# Updates in the Management of Mild Cognitive Impairment and Alzheimer Disease

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## CONTINUING MEDICAL EDUCATION

### LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Implement evidence-based methods for cognitive impairment screening in primary care.
- Identify correct diagnostic criteria for mild cognitive impairment (MCI) and Alzheimer disease (AD) based on current guideline recommendations.
- Design appropriate and effective treatment plans for patients with MCI and AD and refer to a specialist when necessary.
- Describe advances in testing and treatment for AD that may impact dementia care.

### KEY TAKEAWAYS

- Due to the expanding older population and an increased burden of MCI and AD, the shortage of dementia care specialists is expected to worsen, prompting a need for primary care practitioners (PCPs) in managing MCI and AD.
- PCPs should routinely screen patients at risk for AD with a validated cognitive assessment tool to help detect early disease.
- MCI and AD are diagnosed clinically, but newer imaging and biomarker tests can confirm an AD diagnosis. Such tests, however, are not always accessible and are usually only used by specialists and in clinical trials.
- The approved therapies for AD provide only symptomatic benefit and are not indicated in patients with MCI. Research is currently being directed at disease-modifying treatments, including an agent that recently received accelerated approval for AD, pending confirmatory studies for continued approval.

### TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of mild cognitive impairment and Alzheimer disease.

### FACULTY

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## INTRODUCTION

Alzheimer disease (AD) is a progressive neurodegenerative disease often present decades before symptoms are evident.[1] As of 2021, approximately 6.2 million patients in the United States aged 65 and older had AD with dementia, and estimates predict this number to double by the year 2050.[1] AD and other dementias represent a significant cost burden in the US, with an estimated $305 billion spent on healthcare, long-term and hospice care for patients, as well as lost patient and caregiver productivity.[2]

AD is characterized by the progressive dysfunction and loss of synapses and neurons associated with neurotoxic protein aggregates—neurofibrillary tangles (composed primarily of phosphorylated tau) and beta-amyloid plaques—resulting in cognitive, behavioral, and functional changes in affected individuals.[3] AD is the most common cause of dementia, accounting for approximately 60% to 80% of dementia cases.[4] Notably, about 50% of patients with AD have a "mixed" etiology, exhibiting pathology and symptoms related to other dementia types in addition to AD.[2]

AD progresses along a continuum that begins with preclinical or asymptomatic AD and progresses to mild cognitive impairment (MCI), mild dementia, and eventually moderate and severe AD (**FIGURE**).[5] Several different staging systems describe the progression of AD, with variations in nomenclature but overall similarities with regard to pathophysiology and neurologic deficits.[5,6] Symptoms become evident in the MCI phase of the AD continuum, characterized by subtle cognitive changes that may only be noticeable to the patient, family members, friends, and caregivers.[1] Biomarkers of AD can be detected much earlier than symptoms; for example, plaque deposition can occur up to 20 years prior to onset of cognitive symptoms.[6,7]

## THE PCP'S ROLE IN DEMENTIA CARE

The aging population and increase in older patients overall creates an urgent need for better management and treatment of AD. Due to a shortage of dementia care specialists, and since primary care practitioners (PCPs) are capable of managing cognitive impairment and dementia, it often falls to PCPs to care for patients with MCI and AD.[2] Patients with early signs of dementia or AD often present first to their PCP, who can help detect, diagnose, and manage early-stage AD.[8]

### 2020 Alzheimer's Association primary care surveys

In 2020, the Alzheimer's Association published a series of surveys including approximately 1400 PCPs in the US.[2] About half of the survey respondents believed that the medical profession is unprepared to meet the expected increase in demand for providing care for AD and other dementias, and that there are not enough specialists to receive referrals for all patients with AD.[2] However, about 32% of PCPs reported referring patients with dementia to specialists at least once a month.[2] Most PCPs reported answering questions about AD or dementia every few days, and about 1 in 5 PCPs reported responding to these questions daily.[2] Approximately 82% of survey respondents answered that they feel they are on the front lines of providing dementia care.[2]

In addition to spending time during annual wellness visits (AWVs) or other appointments dedicated to cognitive evaluation, PCPs may detect cognitive or behavioral changes as part of routine visits, prompting follow-up cognitive testing.[8] Once a diagnosis of MCI or AD is established, PCPs can treat many of the patients in primary care, and those who are not candidates for treatment by the PCP can be referred to a specialist.[5]

### CASE SCENARIO

An 82-year-old woman presented to her PCP for a routine AWV. She had a history of hypertension and a family history of dementia. Her routine labs were within normal limits, and her blood pressure was 118/70 mm Hg. She had been treated with amlodipine 10 mg daily. She presented with her husband, who usually accompanies her to appointments. She did not have any specific complaints and was "just here for the yearly check-up."

