effects on the gastrointestinal (GI) tract. For the oral preparations, the adverse GI effects of ChEI can be minimized by administering the drug after a meal or in combination with memantine. Others can experience vivid dreams or mild insomnia; therefore, doses should ideally be given after a meal in the morning. The rivastigmine transdermal patch can also cause skin irritation, redness, or rash at

the site of application. Overall, adverse effects may occur in 5% to 20% of patients starting on ChEIs but are usually mild and transient, and often related to the dosage and rate of dosage escalation. These medications may also decrease heart rate and increase the risk of syncope, particularly in susceptible individuals (eg, those with sick sinus syndrome or atrioventricular block) and with overdose. Use of these agents is contraindicated in patients with unstable or severe cardiac disease, uncontrolled epilepsy, unexplained syncope, and active peptic ulcer disease.

ChEIs efficacy and effectiveness In more than 40 short-term randomized controlled trials (RCTs) using placebos over 24 to 52 weeks investigating efficacy, and in meta-analyses of RCTs, all 3 ChEIs have demonstrated small to medium effect size treatment benefits at the sibject-group level in terms of improving, stabilizing, or delaying decline in cognition, ADL, and global status, and in ameliorating BPSD and caregiver burden.[35,65,70,71,76–87] Longer term benefits, from 2 to 4 or more years have been demonstrated in open-label extension[69,88–90] and long-term prospective observational clinical cohort studies.[91–95]

Level II or equivocal level I evidence suggest donepezil treatment may be beneficial in very mild stage AD or for subgroups with MCI due to AD (ie, carriers of APOE-ε4 allele,[96] those with depression or depressive symptoms[97]). Such off–FDA label pharmacotherapy is not sufficiently supported by level I evidence to warrant an unequivocal recommendation for all patients. However, efficacy or effectiveness, risk (tolerability and safety) and cost data, individual clinical circumstances, and patient–caregiver dyad preferences may warrant a discussion between clinicians, patients, and caregivers about this possibility.[96]

N-methyl-D-aspartate antagonists (memantine)

Memantine was the last FDA-approved treatment of AD dementia (2002) and remains the sole medication in its class. Memantine affects glutamatergic transmission; it is a renally cleared low-to-moderate affinity NMDA-receptor open-channel blocker.

Memantine safety and tolerability Titrated appropriately, memantine has a favorable safety and tolerability profile. Mild and transient treatment-emergent side effects include confusion, dizziness, constipation, headache, and somnolence. These may be encountered during, or soon after, titration to the maximum total daily dosage of 10 mg twice daily for immediate-release memantine (generically available in the United States) or 28 mg once daily for memantine XR. In patients with severe renal insufficiency (creatinine clearance <30 mL/min) a dosage-adjustment to 5 mg twice daily for immediate-release memantine and 14 mg daily for extended-release memantine is recommended.

Memantine efficacy and effectiveness Memantine is FDA-approved in moderate to severe AD dementia, as monotherapy or in combination with a ChEI (often added to an existing ChEI treatment). In moderate and severe AD, short-term efficacy of memantine monotherapy compared with placebo is reported in several RCTs of 12 to 50 weeks duration and supported by meta-analyses. Treatment benefits include improvement, stabilization, or reduced decline in the domains of cognition, function (ADLs), and global status; and by amelioration of BPSD and caregiver burden.[63,71,73,98–111] Short-term (6 months or less) memantine treatment effect sizes are small to medium in size and clinically significant at the moderate to severe stages of AD.[109,110,112,113] Longer-term prospective observational clinical patient cohort studies report reduced clinical decline in patients with AD treated at any stage.[114–119]

Add-on dual combination therapy with acetylcholinesterase inhibitors and memantine

Short-term (6–12 months) RCTs (level I evidence), longer-term (12–36 months) open-label extensions of RCTs (level II or III evidence), and long-term (2 to 5-plus years) observational prospective clinical cohort effectiveness studies (level II evidence) support the safety and benefits of anti-AD treatments in combination, most frequently as memantine added on to a stable regimen of background ChEI treatment.[114–121] Systematic reviews and meta-analysis also provide level II grade evidence for the benefits of ChEI and memantine add-on combination treatment in AD dementia.[63–65,79,80,122–124]

