

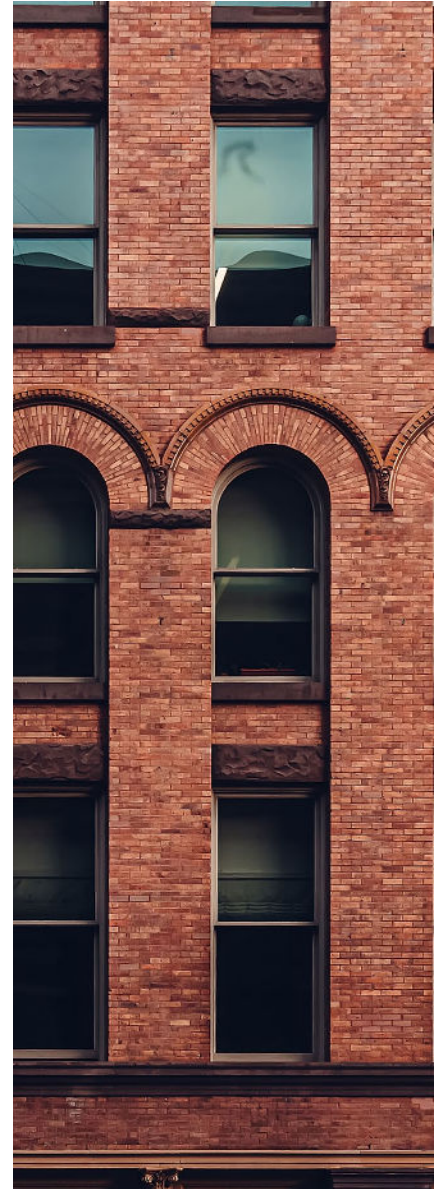


**Working Together:**  
**Improving Early Diagnosis and  
Management of Alzheimer's  
Disease in Primary Care**

*August 26, 2023*

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# Support

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# Expert Panel



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**Sara Leonard, MD – Reports no financial relationships**

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# Speaker Disclosure



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**Mary Masterman, MD** reports no financial relationships.



# Accreditation Statement

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This live activity, *Working Together: Improving Early Diagnosis and Management of Alzheimer's Disease in Primary Care* (live event), on **08/26/2023**, has been reviewed and is acceptable for up to **1.00 Prescribed credit(s)** by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME).

# Case

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- 71 yo M w/ PMH of HTN and HLD who presents to the clinic accompanied by his wife. The visit proceeds as normal. At the conclusion of the visit, as you are walking the patient out to the waiting room, his wife pulls you aside, stating she needs to speak with you privately. She states he has been having increasing difficulty with memory loss, getting lost while driving, and inappropriate behavior towards her. She states she doesn't feel like he's safe to drive any more. She is worried he is coming down with dementia.
- How would you proceed?

# Learning Objectives

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- Explain the importance of early diagnosis of AD;
- Apply office-based cognitive assessment tools to aid in early diagnosis of AD;
- Employ an inter-disciplinary team in the management of behavioral issues in patients with AD;
- Engage in dialogue with patients and caregivers in a subsequent treatment plan;
- Outline a plan to connect patients with AD to community-based resources for long-term management.

# Pretest

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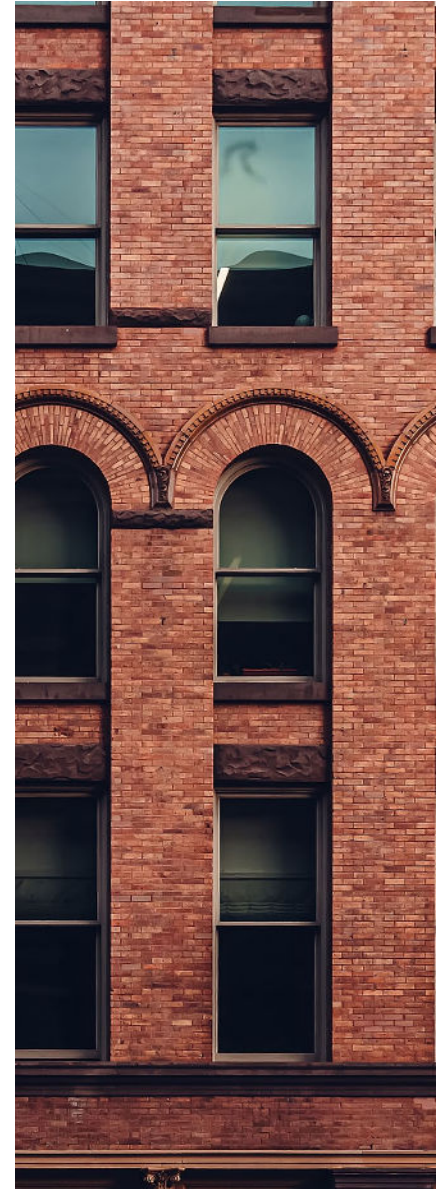
- Complete the pre-test questions now. (Take five minutes)
- There will be a space to record your answers for the case study at the end.
- Complete the post-test at the end of the session and hand it in.
- You will be able to claim CME at the end of the session through the EXPLORE website.





# Alzheimer's Disease (AD): Pathophysiology, Disease Progression, and Impact

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# What is Dementia?

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- A syndrome that describes a group of neurologic conditions that are characterized by difficulties with memory, language, problem-solving, and other thinking skills
- Not part of the normal aging process
- Caused by specific changes in the brain and usually degenerative
- Numerous dementias have been characterized, but four types—AD, **Frontotemporal dementia**, **Lewy body dementia**, and **vascular dementia**--account for the vast majority of cases.
- An individual may concomitantly show symptoms and/or pathologic evidence of more than one type of dementia, a designation known as *mixed dementia*.

**Source:** Alzheimer's Association. *Alzheimers Dement* 2022;18:700-89.

# Dementia vs Mild Cognitive Impairment

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- Dementia (Major Neurocognitive Disorder in the DSM-5) is diagnosed when acquired cognitive impairment has become severe enough to compromise social and/or occupational functioning.
- Mild Cognitive Impairment (or Mild Neurocognitive Disorder) is a state intermediate between normal cognition and dementia, with essentially preserved functional abilities.