## COGNITIVE ASSESSMENT IN PRIMARY CARE

Despite cognitive assessment as a standard component of AWVs for patients with Medicare, only 16% of patients aged 65 years and older report receiving a regular, brief cognitive assessment.[9] PCPs should routinely screen patients at risk for AD with one of several validated tools used in primary care settings.[5] Many of the tools are available online and easily implemented in clinical practice (**TABLE**).

## SELECT METHODS FOR COGNITIVE ASSESSMENT BY PCPs

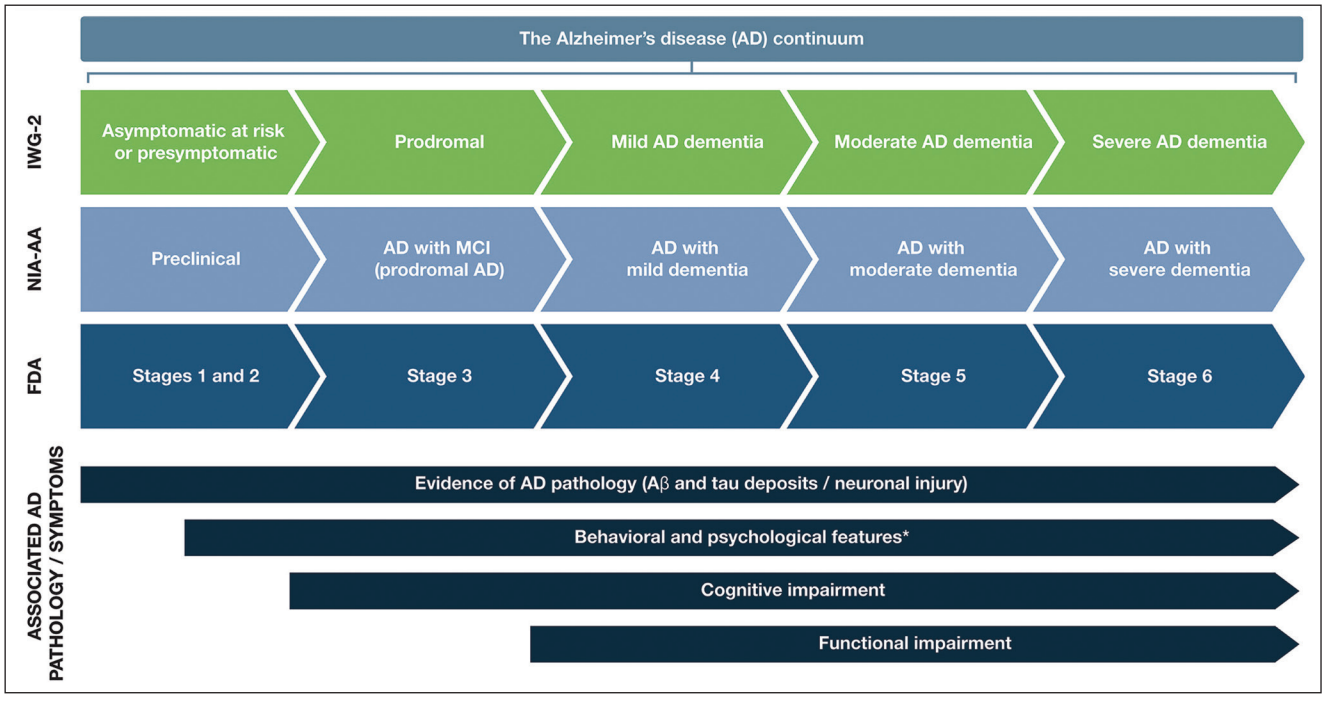
*Mini Mental State Examination (MMSE).* The MMSE is a 30-item instrument administered to the patient, which takes about 5-10 minutes to complete.[10] This tool is sensitive and reliable for detection of memory and language deficits, but may not capture impaired executive functioning.[11]

