Diagnosing and Treating Alzheimer Disease During the Early Stage

Anna D. Burke, MD, and Danielle Goldfarb, MD

Alzheimer disease (AD) is a degenerative brain disease that affects more than 55 million people worldwide[1] and has no cure. Advances in technology show that AD pathology markers can appear 20 years before symptom onset.[2] Available treatments can slow symptom progression,[3–8] and prompt diagnosis is crucial to intervening in the progress of AD. However, less than 40% of patients are diagnosed,[9] and clinicians do not effectively communicate next steps to patients and caregivers.[10]

The following Academic Highlights presents an overview of the teleconference series "Diagnosing and Treating Alzheimer Disease During the Early Stage," which was held on February 18, 2022. Faculty discussed updated guidelines and modalities to facilitate early diagnosis of Alzheimer disease and the current landscape for symptomatic and disease modifying treatments.

TIMELY DIAGNOSIS OF ALZHEIMER DISEASE

Dr Danielle Goldfarb, a dual-trained neurologist and memory specialist, began her presentation by explaining the different stages in Alzheimer diagnosis. She noted that the National Institute on Aging and Alzheimer's Association added a new category to the stages of diagnostic criteria.[2,11] In this newly added preclinical stage, the patient has no cognitive impairment, yet changes in the brain can be identified with neuroimaging techniques and biomarker evidence.[2] These advances in diagnostic modalities are changing clinicians' understanding of, diagnosis of, and clinical care for patients with AD.

Diagnosing Early-Stage Alzheimer Disease

Diagnosing AD based on clinical symptoms and functional changes results in an inaccurate Alzheimer diagnosis in nearly one quarter of patients,[12] compared to autopsy findings, with a greater rate of inaccuracy earlier in the course of disease. The addition of the preclinical, or asymptomatic, stage to the diagnostic criteria can compound diagnostic uncertainty given available diagnostic testing. However, new biomarker tests can detect changes in the brain decades before symptom onset,[13] providing a window of opportunity to diagnose early and

CME Background

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This Academic Highlights section of *The Journal of Clinical Psychiatry* presents the highlights of the teleconference series "Diagnosing and Treating Alzheimer Disease During the Early Stage," which was held in December 2021 and February 2022. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Lilly, LLC.

The teleconference was chaired by **Anna D. Burke, MD**, Barrow Neurological Institute, Phoenix, Arizona. The faculty was **Danielle Goldfarb, MD**, Banner Sun Health Research Institute, Sun City, Arizona.

CME Objective

After studying this article, you should be able to:

- Identify patients with early-stage Alzheimer disease
- Facilitate prompt treatment initiation for patients who have early-stage Alzheimer disease
- Discuss the potential use of current and emerging agents focused on reducing disease progression with patients and their care partners

Accreditation Statement

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All relevant financial relationships have been mitigated. **Dr Burke's and Dr Goldfarb's financial disclosure appears on the next page.**

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Notice of correction: On page 18, under the heading "NMDA antagonists," the first sentence has been corrected.

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Dr Burke has served as a consultant for disease state education for Eli Lilly. Dr Goldfarb has served on the speaker/advisory board for Eisai.

Review Process

The faculty agreed to provide a balanced and evidence-based presentation and discussed the topic and CME objective during the planning sessions. The faculty's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by a peer reviewer who is without conflict of interest.

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change the trajectory of the disease for the patient with AD and their family and caregiver. As the AD field moves toward preclinical diagnosis, the understanding of "early" AD will likely be defined as asymptomatic disease with biomarker evidence of AD.