**Source:** Clin Geriatr Med. 2014 Aug; 30(3): 421–442.



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# Most Common Types of Dementia



# Alzheimers Disease

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- Pathophysiology: Deposits of  $\beta$ -amyloid protein and tangles of tau protein throughout brain
- Symptoms: Impaired memory, language, visual/spatial skills; Apathy and/or depression
- Age: 65+; some cases mid-30s-early 60s

# Lewy Body Dementia

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- Pathophysiology: Deposits of alpha-synuclein protein (“Lewy bodies”) on cortical nerve cells
- Symptoms: Similar to Alzheimer's but w / visual hallucinations; Sleep difficulties including REM sleep behavior disorder; Impaired thinking and motor skills; features of parkinsonism
- Age: 50+

# Frontotemporal dementia

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- Pathophysiology: Accumulation of tau and TDP-43 proteins in frontal and temporal lobes
- Symptoms: Personality changes; Issues with language; Balance issues; palsy; Lack of emotional/impulse control
- Age: 45-64



# Vascular Dementia

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- Pathophysiology: Disrupted blood flow to the brain
- Symptoms: Impaired motor skills & judgement; Memory issues; Hallucinations/delusions
  - May occur post-stroke, or may occur in patients w/o known hx of CVA but with imaging suggestive of cerebrovascular disease
- Age: Over 65





# The Impact of AD (1)

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- Accounts for 60-80% of cases of dementia<sup>1</sup>
- Affects ~6.5 million (10.7%) US adults aged 65 and older<sup>2</sup>
- Projected to rise to 12.7 million by 2050 due to aging of the US population<sup>2</sup>
- Incidence increases with age,<sup>1</sup> but AD can manifest at any time.
- Physiologic changes likely begin several decades before the patient notices symptoms.<sup>3, 4</sup>

**Sources:** <sup>1</sup>Alzheimer's Association. *Alzheimers Dement* 2022;18:700-89; <sup>2</sup>Rajan KB, et al. *Alzheimers Dement* 2021;17:1966-75; <sup>3</sup>Bateman RJ, et al. *N Engl J Med* 2012;367:795-804; <sup>4</sup>Gordon BA, et al. *Lancet Neurol* 2018;17:241-50.



## The Impact of AD (2)

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- Women account for two-thirds of AD cases in the US<sup>1</sup>
- Women have a 1 in 5 lifetime risk for Alzheimer's dementia at age 45, compared to 1 in 10 for men.<sup>2</sup>
- Older non-Hispanic Blacks and Hispanic Americans are disproportionately more likely than older Whites to have dementias,<sup>3</sup> reflecting health disparities more than genetic distinctions.<sup>4</sup>
- The rate of disease progression varies widely, with an average lifespan of 8-12 years from diagnosis.<sup>3</sup>
- In addition to the costs of hired care, friends/family caregivers provided more than \$271 billion dollars in unpaid care to individuals with dementia in 2021.<sup>3</sup>

**Sources:** <sup>1</sup>Rajan L, et al. *Alzheimers Dement* 2021;17:1966-75; <sup>2</sup>Chêne G, et al. *Alzheimers Dement* 2015;11:310-20;  
<sup>3</sup>Alzheimer's Association. *Alzheimers Dement* 2022;18:700-89; <sup>4</sup>Glymour MM, Manly JJ. *Neuropsychol Rev* 2008;18:223-54.

# Pathophysiology of AD



- Characterized by two prototypical brain lesions: 1) senile plaques, or extracellular lesions composed of accumulated insoluble  $\beta$ -amyloid peptide ( $A\beta$ ), and 2) intra-neuronal fibrous tangles (NFT) of hyperphosphorylated tau protein (P-tau).<sup>1</sup>
- Several mechanisms proposed to explain the relationship between these changes and cognitive decline.
- Protein deposits excessively stimulate neurotransmitter receptors in the neuronal membranes, promoting a collapse in calcium homeostasis, inflammation, and the depletion of energy and neuronal factors.<sup>1,2</sup>
- This process irreversibly damages neurons and synapses involved in memory, learning, and other cognitive functions.

**Sources:** <sup>1</sup>Silva MVF, et al. *J Biomed Sci* 2019;26:33; <sup>2</sup>Breijyeh Z, Karaman R. *Molecules* 2020;25:5789.

# The Three Phases of Alzheimer's Disease



<b>Pre-Clinical AD</b>	<ul style="list-style-type: none"><li>• Biomarker evidence of brain changes</li><li>• Asymptomatic</li></ul>
<b>Mild Cognitive Impairment (MCI) due to AD</b>	<ul style="list-style-type: none"><li>• Biomarker evidence of brain changes</li><li>• Subtle symptoms (issues with memory, language, or thinking) that may or may not impair daily activity</li></ul>
<b>Dementia due to AD</b>	<ul style="list-style-type: none"><li>• Changes impair daily function</li></ul>

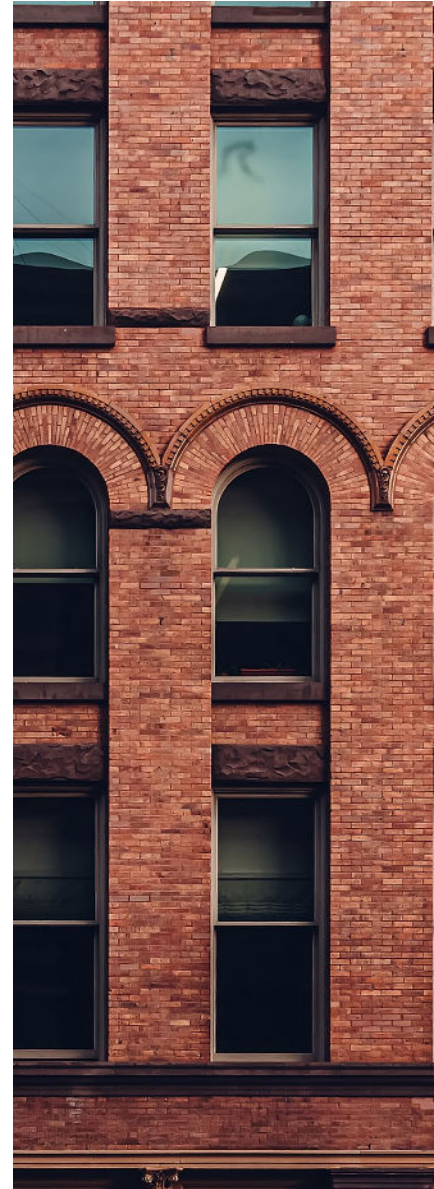
Duration in a phase is influenced by sex, clinical setting, presence of abnormal tau protein, and carrying the *APOE*  $\epsilon$ 4 allele.

**Sources:** Alzheimer's Association. *Alzheimers Dement* 2022;18:700-89; Vermunt L, et al. *Alzheimers Dement* 2019;15:888-98.