***Montreal cognitive assessment (MoCA).*** The MoCA is a 12-item assessment that takes about 10 minutes to complete.[5] This tool was originally developed to improve detection of MCI, and thus is more sensitive than the MMSE for evaluating visuospatial, language, memory, and executive function.[11,12] Clinicians who use the MoCA are mandated to undergo a certification that takes approximately 1 hour to complete.[12]

***Mini cognitive assessment instrument (Mini-Cog).*** This brief evaluation consists of a 3-item recall and clock

FIGURE. **The continuum of Alzheimer disease[5]**

The AD continuum can be classified into different stages from preclinical AD to severe AD dementia; the nomenclature associated with each stage varies between the different clinical and research classifications. This figure provides a summary of the different naming conventions that are used within the AD community and the symptoms associated with each stage of the continuum; *Mild behavioral impairment is a construct that describes the emergence of sustained and impactful neuropsychiatric symptoms that may occur in patients ≥50 years old prior to cognitive decline and dementia (112).




**Abbreviations:** Aβ, amyloid beta. AD, Alzheimer's disease. FDA, Food and Drug Administration. IWG, International Working Group. MCI, mild cognitive impairment. NIA-AA, National Institute on Aging—Alzheimer's Association.

**Source:** Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J Prev Alzheimers Dis*. 2021;8(3):371-386.

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drawing that is administered to the patient and takes about 2-3 minutes to complete.[5] This assessment requires no training, and the results are easy to interpret.[5]

***AD8 dementia screening interview (AD8).*** This short, 2-to-3-minute, 8-item tool is usually administered to an informant to help detect dementia in patients, based on the informant's responses.[5] Some experts suggest that the AD8 may be administered to patients in the absence of an informant, with similar results, especially in patients with mild dementia.[13]

***Informant questionnaire on cognitive decline in the elderly (IQCODE).*** The IQCODE is another questionnaire designed to be administered to an informant, and it takes about 10 minutes to complete.[5,14]

## Exclusion of reversible causes of cognitive impairment

The PCP's initial assessment needs to exclude reversible causes of cognitive impairment, such as hormone imbalances, depression, electrolyte or vitamin deficiencies, and medications that can cause cognitive impairment.[5,15] Reversible causes of impairment need to be identified, addressed, and corrected, if possible, prior to continuing AD evaluation.

***Laboratory testing.*** Vitamin B12 deficiency, vitamin D deficiency, and thyroid disorders are common causes of cognitive impairment that can be ruled out with laboratory tests.[15,16] The following blood analyses are recommended for the initial assessment of AD: complete blood count, blood glucose, electrolytes, liver function, kidney function, thyroid-stimulating hormone, vitamin B12, vitamin D, and folate.[8,16]

***Comorbidities.*** Behavioral symptoms and sleep disturbances are common in patients with MCI or AD.[17] Depression can have similar presenting symptoms as cognitive impairment and can often be a comorbidity for patients with dementia, so

TABLE. **Open-access assessment tools for Alzheimer disease**

| | |
|---|---|
| MMSE | https://www.psychdb.com/cognitive-testing/mmse |
| MoCA | https://www.parkinsons.va.gov/resources/MOCA-Test-English.pdf |
| Mini-Cog | https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit (page 9) |
| AD8 | https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit (page 14) |
| IQCODE | https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit (page 11) |
| QDRS | http://med.fau.edu/research/The%20Quick%20Dementia%20Rating%20System%20Instructions%20and%20Form.pdf |
| FAQ | https://www.alz.org/careplanning/downloads/functional-activities-questionnaire.pdf |
| FAST | https://alzprogression.com/scales/fast/ |
| GDS | https://wwwoundcare.ca/Uploads/ContentDocuments/Geriatric%20Depression%20Scale.pdf |
| NPI-Q | https://www.alz.org/media/documents/npiq-questionnaire.pdf |

**Abbreviations:** MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; Mini-Cog, Mini Cognitive Assessment Instrument; AD8, AD8 Dementia Screening Interview; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; QDRS, Quick Dementia Rating System; FAQ, Functional Activities Questionnaire; FAST, Functional Analysis Screening Tool; GDS, Geriatric Depression Scale; NPI-Q, Neuropsychiatric Inventory Questionnaire.

screening for depression using a validated tool such as the Patient Health Questionnaire-9 (PHQ-9) is recommended.[18] Therapeutic interventions for depression, anxiety, and sleep disorders can alleviate cognitive symptoms associated with these comorbidities and provide a clearer picture of cognitive impairment due to neurologic degeneration.[19,20]

In the case scenario above, it would be prudent for the PCP to include cognitive assessment as part of the AWV due to the patient's multiple risk factors for cognitive impairment, including older age and a family history of dementia. Too often, these screening opportunities may be missed or overlooked.