Safety and tolerability of cholinesterase inhibitor memantine add-on combination treatment Several studies have reported on safety and tolerability of combination therapy; overall, there is a good profile for both. Addition of memantine to stable dosages of a ChEI does not correspond to significant overall increases in adverse events.[63,64] The rates of discontinuation due to adverse events for ChEIs and memantine combination treatment are low, between 5% to 10%, and not generally significantly different from placebo.[100,120,121,125,126]

Vitamins, medical foods, and supplements

Other than vitamin E, large RCTs have failed to provide support from level III or IV epidemiologic association studies for potential benefits of vitamins or supplements at the AD dementia stage. Unless contraindicated due to bleeding diatheses, coronary artery disease, or another comorbidity, high-dose vitamin E (1000 IU twice daily was the regimen tested) may be considered based on results of 2 RCTs that supported approximately 20% lower rate of ADL decline over approximately 2 to 3 years; there were no concerning safely signals or increased mortality with high-dose vitamin E.[127,128] There is no compelling evidence that Souvenaid, a prescription nutritional supplement (ie, medical food) containing Fortasyn Connect provides additional benefits in patients with AD dementia treated with anti-AD medications.[129] Unfortunately, large RCTs have failed to support benefits from ginkgo biloba, high-dose vitamin B_{12} or folic acid combinations, omega-3 fatty acid or fish oil components or preparations, nonsteroidal anti-inflammatory drugs, and statin medications at the dementia stage of AD.[76,81]

Practical recommendations for implementation of pharmacotherapy

Unless contraindicated, ChEI therapy should be initiated and slowly titrated over months to a maximal clinical or tolerated dosage following diagnosis of AD dementia (**Table 6**). For patients with moderate to severe AD, memantine can be initiated (see **Table 6**) after patients have received stable ChEI therapy for several months without adverse effects. Memantine monotherapy can be initiated on-label in moderate or later stage AD. Conversely, a ChEI can be added after several months of stable memantine monotherapy. The latter is a useful strategy in patients who are very sensitive to or experience GI side effects with ChEIs. A very low and slow titration (eg, starting donepezil 2.5 mg daily after breakfast; increasing it to 5 mg daily if no side effects emerge within 6 weeks) may be helpful in patients who are very sensitive to cholinomimetic effects. In highly refractory situations, switching to another ChEI at a low-dosage can be tried. Persistence, higher dosage (in later dementia stages), and duration of treatment are associated with better outcomes, even in those with advanced dementia.[92,95,114,115,130]

Patients should have diligent management of their vascular risk factors, including lipids, blood pressure, and glucose. Managing vascular risk factors in patients with

Table 6
Recommended dosing for US Food and Drug Administration–approved anti–Alzheimer disease medications: cholinesterase inhibitors donepezil, rivastigmine, and galantamine; and the N-methyl-D-aspartate–antagonist, memantine

Drug	Dosage and Notes
Donepezil	Starting dosage: 5 mg/d; can be increased to 10 mg/d after 4–6 wk Before starting donepezil 23 mg/d, patients should be on donepezil 10 mg/d for at least 3 mo
Rivastigmine	Oral: starting dosage 1.5 mg twice daily; if well-tolerated, the dosage may be increased to 3 mg twice daily after 2 wk; subsequent increases to 4.5 and 6 mg twice daily should be attempted after 2-wk minimums at previous dosage; maximum dosage: 6 mg twice daily; oral rivastigmine can be difficult to tolerate Patch: starting dosage 1 4.6 mg patch once daily for a period of 24 h Maintenance dosage 1 9.5 mg or 13.3 mg patch once daily for a period of 24 h; before initiating a maintenance dosage, patients should undergo a minimum of 4 wk of treatment at the initial dosage (or at the lower patch dosage of 9.5 mg) with good tolerability
Galantamine	Extended-release: start at 8 mg once daily for 4 wk; increase to 16 mg once daily for 4 weeks; increase to 24 mg once daily Generic: start at 4 mg twice daily for 4 wk; increase to 8 mg twice daily for 4 wk; increase to 12 mg twice daily
Memantine	Immediate-release: starting dosage 5 mg once daily; increase dosage in 5-mg increments to a maximum of 20 mg daily (divided dosages taken twice daily) with a minimum of 1 week between dosage increases; in earlier stages may consider 10 mg daily dosage; the maximum recommended dosage in severe renal impairment is 5 mg twice daily Extended-release (XR): for patients new to memantine, the recommended starting dosage of memantine XR is 7 mg once daily, and the recommended target dosage is 28 mg once daily; the dosage should be increased in 7-mg increments every seventh day; the minimum recommended interval between dosage increases is 1 week, and only if the previous dosage has been well tolerated; the maximum recommended dosage in severe renal impairment is 14 mg once daily
Memantine XR or donepezil capsule (branded combo capsule)	Combination capsule consisting of 7–28 mg memantine or 10 mg donepezil given orally once daily; can be started in patients already on background stable donepezil 10 mg daily (with memantine dosage titration) or in patients already on combination treatment with each agent; maximum recommended dosage in severe renal impairment is 14 mg memantine XR or 10 mg donepezil once daily