# AD Risk Factors and Potentially Protective Measures Against Cognitive Impairment

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# Genetic Risk Factors for AD

- Genes and polymorphisms linked with AD are nearly always associated with processes implicated in the formation or deposition of A $\beta$  plaques.<sup>1</sup>
- Early-onset disease (symptoms appear before age 65) is associated with mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*).<sup>1,2</sup>
- Late-onset AD is primarily associated with the presence of the  $\epsilon$ 4 allele in the apolipoprotein E gene (*APOE*).<sup>1,2</sup>
- APOE protein binds soluble A $\beta$ , and *APOE*  $\epsilon$ 4 alleles accelerate A $\beta$  deposition and increase the risk of developing AD from 3X (1 allele) to 12X (2 alleles).<sup>3</sup>

**Genetic factors account for an estimated 70% of the risk of developing AD.<sup>2</sup>**

**Sources:** <sup>1</sup>Silva MVF, et al. *J Biomed Sci* 2019;26:33; <sup>2</sup>Ballard C, et al. *Lancet* 2011;377:1019-31; <sup>3</sup>Mendez MF. *Neurol Clin* 2017;35:263-81.



# Acquired Risk Factors for AD

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- Cerebrovascular disease
- Diabetes
- Hypertension
- Obesity
- Hypercholesterolemia
- Marital status (widowhood)
- Stress
- Depression
- Inadequate sleep/Sleep disturbances
- Smoking

**Source:** Silva MVF, et al. *J Biomed Sci* 2019;26:33

# Measures to Reduce the Risk of Cognitive Decline

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## Risk Reduction Strategies

**Cognitive Reserve**

**Diet**

**Physical Activity**



# Cognitive Reserve



**Cognitive Reserve: The capacity to tolerate age- or disease-related changes in the brain without developing clinical symptoms.**

- Can help maintain cognitive function and postpone clinical dementia and AD.<sup>1,2</sup>
- Built through mentally stimulating patterns of behavior (e.g., formal education, hobbies, occupational complexity, a mentally and socially integrated lifestyle) across the age continuum.
- Activities that meld physical, mental, and social stimulation may be most beneficial<sup>2</sup>
- Accessible activities: crossword puzzles/games, playing a musical instrument, participating in a book club, a routine walk with a friend.

**Sources:** <sup>1</sup>Valenzuela MJ, Sachdev P. *Psychol Med* 2006;36:441-54; <sup>2</sup>Fratiglioni L, et.al. *J Alzheimers Dis* 2007;12:11-22.



# Dietary Interventions

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- Antioxidants, fatty acids, and B vitamins have been linked with better cognitive functioning in prospective epidemiologic studies, although the value of any specific nutrient has not been confirmed in RCTs.<sup>1</sup>
- “DASH” or “Mediterranean” diets are rich in whole foods (e.g., fruits, vegetables, fish, nuts, beans, olive oil) but low in processed foods and saturated fats.<sup>2,3</sup>
- Can lower blood pressure, protect against chronic conditions, reduce inflammation, and support weight loss regimens.
- Part of a healthy lifestyle that may positively impact cognitive decline.

**Sources:** <sup>1</sup>Smith PJ, Blumenthal JA. *J Prev Alzheimers Dis* 2016;3:53-64; <sup>2</sup>Harvard Medical School. Harvard health blog: a practical guide to the Mediterranean diet; 2019; <sup>3</sup>Mayo Clinic. DASH diet: healthy eating to lower your blood pressure; 2022.

# Physical Activity



- Meta-analyses suggest that higher levels of physical activity are associated with a reduced risk of cognitive decline and dementia.<sup>1,2</sup>
- Lowers blood pressure, improves lipid profiles, helps regulate glycemic levels, and facilitates weight management.
- Postulated to exert brain-specific effects that could prevent AD, including increasing neurotrophic factors, reducing free radicals in the hippocampus, and stimulating neurogenesis and synaptic plasticity.<sup>3</sup>

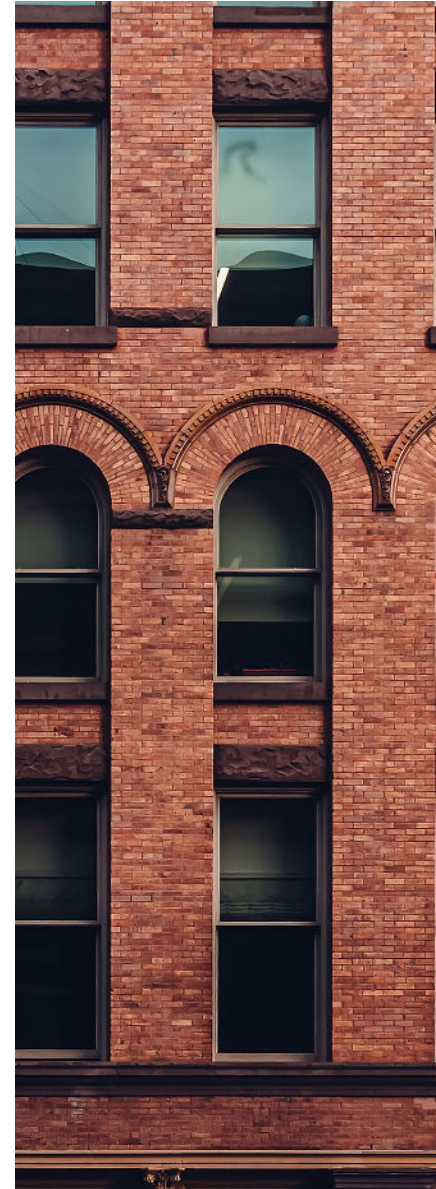
**Patients who have or are at risk for cognitive impairment should be encouraged to be active, with a particular focus on incorporating aerobic activity.**

**Sources:** <sup>1</sup>Blondell SJ, et.al. *BMC Public Health* 2014;14:510; <sup>2</sup>Hamer M, Chida Y. *Psychol Med* 2009;39:3-11; <sup>3</sup>Silva MVF, et al. *J Biomed Sci* 2019;26:33.



# “Where Did I Put my Keys?”: Early-Stage AD versus Typical Age-Related Cognitive Change

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# Hallmark Symptoms of Early-Stage AD



- **Short-term memory loss** (e.g., remembering recent conversations, names, or events)
- **Difficulty completing familiar tasks**
- **Mood/personality changes** (e.g., apathy, depression)

In many instances, a patient's family member will report that their loved one is struggling with short-term memory. Some patients may actively deny this development even though it is happening.