## BEST PRACTICES FOR DIAGNOSIS OF MCI AND AD

Underdiagnosis of AD and other dementias is common in primary care, and a substantial number of Medicare patients meeting AD criteria are undiagnosed.[1] The diagnostic process for AD includes initial detection or suspicion of disease, assessment, diagnosis, and treatment, with various tests and possible specialist referral considered along the way.[5] Additionally, the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup has established core clinical diagnostic criteria for MCI and AD that can facilitate clinical diagnosis.[21,22] Notably, these criteria can help distinguish AD from other major forms of dementia.[23]

After the initial screening and workup for MCI or AD, a full evaluation can be conducted to establish a clinical diagnosis, which should include the following:

- Medical history
- Physical examination
  - o Blood pressure, temperature, pulse, lung auscultation
- Cognitive, functional, and behavioral examinations
  - o Functional examinations include the Functional Activities Questionnaire (FAQ), the Functional Analysis Screening Tool (FAST), and the Quick Dementia Rating System (QDRS)
  - o Behavioral examinations include the Geriatric Depression Scale (GDS) and the Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Laboratory tests
- Interview of a knowledgeable informant
- Medication profile review to assess for drugs that can cause cognitive impairment
- Analysis of risk factors for AD: family history of dementia, older age, female sex, physical inactivity, obesity, diabetes, low education, and apolipoprotein E (ApoE) ε4 carrier status

Historically, confirming a diagnosis of AD was possible only postmortem, but recent advances in imaging and fluid biomarkers for AD allow for diagnostic confirmation. However, these tests are not yet widely used due to lack of access and reimbursement; use of imaging and fluid biomarkers is more common in specialist settings and clinical trials.[24]

While many patients with MCI or AD can be managed in the primary care setting, a specialist referral may be warranted for patients presenting with any of the following characteristics[5,25]:

- Less than 65 years old (ie, early disease onset)
- Presence of parkinsonian features

- Presence of hallucinations or delusions
- Rapid progression or fluctuations of cognitive impairment
- Unexplained visual impairment
- Severe depression

## TREATING MCI AND AD IN PRIMARY CARE

For patients managed in the primary care setting, PCPs should consider how best to disclose the diagnosis to the patient, family members, and caregivers, as well as discuss treatment options and support resources.[5,15] PCPs can encourage patients and family members to have conversations about care planning, in the event the patient is no longer able to make informed decisions for themselves.[5] Monitoring for worsening cognitive function should include cognitive and functional assessments at routine follow-up appointments about every 6-12 months.[5]

### Nonpharmacologic therapy for MCI and AD

Nonpharmacologic therapies can have a positive impact on the quality of life for patients with MCI and AD and are relatively safe and inexpensive.[10,26] Possible nonpharmacologic interventions include dietary changes, physical exercise, cognitive training, social interactions with others, adequate sleep, and proper personal hygiene.[10,26]

### Pharmacologic therapy for AD

Several agents are Food and Drug Administration (FDA)-approved for AD, but no pharmacologic therapy is indicated for patients with MCI. These agents can provide symptomatic benefit but are not disease-modifying treatments.[5,27] The approved acetylcholinesterase inhibitors for AD are rivastigmine, galantamine, and donepezil.[27] Memantine, an *N*-methyl-D-aspartate receptor antagonist, is also approved for use for moderate or severe AD.[27] A complete discussion regarding the benefits, risks, initiation, titration, and side effects of these medications is beyond the scope of this article. Additional information can be found in published review articles.[27] While some patients may be interested in using alternative treatments for AD such as natural products or supplements, there is no clear clinical benefit from these therapies.[28]

