

More Than a Memory: Diagnosis and Treatment of Alzheimer's Disease

Most people will experience memory concerns as they grow older, especially after age 60. Fortunately, many people can benefit from systematic lifestyle interventions to improve cognition.¹

Subjective Cognitive Decline (SCD)²

- Patients may describe “short-term memory loss”; concerns often involve slowed recall of information like proper names
- In-office cognitive screening tests are normal

Mild Cognitive Impairment (MCI)³

- Cognitive complaints are present
- Clear deficits on cognitive screening tests
- Patients are able to maintain their daily activities

Mild Dementia⁴

- Cognitive deficits associated with functional losses (eg, inability to independently manage finances, new technologies, etc)
- Important:** scores on cognitive screening tests alone are not sufficient to diagnose dementia

First Address Potential Medical Causes of Memory Complaints⁵

- Effective treatment of medical conditions often significantly improves cognition even when neuropathologic conditions are present
- Dementia assessment guidelines recommend assessment for vitamin B12 deficiency and thyroid dysfunction
- Frequent medical contributors to cognitive impairments and “brain fog” include:
 - Medication effects (including alcohol)
 - Chronic pain
 - Mood and anxiety issues
 - Sleep disturbances

“The Big Four:” Primary Neurologic Causes of Dementia

Experience in memory specialty clinics identifies 4 frequent neurologic disorders that lead to dementia:

- The most common cause of dementia after age 65
- Key features: failure to make new memories (episodic memory loss), often leading to repetitiveness and disorientation in time



- Key features: slow cognitive processing and lapses in executive function
- Current conceptions of vascular cognitive impairment depend on imaging findings and no longer require the “abrupt onset and stepwise decline” of past definitions⁵

- Labeled “Pick’s disease” in prior classification schemes
- Key features: disturbance of behavioral control or language ability rather than memory-predominant losses
- Performance on cognitive screening is frequently intact; often mistaken for psychiatric illness

- Key features: fluctuating cognition or awareness, early onset of visual disturbances and hallucinations
- Often predated by REM sleep behavioral disturbance
- Screening deficits more commonly seen with visuospatial tests like clock drawing than with word recall

Differential Diagnosis of Neurologic Causes in Cognitive Impairment

MRI⁹

- AD:** typically cortical atrophy in the precuneus, parietal lobes, and hippocampus
- CVD:** most often presents with confluent white matter lesions
- FTD:** more prominent cortical atrophy in the frontal and temporal lobes
- LBD:** lacks distinctive features on structural imaging, but often shows greater atrophy in the posterior cortex

PET¹⁰

- 18F-fluorodeoxyglucose (FDG)-PET** assesses regional glucose metabolism; approved in the US for differentiating AD from FTD
- Several **amyloid-binding 18F ligands** are available to confirm and quantify cortical amyloid plaque burden
- Interpretation requires nuanced clinical judgment: significant age-related accumulation of amyloid may not be associated with cognitive losses (reaching >40% of unimpaired individuals older than 80 years of age)¹¹

Biomarkers

- CSF and blood-based biomarkers for AD pathology have become increasingly available since 2023, with some achieving FDA clearance
- Most common are measures of **phosphorylated tau protein (eg, pTau181 or pTau217)** reflecting cortical amyloid accumulation, although these do not measure tangle burden and thus are not reliable measures of dementia severity
- A 2025 consensus statement suggested that, at their current state of development, blood-based biomarkers are most effective at excluding AD when negative¹²
- Many academic centers use blood-based biomarkers as a triage step to optimize utilization of limited PET resources

Symptomatic Treatments for AD¹³

- **Oral acetylcholinesterase inhibitors** have a well-developed evidence basis and can best be thought of as *delaying* progression of cognitive impairment
 - A mainstay treatment for patients with mild and moderate AD dementia since the 1990s; extended- to severe-stage dementia with more recent formulations
 - Concerns about tolerability based on original clinical trial data have not been as evident with routine clinical use¹⁴
 - Although not FDA approved for MCI, used by many HCPs for this indication especially in the presence of AD biomarkers
- **Memantine** can provide a useful adjunctive therapy in delaying cognitive progression as dementia severity increases
- Treatment of **neuropsychiatric** symptoms may be beneficial although outcomes are less predictable

Amyloid Targeting Therapies for AD

Lecanemab and **donanemab** are amyloid-targeting monoclonal antibody (mAb) therapies FDA approved for the **MCI or mild dementia** stages of AD with **confirmed amyloid beta pathology**.^{15,16} Large phase III trials found both to slow global progression by ~25% over 18 months in in this patient population.^{17,18}

Risk of Amyloid-Related Imaging Abnormalities (ARIA)

Lecanemab and donanemab are associated with risk of ARIA, a serious adverse event that presents on MRI as cerebral effusions or edema (**ARIA-E**) or microhemorrhages or superficial siderosis (**ARIA-H**). A majority of ARIA are **asymptomatic** and must be detected by **scheduled MRI monitoring** as recommended in each product label. Apolipoprotein E ε4 (APOE4) genotype is the major driver in predicting an individual ARIA risk.^{15,16}

Practical Treatment Considerations

- Perform prior to treatment initiation:
- MRI to establish the presence and severity of microhemorrhage/siderosis burden
 - Amyloid PET or CSF to confirm AD amyloid positivity
 - APOE4 genotyping to provide counseling on ARIA risk

Further expert guidance for clinical use of lecanemab and donanemab is available in **recommendations for appropriate use^{19,20}** and **consensus guidelines^{21,22}**

	Lecanemab ¹⁵	Donanemab ¹⁶
Initial administration	IV*	IV
Initial dose frequency	Q2W	Q4W
Duration of initial regimen	18 mo	12 mo
MRI monitoring	Prior to initiation and to infusions 3, 5, 7, and 14 (Wk 0, 4, 8, 12, 26)	Prior to initiation and to infusions 2, 3, 4, and 7 (Wk 0, 4, 8, 12, 24)
Continue regimen?	Maintenance recommended	Consider stopping based on amyloid PET
Continued administration	IVSC	IV
Continued dose frequency	Q4WQW	Q4W

*sBLA for subcutaneous initiation of lecanemab submitted in November 2025.
Label information as of January 2026.

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For more information on diagnosis and treatment of Alzheimer’s disease, including accredited CME/CE activities, please visit:

deceraclinical.com/ADManagementATTprogram