**Source:** Alzheimer's Association. *Alzheimers Dement* 2022;18:700-89.

# Early-Stage AD versus Typical Age-Related Changes (1)



Sign	Examples of AD	Typical Age-Related Change
<b>Memory loss that disrupts daily life</b>	<ul style="list-style-type: none"> <li>• <b>Forgetting recently-learned information or important dates/events</b></li> <li>• <b>Asking the same questions over and over</b></li> <li>• <b>Increasingly relying on memory aids or family members for things previously handled solo</b></li> </ul>	<b>Sometimes forgetting names or appointments but remembering them later.</b>
<b>Challenges in planning or solving problems</b>	<ul style="list-style-type: none"> <li>• <b>Difficulty developing a plan or working with numbers</b></li> <li>• <b>Trouble following a familiar recipe or monthly bills</b></li> <li>• <b>Difficulty concentrating; taking much longer to do things than previously needed</b></li> </ul>	<b>Occasionally erring when managing finances or household bills.</b>

Source: Alzheimer's Association. [https://www.alz.org/alzheimers-dementia/10\\_signs](https://www.alz.org/alzheimers-dementia/10_signs).

# Early-Stage AD versus Typical Age-Related Changes (2)



Sign	Examples of AD	Typical Age-Related Change
<b>Trouble with visual images and spatial relationships</b>	<ul style="list-style-type: none"> <li>• <b>Vision problems that cause difficulty with balance or trouble reading</b></li> <li>• <b>Problems judging distance and determining color or contrast, causing issues with driving</b></li> </ul>	<b>Vision changes related to cataracts.</b>
<b>New problems with words when speaking or writing</b>	<ul style="list-style-type: none"> <li>• <b>Trouble following or joining a conversation</b></li> <li>• <b>Stopping in mid-conversation with no idea how to continue</b></li> <li>• <b>Repeating one's own statements</b></li> <li>• <b>Struggling with vocabulary</b></li> <li>• <b>Trouble naming a familiar object</b></li> </ul>	<b>Sometimes having trouble finding the right word.</b>

Source: Alzheimer's Association. [https://www.alz.org/alzheimers-dementia/10\\_signs](https://www.alz.org/alzheimers-dementia/10_signs).

# Early-Stage AD versus Typical Age-Related Changes (3)



Sign	Examples of AD	Typical Age-Related Change
Misplacing items and losing the ability to retrace steps	<ul style="list-style-type: none"><li>• <b>Putting items in unusual places</b></li><li>• <b>Losing items and being unable to retrace their steps to locate them</b></li><li>• <b>Accusing others of stealing, especially as the disease progresses.</b></li></ul>	Misplacing things from time to time and retracing steps to find them.
Decreased or poor judgement	<ul style="list-style-type: none"><li>• <b>Changes in judgment or decision-making</b></li><li>• <b>Using poor judgment when dealing with money</b></li><li>• <b>Paying less attention to grooming or keeping clean.</b></li></ul>	Making a bad decision or mistake once in a while, like neglecting to change the oil in the car.

Source: Alzheimer's Association. [https://www.alz.org/alzheimers-dementia/10\\_signs](https://www.alz.org/alzheimers-dementia/10_signs).



# Early-Stage AD versus Typical Age-Related Changes (4)



Sign	Examples of AD	Typical Age-Related Change
<b>Withdrawal from work or social activities</b>	<ul style="list-style-type: none"> <li>• Experience changes in the ability to hold or follow a conversation</li> <li>• Withdraw from hobbies, social activities, or other engagements</li> <li>• Trouble keeping up with favorite team or activity.</li> </ul>	Sometimes feeling uninterested in family or social obligations.
<b>Changes in mood or personality</b>	<ul style="list-style-type: none"> <li>• Experience mood and personality changes</li> <li>• Become confused, suspicious, depressed, fearful, or anxious</li> <li>• Be easily upset at home, with friends, or when out of a comfort zone.</li> </ul>	Developing very specific ways of doing things and becoming irritable when a routine is disrupted.

Source: Alzheimer's Association. [https://www.alz.org/alzheimers-dementia/10\\_signs](https://www.alz.org/alzheimers-dementia/10_signs).

# Early-Stage AD versus Typical Age-Related Changes (5)



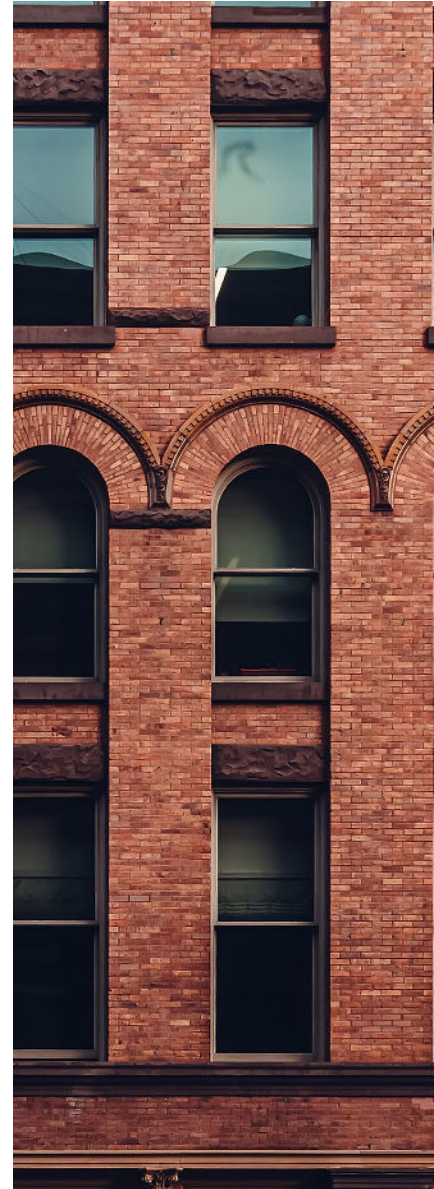
Sign	Examples of AD	Typical Age-Related Change
Difficulty completing familiar tasks	<ul style="list-style-type: none"><li>• <b>Trouble driving to a familiar location or organizing a grocery list</b></li><li>• <b>Difficulty remembering the rules of a favorite game</b></li></ul>	Needing occasional help with microwave settings or to record a TV show.
Confusion with time or place	<ul style="list-style-type: none"><li>• <b>Losing track of the passage of time</b></li><li>• <b>Trouble understanding non-immediate things</b></li><li>• <b>Forgetting where one is or how one arrived there</b></li></ul>	Getting confused about the day of the week but figuring it out later.

Source: Alzheimer's Association. [https://www.alz.org/alzheimers-dementia/10\\_signs](https://www.alz.org/alzheimers-dementia/10_signs).