Alzheimer disease stages. Dr Goldfarb suggested that one approach to determining the preclinical/early stage is detecting subtle cognitive changes, subjective cognitive decline, or mild cognitive impairment (MCI).[2] This compares to some primary care physicians' interpretation of "early" as cognitive changes that are conclusively impacting the patient's life and function.[14] Dr Goldfarb stated that at that point, the patient could have already reached the later stage of mild dementia. Primary care physicians' decisions on making an early diagnosis of AD are further complicated by how the clinical presentation is delivered, by whom it is delivered, and whether an informant is present. This clinical setting compares to specialty cognitive evaluation, in which there is some preliminary acknowledgment of symptoms.[15]

The AD preclinical stage is followed by MCI.[16] MCI is marked by symptoms of memory loss and/or thinking problems that are greater than normal for a person's age or education but that do not affect his or her daily functions. People with MCI may or may not progress to Alzheimer dementia.[16]

The third stage is categorized as Alzheimer dementia. During this stage, the patient might present with memory loss, word-finding difficulties, and visual/spatial problems. These symptoms have progressed enough to interfere with the individual's ability to function independently.[17]

The complexity of diagnosing AD is evidenced by the fact that more than 60% of individuals with dementia are never diagnosed.[9]

Diagnostic criteria. New modalities are changing physicians' ability to accurately diagnose AD. Routinely, clinicians examine patient history, cognition, mood, neurologic symptoms, and any mental health or substance abuse issues. This can be followed by structural brain imaging (magnetic resonance imaging [preferred] or non-contrast helical computed tomography) to look for neurodegeneration through structural and volumetric changes; cerebrospinal fluid testing (CSF) via lumbar puncture to investigate Aβ42, total-tau (t-tau), and phosphorylated-tau (p-tau) biomarkers; and/or a fluorodeoxyglucose (FDG)-positron emission tomography scan to assess patterns of cerebral glucose metabolism characteristic of neurodegenerative disease.[17]

Recently, a new blood test became available that detects the ratio of the levels of amyloid β proteins Aβ42 and Aβ40 in the blood to indicate whether amyloid proteins have begun to gather in the brain[18] (Figure 1). "Until now, if we wanted to bolster a diagnosis of Alzheimer's disease with biomarkers such as amyloid and tau levels, we would have to do a lumbar puncture and CSF studies, or a patient would have to pay for an expensive amyloid scan of the brain," Dr Anna Burke offered during her discussion with Dr Goldfarb. "Now we are starting to see technologies such as blood tests assessing for these pathological proteins. With time, I suspect that those will become more readily available in the primary care setting, allowing primary care physicians to feel more comfortable with identifying a particular diagnosis and engaging patients in earlier treatment."

Such specificity offered by multiple testing modalities can offer an accurate diagnosis and therefore relief to the patient and family and direct their plan of care.

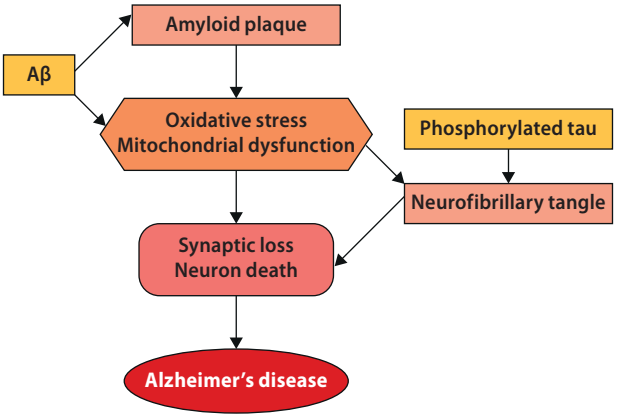
Barriers to Early Diagnosis

Many barriers contribute to the underdiagnosis of AD. Primary care physicians, along with the patient and their family, lack information and resources, and symptoms can go unreported.

Dr Goldfarb emphasized the importance of primary care providers' role in the diagnostic process and in turn pointed to studies that demonstrate the difficulties that clinicians face. Clinicians reported lack of time, lack of training and experience, and lack of confidence as barriers to diagnosing AD.[14] Physicians, along with patients, can also interpret cognitive changes as normal aging, particularly if neither family members nor patients have reported any concerns.[14] "The thought process understandably is, 'Why would I go there, because there [are] no disease-modifying treatments yet,'" Dr Goldfarb said.