AD is associated with slower cognitive decline (Deschaintre, Neurol 2009).[2] Anxiety and clinical depression should be monitored and treated (use a selective serotonin reuptake inhibitor with a low anticholinergic load and a favorable geriatric profile; eg, citalopram, escitalopram, sertraline). There should be proactive monitoring and optimization of sleep, stress level, hydration, and nutrition status; and any deficiencies (eg, thyroid, vitamin B_{12}) and systemic conditions that can decompensate mental functions should be treated (eg, urinary tract infection, dehydration, hyponatremia). Along with social and mental engagement, and stress management, daily exercise and physical activity should be an integral part of the care plan.

Potentially deleterious medications, including anticholinergics and benzodiazepines, should be weaned and avoided.[44] Off-label use of antipsychotics should be used with great caution, and only under specific circumstances when behavioral or

environmental interventions have failed, and after careful consideration of risks, benefits, side-effects, and alternatives.[56] Stimulants are seldom indicated and may lower the threshold for irritability, agitation or aggression, and dysphoria.

When to start and stop anti-Alzheimer disease medications

Per FDA prescribing information, clinicians may start a ChEI in mild, moderate, or severe AD, and memantine in moderate or severe AD. In moderate stages, a ChEI or memantine can be started and, ultimately, the complementary agent can be added to achieve dual-combination therapy. Based on the patient–caregiver dyad preferences and clinician comfort and expertise, an individualized discussion can be prompted regarding the pros and cons, cost, and uncertainties of potential off-label prescription of anti-AD medications, such as ChEIs in MCI due to AD[96] and high-dose vitamin E.[127,128]

Box 4
Key elements of effective multifactorial management of Alzheimer's disease

Individualization of evaluation process, diagnosis, disclosure process, and care plan
- Early detection of symptoms, timely assessment and diagnosis, and appropriate disclosure
- Shared goal setting for diagnostic, disclosure, and management processes; sustained targeting and tailoring of a proactive care plan to patient and caregivers

Nonpharmacologic interventions and behavioral approaches to management
- Psychoeducation about AD; dementia in general; effects on cognition, function, and behaviors; dementia care; expectations; "the progression and regression model of aging and dementia"
- Behavioral approaches, both general and targeted to the patient–caregiver dyad; including simplification of environment; establishing routines; providing a safe, calm, and consistent care environment; using strategies such as interacting calmly, redirection to pleasurable activities and environment, reassurance, providing only necessary information in a manner that the patient can appreciate (ie, in simple language and small chunks) and at the appropriate time; benign therapeutic fibbing and never saying no (unless immediate safety is concerned) to allow the moment to pass
- Establishing and fostering support networks for the patient and caregivers
- Identifying and monitoring health and safety risks for patient and others, advance planning for medical, legal, and financial decision-making and needs (eg, stove, weapon, and driving safety; falling prey to fraud or poor work or financial decision-making)
- Caring for caregivers, including caregiver support and respite care