# Assessing Cognitive Impairment in Primary Care

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# The Importance of Early Detection

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- Improves the quality of life for patients who will ultimately experience cognitive decline and for their caregivers.
- Enhances caregivers' understanding of behavioral changes and facilitates interventions to maintain daily functioning and slow cognitive decline.
- Enables opportunity for needed future planning and management.
- Cognitive assessment for signs of dementia is included in the Annual "Wellness" Visits covered by Medicare Part B. When performing AWWs, clinicians should use a brief, validated cognitive assessment instrument rather than relying on subjective history alone (Level B)

**Cognitive Assessment Toolkits are available from the Alzheimer's Association, the American Academy of Family Physicians, and ACT on Alzheimer's.<sup>1-3</sup>**

**Sources:** <sup>1</sup>Alzheimer's Association. <https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit>; <sup>2</sup>American Academy of Family Physicians. <https://www.aafp.org/family-physician/patient-care/care-resources/cognitive-care.html>; <sup>3</sup>ACT on Alzheimer's. <https://actonalz.org/medical-providers>.

# Cognitive Evaluation in Primary Care



- Need adequate time to address concerns
- Conduct a complete history and physical examination including complete neurologic exam, family history, medical history, and consider laboratory tests as needed to rule out conditions (e.g., assess for vitamin B<sub>12</sub> deficiency with B12, hypothyroidism with TSH, CBC/CMP) that could produce symptoms similar to those of dementia
- RPR or HIV only when high clinical suspicion/an area with high numbers of cases
- Routine neuroimaging is controversial
  - Many patients will have already had prior head imaging, e.g. in ER

# Non-Dementia Conditions with Dementia-Like Symptoms



- Depression
- Sleep Apnea
- Delirium
- Medication side-effects
- Lyme disease
- Hypothyroidism
- Vitamin B<sub>12</sub> deficiency
- Excessive alcohol consumption<sup>1</sup>

Medications which may be associated with cognitive impairment and dementia:<sup>2</sup>

Benzodiazepines

Anticholinergics (e.g., diphenhydramine, oxybutynin)

Antihistamines

Opioids

PPIs

**Source:** 1. Alzheimer's Association. *Alzheimers Dement* 2022;18:700-89; 2. Drugs Aging 2012 Aug 1;29(8):639-58. doi: 10.1007/BF03262280.

# Cognitive Evaluation in Primary Care



- Cognitive evaluation in a medical setting establishes a baseline that can be followed over time to track changes.
- Many easy-to-use detection tools can be implemented in the office:
  - **Mini-Mental State Examination (MMSE)**
  - **Clock Drawing Test (CDT)**
  - **Memory Impairment Screen (MIS)/MIS by Telephone (MIS-T)**
  - **Abbreviated Mental Test (AMT-10)**
  - **Montreal Cognitive Assessment (MoCA)** – requires certification to administer
  - **Short Portable Mental Status Questionnaire (SPMSQ)**
- Need adequate time to administer and address concerns

# Evaluating a Screening Test Score

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- Provides insight into the type and severity of impairment
- Cannot be used solely to diagnose dementia
- Must be evaluated within a holistic context
- Perspective from an informant who has a close relationship with the patient will often prove insightful.



# Mild Cognitive Impairment



- If close contacts voice concern about memory or cognition, assess for MCI; don't assume normal aging<sup>1</sup>
- For patients with MCI, assess for the presence of functional impairment related to cognition before giving a diagnosis of dementia-i.e. ADLs<sup>1</sup>
- For patients with MCI, evaluate for risk factors that are potentially modifiable and monitor cognitive status over time<sup>1</sup>
- Screen for depression using a validated tool such as PHQ-2 or PHQ-9

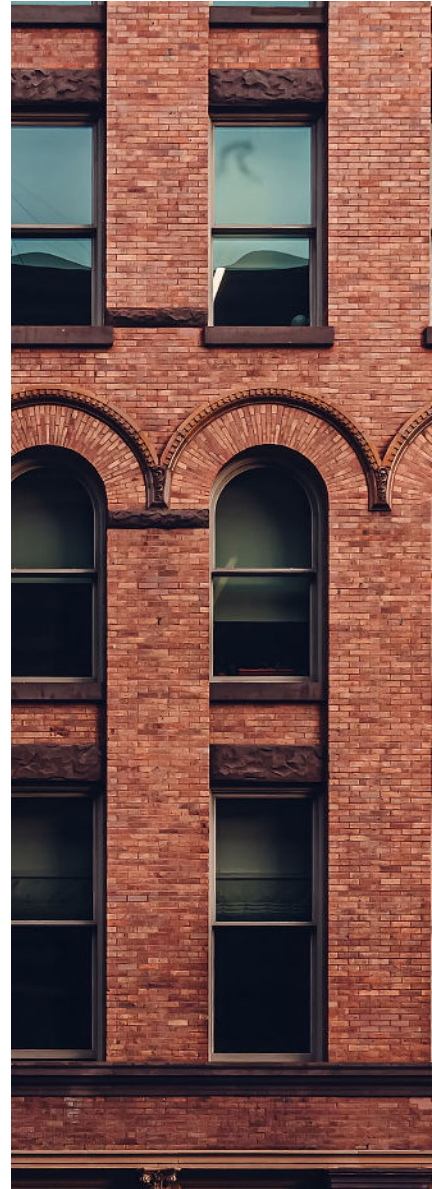
(all Level B recommendations)

**There are no recommendations to support the routine use of neuroimaging in patients with dementia or routine genetic testing for the *APOE*  $\epsilon$ 4 allele.**



# Tenets of Proactive AD Management

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# The Role of the Primary Care Clinician

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- Identify patients at risk for AD or other cognitive disorders
- Understand cultural factors and patient preferences for treatment
- Discuss practical considerations for managing cognitive impairment
- Discuss management with patient and caregivers
- Coordinate efforts with an AD care team (e.g., neurologist, gerontologist, social worker)
- Keep the patient actively engaged in disease management.

**Primary care clinicians play critical roles in identifying patients who have or are at risk for AD and ensuring that they receive prompt and effective care.**



# MCI Treatment

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- Recommend regular exercise (Level B)
- May recommend cognitive training (Level C)
- Discuss diagnosis, prognosis, long-term planning, and lack of effective medicine options or dietary agents (Level B)
- May discuss biomarker research with patients and families (Level C)

# Central Tenets of Proactively Managing Dementia (1)

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- Appropriate use of available treatment options.
- Effective management of coexisting conditions.
- Providing family caregivers with effective training in managing the day-to-day life of the care recipient.
- Coordination of care among physicians, other health care professionals, and lay caregivers.

# Central Tenets of Proactively Managing Dementia (2)

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- Participation in activities that are meaningful to the individual with dementia and bring purpose to their life.
- Maintaining a sense of self-identity and relationships with others.
- Having opportunities to connect with others living with dementia, such as support groups and supportive services.
- Becoming educated about the disease.
- Planning for the future.