At times, symptoms of Alzheimer mimics can confuse a diagnostic workup, and access to the right kind of technology helps distinguish which pathologic entities are causing the cognitive impairment. Importantly, perceptions of stigma can affect decisions on giving a diagnosis. Patients have concerns about their employment, their ability to drive, and their participation in decision-making. Compounded with a lack of patient

Figure 1. The Role of Aβ and Phosphorylated Tau in Pathological Changes in AD[a]



[a]Reprinted with permission from Wang and Reddy.[19] Glutamate activates extrasynaptic NMDARs that overcome synaptic NMDAR-mediated survival signaling, leading to neuronal death.
Abbreviation: NMDAR = *N*-methyl-D-aspartate receptor.

and caregiver resources and support, physicians at times perceive a diagnosis as a disservice.[14,15]

Half of primary care providers reported that they keep up with new developments in dementia "only a little" or "not at all,"[13] and 39% noted that they are "never" or "only sometimes" comfortable making a diagnosis of AD.[18] More than half acknowledge that local specialist resources are insufficient to meet patient demand.[18] In a study of European practitioners from 5 countries, 74% stated that they thought early-stage diagnosis of AD was of value, and 58% thought the benefits of early diagnosis outweighed the risks.[20]

Dr Burke underscored Dr Goldfarb's comments with her experiences as director of the Alzheimer's and Memory Disorders Division at Barrow Neurological Institute: "The primary care physician has anywhere from 7 to 10 minutes to spend with the patient, and often, they're focused on a multitude of problems to treat, everything from the patient's high cholesterol to their diabetes. They have . . . this fear of opening Pandora's box without necessarily having the tools that they need to be able to treat that patient," Dr Burke said. "We've created, for example, at our institute, a website with resources for patients and families. We're in the process of developing additional resources for primary care physicians who want to learn more about the disease and ways to manage it, also allowing them to connect with organizations like the Alzheimer's Association, Lewy Body Dementia Association, and other societies that target different types of dementias."

Best Practices in Early Diagnosis

Evidence with respect to best practices for diagnosing dementia has proven difficult to collate. Research into the effect of the timing of diagnosis upon subsequent disease course and outcomes for the person with dementia and their care partners is limited.[21] Better understanding of the scope of the problem and characteristics of the population living with undiagnosed dementia can help identify these links. Furthermore, unique characteristics of undiagnosed individuals could be translated into targeted dementia detection, education, and support.

Brain health disparities exist for Alzheimer diagnosis and care. One cross-sectional study conducted by Johns Hopkins Institute looked at 3 years of Medicare claims of 585 older adults with probable dementia to identify characteristics associated with dementia diagnosis and awareness of diagnosis. Undiagnosed individuals were more likely to be non-White, have lower educational attainment, have less functional impairment, and be more likely to attend visits without a companion. Among persons diagnosed, those who were unaware of their diagnosis were more likely to have lower educational attainment and to attend their doctors' visits alone. Individuals who had impairments in managing finances and medications were more likely to receive a diagnosis compared with those who had impairments with cooking, cleaning, and laundry.[21]

An update from the US Preventative Task Force Recommendation on Screening for Cognitive Impairment in Older Adults stated that there is insufficient evidence to assess the balance of benefits and harms of screening for cognitive impairment in older adults, based on a single study.[22] Dr Goldfarb called for the development of more evidence in this arena.

The current recommendation for screening in primary care includes performing a brief cognitive assessment to detect any evidence of cognitive concern, whether by direct observation or patient or family report[18] (Figure 2).