Pharmacologic treatment
- Elimination of redundant and inappropriate medications listed in Beers criteria.[44]
- Treating underlying medical and psychiatric conditions, and associated symptoms that can exacerbate cognitive-behavioral impairment or dementia (eg, dehydration, pain, constipation, infections, electrolyte and metabolic derangements, anxiety, depression, psychosis)
- Prescription of stage-appropriate FDA-approved anti-AD medications (ChEIs: donepezil, rivastigmine, galantamine; NMDA-antagonist: memantine) as monotherapy or add-on dual combination therapy (ChEI plus memantine)

Pragmatic modifications to sustain alliance, adherence, and well-being of patient–caregiver dyad
- Flexibility to modify care plan according to important changes in the patient–caregiver dyad
- Forging and sustaining a therapeutic alliance
- Promoting the safety, health, and well-being of the patient and her or his caregivers
- Adopting a pragmatic approach to ongoing care that includes establishing and simplifying care routines if possible; modifying the environment to suit the patient–caregiver dyad; and consideration of patient and caregiver preferences, capacity, environment, and resources in devising and implementing care plans

Anti-AD medications can be maintained in late-stages to support basic psychomotor processes, praxis, functional communication, the behavioral responses required to assist caregivers to deliver basic ADL care, and the elementary processes of movement and eating. The benefits may also extend to reducing antipsychotic use. In the end or terminal stages of AD, when personhood has disintegrated and when there is no meaningful communication or interaction, patients should only receive care (pharmacologic or otherwise) that is directed to provide palliation and comfort.[131]

SUMMARY OR FUTURE CONSIDERATIONS

Box 4 provides a summary of the evaluation, diagnosis, disclosure, and management process. Evaluation should use a structured history and multidomain symptom and function review from the patient and a care partner or informant, and a focused examination to assess the level of change or impairment and to characterize the CBS. Etiologic diagnosis is aided by a multitiered approach to tests, including laboratory tests and neuroimaging. The current AD treatment paradigm is to reduce progression of symptoms and disability. Despite ongoing efforts, a magic bullet or cure for AD in the dementia stages is unrealistic in the near future. By the time AD is in the dementia stages, neurodegeneration has wrought devastation in synapses, cells, and networks for a decade or more.

Nonpharmacologic management and pharmacologic therapies for AD dementia seek to minimize the disabling effects of cognitive and functional decline and emergence of problem BPSD. The FDA-approved anti-AD pharmacotherapies; the ChEIs donepezil, galantamine, and rivastigmine; and the NMDA antagonist memantine can reduce progression of clinical symptoms and disability.

Clinicians should establish a proactive and flexible individualized approach to compassionately care for individuals and caregivers. It is necessary to maintain a strong therapeutic alliance that is holistic, pragmatic, and involves psychoeducation, behavioral and environmental approaches to care, planning for current and future care needs, and promoting brain health and psychosocial well-being.

Intensive research efforts are underway to develop more accurate diagnostic tools (eg, using neuroimaging, blood, CSF, proteomic, and genomic biomarkers of AD) and better AD therapeutics. A myriad of ongoing phase1 to 3 human clinical trials for primary and secondary prevention, and symptomatic and disease-modifying treatment, are directed at diverse therapeutic targets in AD, including neurochemicals, amyloid and tau pathologic processes, mitochondria, inflammatory pathways, neuroglia, and multimodal lifestyle interventions.

REFERENCES

1. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390(10113):2673–734.
2. Deschaintre Y, Richard F, Fau-Leys D, et al. Treatment of vascular risk factors is associated with slower decline in Alzheimer's disease. Neurology 2009;73(9): 674–80.
3. Atri A. Alzheimer's disease and Alzheimer's dementia. In: Dickerson BC, Atri A, editors. Dementia: comprehensive principles and practices. 1st edition. New York: Oxford University Press; 2014. p. 360–432.
4. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. Alzheimers Dement 2018;14(3):367–429.
5. Prince MJ, Wimo A, Guerchet MM, et al. World alzheimer report 2015 - the global impact of dementia: an analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International (ADI); 2015.