**Source:** Alzheimer's Association. *Alzheimers Dement* 2022;18:700-89.

# Other Therapies for Dementia



- Recent Cochrane review on **cognitive stimulation** found small, short-term cognitive benefits (2 pt improvement in MMSE),<sup>1</sup> and these should be recommended for patients with mild to moderate cognitive impairment<sup>2</sup> (Level B)
- Evidence that **physical activity** may slow functional decline, but more trials are needed;<sup>3</sup> a structured physical exercise program should be recommended for patients with Alzheimer's (Level A)<sup>2</sup>
- Some evidence of slower functional decline in patients taking alpha tocopherol (**vitamin E**), but evidence is mixed;<sup>4</sup> AAFP recommends for patients with mild to moderate cognitive impairment<sup>2</sup> (Level B)

**Source:** (1) Cochrane Database Syst Rev. 2023 Jan 31; 2023(1):CD005562. doi: 10.1002/14651858.CD005562.pub3.; (2) Am Fam Physician. 2017;95(12):771-778; (3) Cochrane Database Syst Rev. 2015 Apr 15;2015(4):CD006489. doi: 10.1002/14651858.CD006489.pub4; (4) *JAMA*. 2014;311(1):33-44. doi:10.1001/jama.2013.282834

# Talking about AD with Patients and Caregivers

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- Frankly and honestly discuss what to expect.
- Aim to build a trusting relationship that will promote effective long-term management.
- Be straightforward and open about management challenges, addressing practical issues such as:
  - Advanced directives (e.g., power of attorney, living wills, guardianship, end-of-life care/portable medical orders); estate planning and finances
  - Driving safety
  - The possibility of developing comorbidities such as anxiety or depression
  - Behavioral changes that the afflicted individual may experience.
- At follow-up visits, have the patient and/or caregiver write questions before coming to the office so that no concern is overlooked.



# Pharmacotherapy for Cognitive Decline

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- The neuronal damage associated with MCI is irreversible; there is no cure for AD.
- Lifestyle modifications can be beneficial.
- FDA-approved pharmacotherapies that may apply to patients with AD fall within two general categories:
  - 1) Treatments that address the underlying disease biology**
  - 2) Agents that may help lessen symptoms (e.g., memory loss, confusion)**

# Agents that Address Underlying Disease Biology: Aducanumab and Lecanemab



- **Aducanumab** and **lecanemab** approved through FDA's Accelerated Approval Pathway to treat patients with MCI or mild dementia due to AD.<sup>1,2</sup>
- Target  $\beta$ -amyloid protein isoforms that can form plaques, decreasing (but not halting)  $A\beta$  production.
- Reduce cognitive and functional decline in individuals who have early-stage AD.<sup>3,4</sup>
- No evidence for restoring lost memories or cognitive function.

**Sources:** <sup>1</sup>US FDA. Aduhelm prescribing information; 2021; <sup>2</sup>US FDA. Lequembi prescribing information; 2023; <sup>3</sup>Budd Haeberlein S, et al. *J Prev Alzheimers Dis* 2022;9:197-210; <sup>4</sup>van Dyck, et al. *N Engl J Med* 2023;388:9-21.

# Agents that Address Underlying Disease Biology: Aducanumab and Lecanemab



- Presence of A $\beta$  plaques should be confirmed before prescribing. (amyloid PET or lumbar puncture)
- No contraindications for use, although precautions for amyloid-related imaging abnormalities and infusion-related reactions are noted.<sup>1,2</sup>
- Approvals have been controversial based on safety and efficacy concerns and cost.<sup>3,4</sup>
- Currently of limited availability and are not covered by Medicare for persons who are not enrolled in a clinical trial.

**Sources:** <sup>1</sup>US FDA. Aduhelm prescribing information; 2021; <sup>2</sup>US FDA. Lequemi prescribing information; 2023; <sup>3</sup>Ebell MH, Barry HC. *Am Fam Physician* 2022;105:353-54; <sup>4</sup>Reardon S. *Nature* 2023;613:227-28.

# Agents that May Help Lessen AD Symptoms



- The FDA has approved three cholinesterase inhibitors (**donepezil**, **galantamine**, **rivastigmine**) and one glutamate regulator (**memantine**) to treat symptoms related to memory, language, and other thought processes in patients with AD.<sup>1-4</sup>
- Cholinesterase inhibitors prevent the breakdown of acetylcholine, thereby enhancing communication between neurons. Agents appear to be equally efficacious, and it is not possible to identify responders upfront.<sup>5</sup>
- Side effects may include nausea, vomiting, loss of appetite, and increased frequency of bowel movements; as well as CV SEs-bradycardia, AV block, lightheadedness and syncope
- Memantine side effects include headache, constipation, confusion, and dizziness.
- Donepezil plus memantine is also approved as a combined agent.

**Sources:** <sup>1</sup>US FDA. Aricept prescribing information; 2012; <sup>2</sup>US FDA. Razadyne ER prescribing information; 2015; <sup>3</sup>US FDA. Exelon prescribing information; 2018; <sup>4</sup>US FDA. Namenda prescribing information; 2013; <sup>5</sup>Birks J. *Cochrane Database Syst Rev* 2006;1:CD005593.

# Agents that May Help Lessen AD Symptoms



- The FDA has also approved suvorexant to treat insomnia, and the agent has been shown effective as a sleep aid in persons with mild to moderate AD.<sup>1</sup> Side effects include impaired alertness and motor coordination, worsening of depression or suicidal ideation, complex sleep behaviors or sleep paralysis, and compromised respiratory function.
- Agents that may lessen symptoms are not indicated for MCI.

**None** of the agents that may lessen symptoms slows the progression of cognitive decline. Studies of cholinesterase inhibitors in individuals with MCI showed no benefit on cognitive outcomes or reduction in progression from MCI to dementia.<sup>2</sup> (Level A evidence)

**Sources:** <sup>1</sup>Blackman J, et al. *J Sleep Res* 2021;30:e13229; <sup>2</sup>Petersen RC, et al. *Neurology* 2018;90:126-35.

# Recommendations from Choosing Wisely



- Don't use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia.
- Don't prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects.
- Don't recommend percutaneous feeding tubes in patients with advanced dementia; instead offer oral assisted feeding.