Benefits of Early Diagnosis

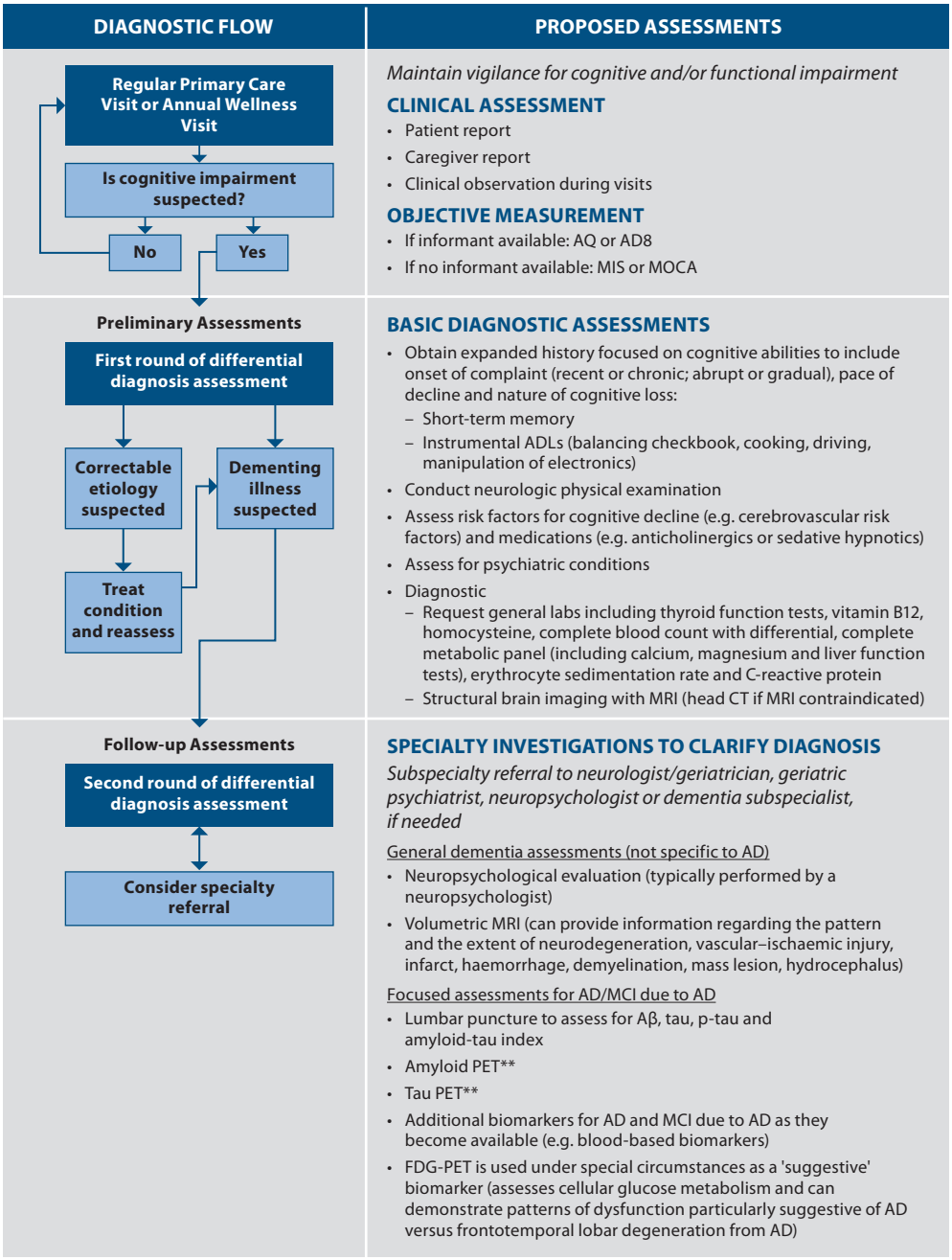
There are a number of benefits of early AD diagnosis that can be categorized into personal, caregiver and family, economic, and research.