6. Prince M, Prina M, Guerchet M. The world Alzheimer report 2013 'Journey of Caring: an analysis of long-term care for dementia'. Alzheimer's Disease International (ADI); 2013.
7. Wimo A, Prince M. The world Alzheimer report 2010 'The Global Impact of Dementia. Alzheimer's Disease International (ADI); 2010.
8. Saxena S. Dementia world report: a public health priority. World Health Organization (WHO); 2012.
9. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol 2017;134(2):171–86.
10. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the amyloid imaging task force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimers Dement 2013;9(1):e-1-16.
11. Simonsen AH, Herukka SK, Andreasen N, et al. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. Alzheimers Dement 2017; 13(3):274–84.
12. 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):126–35.
13. Hebert LE, Weuve J, Scherr PA, et al. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013;80(19):1778–83.
14. Braak H, Alafuzoff I, Arzberger T, et al. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 2006;112:389–404.
15. Jellinger KA, Bancher C. Neuropathology of Alzheimer's disease: a critical update. J Neural Transm 1998;54:77–95.
16. Parvizi J, Van Hoesen GW, Damasio A. The selective vulnerability of brainstem nuclei to Alzheimer's disease. Ann Neurol 2001;49:53–66.
17. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8(1):1–13.
18. Jack C, Knopman D, Jagust W, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet 2010;9(1):119–28.
19. Attems J, Jellinger K, Thal DR, et al. Review: sporadic cerebral amyloid angiopathy. Neuropathol Appl Neurobiol 2011;37:75–93.
20. Atri A, Locascio JJ, Lin JM, et al. Prevalence and effects of lobar microhemorrhages in early-stage dementia. Neurodegener Dis 2005;2(6):305–12.
21. Loy CT, Schofield PR, Turner AM, et al. Genetics of dementia. Lancet 2014; 383(9919):828–40.
22. Bertram L, McQueen MB, Mullin K, et al. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet 2007; 39(1):17–23.
23. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261(5123):921–3.
24. Davies P. A very incomplete comprehensive theory of Alzheimer's disease. Ann N Y Acad Sci 2000;924:8–16.
25. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 2011;12(12):723–38.

26. Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. Arch Neurol 2011;68(8):1062–4.
27. Selkoe DJ, Abraham CR, Podlisny MB, et al. Isolation of low-molecular-weight proteins from amyloid plaque fibers in Alzheimer's disease. J Neurochem 1986;46(6):1820–34.
28. Haass C, Koo EH, Mellon A, et al. Targeting of cell-surface beta-amyloid precursor protein to lysosomes: alternative processing into amyloid-bearing fragments. Nature 1992;357(6378):500–3.
29. Selkoe DJ. Amyloid protein and Alzheimer's disease. Sci Am 1991;265(5): 68–71, 74–6, 78.
30. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science 1992;256(5054):184–5.
31. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297(5580):353–6.
32. 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):263–9.
33. Petersen RC, Aisen P, Boeve BF, et al. Criteria for mild cognitive impairment due to Alzheimer's disease in the community. Ann Neurol 2013;74(2):199–208.
34. Chhatwal JP, Schultz AP, Johnson KA, et al. Preferential degradation of cognitive networks differentiates Alzheimer's disease from ageing. Brain 2018;141(5): 1486–500.
35. Farlow MR, Cummings JL. Effective pharmacologic management of Alzheimer's disease. Am J Med 2007;120(5):388–97.
36. Jost BC, Grossberg GT. The natural history of Alzheimer's disease: a brain bank study. J Am Geriatr Soc 1995;43(11):1248–55.
37. Jost BC, Grossberg GT. The evolution of psychiatric symptoms in Alzheimer's disease: a natural history study. J Am Geriatr Soc 1996;44(9):1078–81.
38. Alzheimer's-Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement 2013;9(2):208–45.
39. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9(11):1118–27.
40. Dubois B, Feldman H, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6(8):734–46.
41. APA. Diagnostic and statistical manual of mental disorders - (DSM-V). 5th edition. Washington, DC: American Psychiatric Publishing; 2013.
42. Atri A, Norman M, Knopman D, et al. Alzheimer's association best clinical practice guidelines for the evaluation of neurodegenerative cognitive behavioral syndromes, Alzheimer's disease and dementias in the United States. Alzheimer's Association International Conference. Chicago, 22 July, 2018.
43. Galvin JE, Roe CM, Powlishta KK, et al. The AD8: a brief informant interview to detect dementia. Neurology 2005;65(4):559–64.
44. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60(4):616–31.
45. Rosenbloom MH, Atri A. The evaluation of rapidly progressive dementia. Neurologist 2011;17(2):67–74.
46. Gomperts SN, Rentz DM, Moran E, et al. Imaging amyloid deposition in Lewy body diseases. Neurology 2008;71(12):903–10.