## RECENT ADVANCES IN AD MANAGEMENT

Emerging diagnostics and therapeutics have the potential for practice-changing advances in diagnosing, treating, and preventing AD in the coming years. Laboratory testing and/or imaging biomarkers can help detect AD much earlier in the disease process, and research is under way to evaluate potential disease-modifying agents for early AD.[5]

### Advances in imaging

Structural magnetic resonance imaging (MRI) can assess atrophy and tissue changes in the brain, and functional MRI provides a measure of neuronal activity.[29] Structural brain MRI is readily accessible, but both structural and functional MRI lack the ability to detect amyloid plaques and tau tangles specific to the AD disease process.[29] Fluorodeoxyglucose (FDG) positron emission tomography (PET) uses FDG as a marker of brain glucose metabolism, which reflects neuronal function. Regional metabolic patterns help distinguish AD from frontotemporal dementia, and Medicare will reimburse for such scans.[29] Amyloid-PET imaging identifies amyloid plaques in the brain and can be helpful to confirm the diagnosis of AD for inconclusive cases; however, its clinical use is limited due to cost and concerns for variation in protocols and cutoffs for interpreting results.[29,30] Tau-PET can distinguish AD dementia from other neurodegenerative disorders and potentially predict cognitive change, but it is expensive and has limited availability.[31]

### Advances in biomarkers

In 2018, the NIA proposed a research framework for biomarkers in AD, intended to separate biomarkers specific for pathologic tau from nonspecific neurodegeneration that can occur in non-AD conditions.[6] Currently, biomarkers are not used in clinical care protocols, but they are used in research.[6] The NIA uses an AT(N) biomarker grouping as follows[6]:

- A: Aggregated amyloid beta; measured using cerebrospinal fluid (CSF) amyloid beta (also amyloid-PET)
- T: Aggregated tau; measured using CSF phosphorylated tau (also tau-PET)
- (N): Neurodegeneration or neuronal injury; measured using CSF total tau (also anatomic MRI, FDG-PET)

### Advances in treatment

Aducanumab was FDA-approved in June 2021, the first new agent for AD in almost 20 years.[32] It was approved under the accelerated pathway, and confirmatory trials are needed for continued approval.[32] The approval was based on 2 phase 3 studies that showed a statistically significant reduction in brain amyloid plaques for the aducanumab groups compared to placebo.[33,34] Notably, there has been controversy in the scientific community regarding the accelerated approval of aducanumab, as well as its safety and costs, in consideration of its observed clinical benefit.[35]

In the EMERGE study (NCT02484547), the 1643 participants, aged 50-85 years, met criteria for MCI or mild AD, and had a positive amyloid-PET scan.[33] Patients were randomized 1:1:1 to placebo, low-dose aducanumab, and high-dose

aducanumab groups. Results demonstrated a 22%, statistically significant reduction ($P$=0.012) in clinical decline in the amyloid-PET and CSF biomarker substudies (total of 302 patients evaluated).[33]

The ENGAGE trial (NCT02477800) enrolled 1647 patients aged 50-85 years with MCI or mild AD and a positive amyloid-PET scan.[34] Similar to EMERGE, patients were randomized 1:1:1 to placebo, low-dose aducanumab, and high-dose aducanumab. In the amyloid-PET and CSF biomarker substudies (374 patients), no statistically significant difference was observed in the rate of clinical decline.[34]

Aducanumab is indicated for AD in patients with MCI or mild dementia and is administered as an intravenous infusion given over 60 minutes, every 4 weeks.[36] The dose of aducanumab starts at 1 mg/kg for infusions 1 and 2, then increases to 3 mg/kg (infusions 3 and 4), then increases to 6 mg/kg (infusions 5 and 6), and the maintenance dose is 10 mg/kg starting with infusion 7. Doses should be administered at least 21 days apart.[36]

## SUMMARY

MCI and AD are frequently encountered in primary care. As the population continues to age and these diseases become more prevalent, the role of PCPs in early diagnosis and management will become increasingly important, especially considering the shortage of dementia care specialists. PCPs should implement protocols for routine cognitive evaluation (such as AWVs) that involve use of validated tools to screen for cognitive impairment. Diagnosis and management of MCI and AD can be accomplished in primary care, but patients with atypical or complex presentations may require referral to specialists. Emerging diagnostics and therapeutics may prompt changes in practice for managing MCI and AD in the coming years. ●

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