**Sources:** Ten Things Physician and Patients Should Question. American Geriatrics Society. Feb 21, 2013.  
<https://www.healthinaging.org/sites/default/files/pdf/Choosing.Wisely.Ten.Things.pdf>



# When to Refer to a Neurologist

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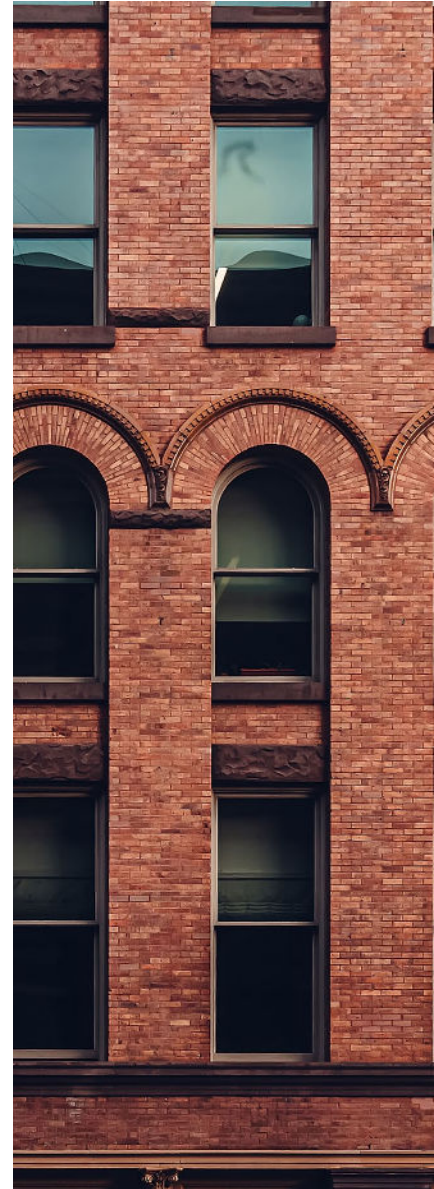
**Diagnosing and treating uncomplicated dementia falls well within the scope of family medicine.** Situations that warrant referral include:

- Patients under age 65 who present with memory loss or cognitive changes
- Patients with acute or rapidly-progressing cognitive impairment
- Individuals with findings suggestive of stroke, cerebral hemorrhage, or subdural hematoma
- Case-specific factors, including complicated or atypical presentation, symptoms, or disease progression
- Other reasons at the discretion of the primary care clinician.



# Addressing Disparities in AD Care

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# The Culturally-Informed Office

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- Language- and topic-appropriate materials
- Staff to match population served
- Bilingual or language-appropriate wall posters and signs
- Written text geared for comprehension
- A trained medical interpreter or access to interpretation services
- Staff trained to overcome cultural misconceptions
- Recognition of culturally-observed holidays.

**Establishing a culturally-informed office is the first step toward providing culturally-appropriate care.**

# Considerations for Providing Culturally-Appropriate Care (1)

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- Education level and health literacy (e.g., ability to understand concepts)
- Family integration and support systems (church, community)
- Cultural judgments about disease and norms regarding body image
- Knowledge about AD
- Learning styles and motivational strategies

**Source:** Juckett G. *Am Fam Physician* 2005;72:2267-74.

# Considerations for Providing Culturally-Appropriate Care (2)

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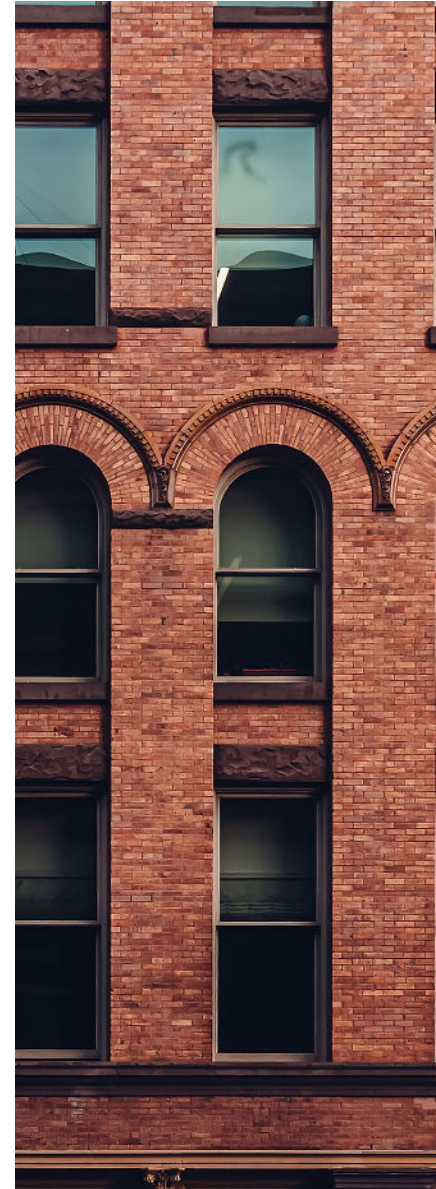
- Spiritual beliefs (e.g., belief that events are predetermined by fate)
- Nutritional preferences
- Alternative/herbal practices and folk remedies
- Language issues

**Source:** Juckett G. *Am Fam Physician* 2005;72:2267-74.



# Partnering with Minority Patients

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# Partnering with Minority Patients

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- Appreciate value system associated with patient's cultural heritage
- Emphasize holistic care by recognizing biologic, psychologic, and faith-based components
- Provide framework to understand level of disease severity and realistic treatment options
- Promote trust through engaged attitude
- Avoid paternalistic stance

**Culturally-informed care is based on a partnership between the patient and the healthcare provider.**

# The “Teach-Back” Approach

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## “Teaching back”



Have the patient repeat your statements in their own words.

- Assesses patient’s health literacy and language proficiency
- Promotes understanding of cultural issues
- May facilitate adherence to an intervention.

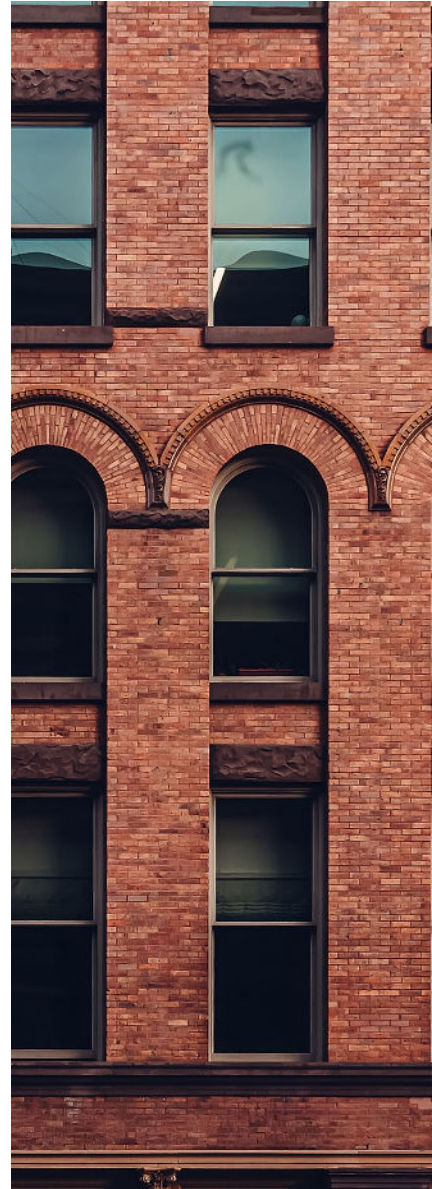


## Case Study: Lena

### Diagnosing AD in Primary Care

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**Photo Credit:** Unsplash.