47. Atri A. Imaging of neurodegenerative cognitive and behavioral disorders: practical considerations for dementia clinical practice. Handb Clin Neurol 2016;136:971–84.
48. 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):141–50.
49. Jellinger KA, Attems J. Prevalence and impact of vascular and Alzheimer pathologies in Lewy body disease. Acta Neuropathol 2008;115(4):427–36.
50. Schneider JA, Arvanitakis Z, Bang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69(24):2197–204.
51. Bhalerao S, Seyfried LS, Kim HM, et al. Mortality risk with the use of atypical antipsychotics in later-life bipolar disorder. J Geriatr Psychiatry Neurol 2012;25(1):29–36.
52. National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers (NG97). NICE, UK, June 20, 2018.
53. Okura T, Plassman BL, Steffens DC, et al. Neuropsychiatric symptoms and the risk of institutionalization and death: the aging, demographics, and memory study. J Am Geriatr Soc 2012;59(3):473–81.
54. Kales HC, Chen P, Blow FC, et al. Rates of clinical depression diagnosis, functional impairment, and nursing home placement in coexisting dementia and depression. Am J Geriatr Psychiatry 2005;13(6):441–9.
55. Ballard C, Corbett A, Howard R. Prescription of antipsychotics in people with dementia. Br J Psychiatry 2014;205(1):4–5.
56. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015;350:h369.
57. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA 2012;308(19):2020–9.
58. Rudolph JL, Salow MJ, Angelini MC, et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med 2008;168(5):508–13.
59. Fong TG, Davis D, Growdon ME, et al. The interface between delirium and dementia in elderly adults. Lancet Neurol 2015;14(8):823–32.
60. Oh ES, Fong TG, Hshieh TT, et al. Delirium in older persons: advances in diagnosis and treatment. JAMA 2017;318(12):1161–74.
61. Schmidt R, Hofer E, Bouwman FH, et al. EFNS-ENS/EAN guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. Eur J Neurol 2015;22(6):889–98.
62. Gauthier S, Patterson C, Chertkow H, et al. Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). Can Geriatr J 2012;15(4):120–6.
63. Atri A, Molinuevo JL, Lemming O, et al. Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy. Alzheimers Res Ther 2013;5(1):6–16.
64. Tricco AC, Ashoor HM, Soobiah C, et al. Comparative effectiveness and safety of cognitive enhancers for treating alzheimer's disease: systematic review and network metaanalysis. J Am Geriatr Soc 2018;66(1):170–8.
65. Rountree SD, Atri A, Lopez OL, et al. Effectiveness of antidementia drugs in delaying Alzheimer disease progression. Alzheimers Dement 2013;9(3):338–45.

66. Cappell J, Herrmann N, Cornish S, et al. The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease. CNS Drugs 2010;24(11):909–27.
67. Raskind MA, Peskind ER, Wessel T, et al. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 study group. Neurology 2000;54:2261–8.
68. Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004;363(9427):2105–15.
69. Doody R, Geldmacher D, 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):427–33.
70. Farlow M, Anand R, Messina J Jr, et al. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. Eur Neurol 2000;44(4):236–41.
71. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012;366(10):893–903.
72. 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):1171–81.
73. Weycker D, Taneja C, Edelsberg J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Curr Med Res Opin 2007;23(5):1187–97.
74. Getsios D, Blume S, Ishak KJ, et al. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimers Dement 2012;8(1):22–30.
75. Getsios D, Blume S, Ishak KJ, et al. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics 2010;28(5):411–27.
76. Tayeb H, Yang H, Price B, et al. Pharmacotherapies for Alzheimer's disease: beyond cholinesterase inhibitors. Pharmacol Ther 2012;134:8–25.
77. Cummings JL. Alzheimer's disease. N Engl J Med 2004;351(1):56–67.
78. Cummings JL, Schneider L, Tariot PN, et al. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. Am J Psychiatry 2004;161(3):532–8.
79. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008;148(5):379–97.
80. Atri A, Rountree S, Lopez O, et al. Validity, significance, strengths, limitations, and evidentiary value of real-world clinical data for combination therapy in alzheimer's disease: comparison of efficacy and effectiveness studies. Neurodegener Dis 2012;10(1–4):170–4.
81. Ballard C, Gauthier S, Corbett A, et al. Alzheimer's disease. Lancet 2011;377(9770):1019–31.
82. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;(1):CD005593.
83. Greenberg SM, Tennis MK, Brown LB, et al. Donepezil therapy in clinical practice: a randomized crossover study. Arch Neurol 2000;57(1):94–9.
84. van de Glind EM, van Enst WA, van Munster BC, et al. Pharmacological treatment of dementia: a scoping review of systematic reviews. Dement Geriatr Cogn Disord 2013;36(3–4):211–28.

85. Rockwood K. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004;75(5):677–85.
86. Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57(3): 481–8.
87. Cummings JL, McRae T, Zhang R. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. Am J Geriatr Psychiatry 2006;14(7):605–12.
88. Burns A, Gauthier S, Perdomo C. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2007;22(8):806–12.
89. 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):252–6.
90. Doody RS, Dunn JK, Clark CM, et al. Chronic donepezil treatment is associated with slowed cognitive decline in Alzheimer's disease. Dement Geriatr Cogn Disord 2001;12(4):295–300.
91. Gillette-Guyonnet S, Andrieu S, Cortes F, et al. Outcome of Alzheimer's disease: potential impact of cholinesterase inhibitors. J Gerontol A Biol Sci Med Sci 2006; 61(5):516–20.
92. Wattmo C, Wallin A, Londos E, et al. Long-term outcome and prediction models of activities of daily living in Alzheimer disease with cholinesterase inhibitor treatment. Alzheimer Dis Assoc Disord 2011;25:63–72.
93. Wallin A, Andreasen N, Eriksson S, et al. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. Dement Geriatr Cogn Disord 2007;23:150–60.
94. Wallin A, Gustafson L, Sjogren M, et al. Five-year outcome of cholinergic treatment of Alzheimer's disease: early response predicts prolonged time until nursing home placement, but does not alter life expectancy. Dement Geriatr Cogn Disord 2004;18(2):197–206.
95. Wallin A, Wattmo C, Minthon L. Galantamine treatment in Alzheimer's disease: response and long-term outcome in a routine clinical setting. Neuropsychiatr Dis Treat 2011;7:565–76.
96. 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):2379–88.
97. Lu PH, Edland SD, Teng E, et al. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology 2009;72(24):2115–21.
98. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane database Syst Rev 2006;(2):CD003154.
99. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999;14(2):135–46.
100. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348(14):1333–41.
101. Bullock R. Efficacy and safety of memantine in moderate-to-severe Alzheimer disease: the evidence to date. Alzheimer Dis Assoc Disord 2006;20(1):23–9.
102. Doody R, Wirth Y, Schmitt F, et al. Specific functional effects of memantine treatment in patients with moderate to severe Alzheimer's disease. Demenr Geriatr Cogn Disord 2004;18(2):227–32.