# Case Study: Lena



- 65 y/o African-American woman accompanied by her daughter and son-in-law, who state that Lena has trouble remembering details about her home and sometimes loses track of who she is speaking to.
- Lena says that she sometimes forgets details due to “just getting old and tired.”
- Daughter also notes that Lena has periods where she does not seem to be her usual self and appears to be in a mental fog, forgetting recent conversations and events.
- Son-in-law states that he first noticed Lena’s confusion about a year ago but that it has evolved from an isolated instance or two to occur nearly every time he speaks with her.
- Lena lives alone; her family is increasingly concerned for her daily welfare.





# Case Study: Lena

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With only this information, should you suspect cognitive impairment or early-stage AD?

- a) **Yes.** Lena shows hallmark symptoms of early-stage AD, such as difficulty remembering recent conversations, names, or events. Her self-characterization as “old and tired” may also suggest depression, another AD-associated symptom and a risk factor.
- b) **No.** Dementia is unlikely to affect an otherwise healthy 65-year-old, and sometimes forgetting names or appointments is typical as long as they can be recalled at a later point.



# Case Study: Lena

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## Lena's exam results:

**BP:** 130/80 mm Hg

**Pulse:** 78 beats/minute

**Physical exam:** Normal

**BMI:** 25 kg/m<sup>2</sup>

**Alcohol or tobacco use:** No

**Prescription medications:** lisinopril



# Case Study: Lena

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What other assessments can help you determine whether Lena's symptoms represent cognitive impairment?

- a) A validated test of memory and cognitive function, such as the MMSE or MoCA
- b) A depression screen, such as the PHQ-2 or PHQ-9
- c) Family history
- d) Laboratory tests as needed to rule out conditions (e.g., vitamin B<sub>12</sub> deficiency, hypothyroidism) that could produce symptoms similar to those of dementia
- e) All of the above



# Case Study: Lena



You administer the MMSE and PHQ-2. Lena's score on the former falls into the range of abnormal function. How can you interpret this result in the context of what you know so far?

- a) **Lena definitely has cognitive impairment that extends beyond age-related change.** The MMSE and other validated tests of memory and cognitive function can serve as definitive instruments to diagnose cognitive impairment in the presence of other symptoms.
- b) **Lena likely has cognitive impairment that extends beyond age-related change.** There is no single test that will diagnose cognitive impairment or AD unequivocally. However, a score below the threshold for normal cognition, when taken in the context of other information present, is suggestive of cognitive impairment.
- c) **The results of these screens are inconclusive.**



# Case Study: Lena



Lena's cognitive function impacts daily life, and proactive management is warranted to maintain her quality of life and ensure that she receives needed assistance. Which of the following should you consider when developing a management plan with a care team?

- a) Effectively managing coexisting conditions
- b) Providing family caregivers with effective training in managing Lena's day-to-day life going forward
- c) Coordinating care among physicians, other health care professionals, and lay caregivers
- d) Using appropriate available treatment options
- e) Educating Lena and her caregivers about MCI and AD
- f) Planning for the future
- g) Connecting the family with others living with dementia, such as support groups and supportive services
- h) All of the above



# Case Study: Lena



Lena's daughter asks about a supplement that she saw on social media--a natural memory aid that boosts brain function. Would you recommend that Lena take this supplement?

a) **No.** Memory aid" supplements have been marketed aggressively but are not supported by any clinical evidence to date. There is no proof that such agents have any benefit on cognition.

b) **Yes.** These formulations are relatively harmless in that their components are natural products that can be found in various diets. There is no harm in trying one of these products, although it may or may not work.



# Case Study: Lena

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Lena asks about medicines that she can take to restore lost memory function. Which of the following agents can reverse neuronal damage, effectively restoring some lost cognitive function?

- a) Aducanumab
- b) Donepezil
- c) Galantamine
- d) Lecanemab
- e) Rivastigmine
- f) Memantine
- g) *a* and *d* only
- h) None of the above.



# Case Study: Lena



You schedule a follow-up visit with Lena, her daughter, and her son-in-law in a week to discuss laboratory results and to establish a plan forward. What elements should you address in this conversation?

- a) Practical issues such as advanced directives (e.g., power of attorney, living wills, driving issues, guardianship)
- b) Addressing comorbidities such as anxiety or depression
- c) Planning for behavioral changes that Lena may experience
- d) Uncertainties regarding prognosis and limitations of treatment options
- e) All of the above.





# AD Resources for Clinicians and Patients



<b>Alzheimer's Association</b>	<b><a href="http://www.alz.org">www.alz.org</a></b>
<b>Alzheimer's Foundation of America</b>	<b><a href="http://www.alzfdn.org">www.alzfdn.org</a></b>
<b>National Institute on Aging (NIA)</b>	<b><a href="http://www.nia.nih.gov/alzheimers">www.nia.nih.gov/alzheimers</a></b>
<b>National Institute of Neurological Disorders and Stroke (NINDS)</b>	<b><a href="http://www.ninds.nih.gov">www.ninds.nih.gov</a></b>
<b>Caring.com</b>	<b><a href="https://www.caring.com/senior-living/memory-care-facilities">https://www.caring.com/senior-living/memory-care-facilities</a></b>

# Conclusion and Clinical Pearls

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- Alzheimer's disease progresses through pre-clinical AD; mild cognitive impairment (MCI) due to AD; and Alzheimer's dementia.
- Hallmark symptoms of early-stage AD include difficulty remembering recent conversations, names, or events, apathy, or depression.
- Early signs of AD can often be distinguished from natural age-related cognitive changes.
- Many convenient screening tools for cognitive impairment can be implemented in primary care.
- Effective management requires honest and frank conversations that educate and prepare the patient and caregivers about what to expect.
- Management includes establishing a professional AD care team (e.g., neurologist, gerontologist, social worker, psychiatrist) and ensuring that family caregivers receive effective training in managing the day-to-day life of the care recipient.



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# Questions?