103. Grossberg GT, Pejovic V, Miller ML, et al. Memantine therapy of behavioral symptoms in community-dwelling patients with moderate to severe Alzheimer's disease. Dement Geriatr Cogn Disord 2009;27(2):164–72.
104. Schmitt F, van Dyck C, Wichems C, et al, Memantine MEM-MD-02 Study Group. Cognitive response to memantine in moderate to severe Alzheimer disease patients already receiving donepezil: an exploratory reanalysis. Alzheimer Dis Assoc Disord 2006;20:255–62.
105. van Dyck CH, Tariot PN, Meyers B, et al. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. Alzheimer Dis Assoc Disord 2007;21(2):136–43.
106. Wilcock G, Ballard C, Cooper J, et al. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. J Clin Psychiatry 2008;69:341–8.
107. Wilkinson D, Andersen H. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. Dement Geriatr Cogn Disord 2007;24:138–45.
108. Wimo A, Winblad B, Stoffler A, et al. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. Pharmacoeconomics 2003;21(5):327–40.
109. Winblad B, Jones R, Wirth Y, et al. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord 2007;24:20–7.
110. Livingston G, Katona C. The place of memantine in the treatment of Alzheimer's disease: a number needed to treat analysis. Int J Geriatr Psychiatry 2004; 19(10):919–25.
111. Puangthong U, Hsiung GY. Critical appraisal of the long-term impact of memantine in treatment of moderate to severe Alzheimer's disease. Neuropsychiatr Dis Treat 2009;5:553–61.
112. Abbott BP, Abbott R, Adhikari R, et al. All-sky LIGO search for periodic gravitational waves in the early fifth-science-run data. Phys Rev Lett 2009;102(11): 111102.
113. Wilkinson D, Schindler R, Schwam E, et al. Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate Alzheimer's disease. Dement Geriatr Cogn Disord 2009;28:244–51.
114. Atri A, Shaughnessy L, Locascio J, et al. Long-term course and effectiveness of combination therapy in Alzheimer disease. Alzheimer Dis Assoc Disord 2008; 22:209–21.
115. Rountree S, Chan W, Pavlik V, et al. Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. Alzheimers Res Ther 2009;1(2):7.
116. Chou YY, Lepore N, Avedissian C, et al. Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. Neuroimage 2009;46(2):394–410.
117. Lopez OL, Becker JT, Wahed AS, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. J Neurol Neurosurg Psychiatry 2009;80(6):600–7.
118. Gillette-Guyonnet S, Andrieu S, Nourhashemi F, et al. Long-term progression of Alzheimer's disease in patients under antidementia drugs. Alzheimers Dement 2011;7(6):579–92.

119. Vellas B, Hausner L, Frolich L, et al. Progression of Alzheimer disease in Europe: data from the European ICTUS study. Curr Alzheimer Res 2012;9(8):902–12.
120. Tariot P, Farlow M, Grossberg G, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004;291:317–24.
121. Porsteinsson A, Grossberg G, Mintzer J, et al. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008;5:83–9.
122. Patel L, Grossberg G. Combination therapy for Alzheimer's disease. Drugs & aging 2011;28:539–46.
123. Molinuevo JL. Memantine: the value of combined therapy. Rev Neurol 2011; 52(2):95–100 [in Spanish].
124. Gauthier S, Molinuevo JL. Benefits of combined cholinesterase inhibitor and memantine treatment in moderate-severe Alzheimer's disease. Alzheimers Dement 2013;9(3):326–31.
125. Choi SH, Park KW, Na DL, et al. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study. Curr Med Res Opin 2011;27(7):1375–83.
126. Grossberg GT, Manes F, Allegri RF, et al. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. CNS Drugs 2013;27(6):469–78.
127. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997;336(17):1216–22.
128. 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. JAMA 2014;311(1):33–44.
129. Shah RC, Kamphuis PJ, Leurgans S, et al. The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. Alzheimers Res Ther 2013;5(6):59.
130. Wattmo C, Wallin AK, Londos E, et al. Predictors of long-term cognitive outcome in Alzheimer's disease. Alzheimers Res Ther 2011;3(4):23.
131. van der Steen JT, Radbruch L, Hertogh CM, et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. Palliat Med 2014;28(3): 197–209.
132. Stern Y. Cognitive reserve. Neuropsychologia 2009;47:2015–28.
133. Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. Neurology 1997;49(6):1498–504.
134. Salthouse TA. When does age-related cognitive decline begin? Neurobiol Aging 2009;30(4):507–14.
135. Weintraub S, Dikmen SS, Heaton RK, et al. Cognition assessment using the NIH Toolbox. Neurology 2013;80(11 Suppl 3):S54–64.
136. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44(12): 2308–14.