Personal benefits. Patients can optimize their medical management, addressing sleep, mood, medication, and lifestyle changes, and receiving specific information about their symptoms and being included in the decision-making provides relief and impacts their quality of life. An earlier diagnosis allows the patient to initiate treatment earlier, which can slow down the progression of cognitive and functional change. And, overall, an earlier diagnosis helps to decrease safety issues and allows the patient to plan for the future.[1]

Caregiver benefits. With an early diagnosis, caregivers and families can also make sense of what is happening, how they fit in, and how they can adapt over time, which can decrease their chance of burnout, stress, and burden and improve their quality of life. In addition, they gain access to knowledge, education, resources, and support groups and find community.[23]

Economic benefits. Early diagnosis can potentially delay institutionalization and improves quality of life for both patient and caregiver, which could contribute to long-term

Figure 2. A Pathway for Monitoring and Evaluating Individuals at Risk of Cognitive Impairment[a]



[a]Reprinted from Liss et al.[18]
**Although approved by the FDA, this imaging procedure is not yet reimbursed by Centers for Medicare & Medicaid Services.
Abbreviations: AD = Alzheimer disease, ADL = activities of daily living, AQ = Alzheimer's Questionnaire, AD8 = Ascertain Dementia 8-Item Informant Questionnaire, CT = computed tomography, FDG = fluorodeoxyglucose, MCI = mild cognitive impairment, MIS = Memory Impairment Screen, MOCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, PET = positron emission tomography.

health cost savings.[24] This could translate to $7 trillion in managed MCI as opposed to unmanaged MCI and dementia.[13]

Research benefits. With early diagnosis, patients can consider pursuing clinical trials of novel investigational treatments and disease-modifying therapies, which hold promise for changing disease trajectory.[25] As in cancer care, clinical trials will likely eventually be considered a standard component of the AD treatment armamentarium.[1]

Potential Risks of Early Diagnosis

Stigma and discrimination against a person with Alzheimer diagnosis in terms of employment, driving,

insurance premiums, and financial control are concerns. Diagnosis and repeated cognitive tests can provoke feelings of demoralization and anxiety, and issues with privacy and confidentiality could be linked. There is the risk of misdiagnosis as well, especially due to an Alzheimer mimic.[14,26]

Best Practices

There are ongoing investigations as to guidelines for diagnosing Alzheimer disease. Dr Goldfarb suggested a multicomponent approach including clinician education and training for every step of the disease process. Antistigma campaigns that could empower patients and families to advocate for one another should be incorporated, as well as enhanced therapeutic services, such as cognitive rehabilitation, with widespread access. Greater reimbursement and efficacy research is also needed.[15]

Closing Remarks

Dr Goldfarb closed her presentation with a message of hope. By diagnosing patients early, clinicians can equip patients and caregivers with knowledge and understanding of what to expect currently and in the future. Approaching their care from a standpoint of partnership can provide a team attitude, including family, so that they feel supported throughout their disease course. "This approach of infusing hope—while we don't have yet the evidence or the data to say that that's the most helpful anecdotally—it clearly has benefits for my patients and [their] families," Dr Goldfarb said.

FACILITATING TREATMENT INITIATION IN EARLY-STAGE ALZHEIMER DISEASE

Dr Anna Burke opened her discussion reiterating the importance of a holistic approach in treating patients with Alzheimer disease. Pharmacologic treatments include symptomatic and disease-modifying therapies as well as treatments for secondary symptoms, called behavioral and psychological symptoms of dementia, which can be anxiety, depression, agitation, and psychotic symptoms. Education and support for the patient and their family and caregivers are also vital to treatment of early-stage Alzheimer disease.

Stages of Disease

Dr Burke spoke about the stages of Alzheimer disease and how to diagnose them so that the appropriate treatment can be initiated. Simple staging divides the disease into MCI, mild illness, moderate illness, and severe illness.[27]

MCI. People with MCI will begin to display symptoms of memory and/or other thinking problems that are greater than normal for their age and education but that do not interfere with their independence. Individuals may or may not progress to Alzheimer dementia.[2]

Mild dementia. Mild dementia is marked by the emergence of cognitive impairment and/or functional changes. It could manifest in the higher functions and instrumental activities of daily living, such as managing finances, managing medications, or using complex appliances. Patients with mild dementia generally score between 21 and 25 on the Mini Mental State Examination (MMSE). The Montreal Cognitive Assessment (MoCA) test score will be 18 to 25, and the patient's Clinical Dementia Rating (CDR) will be 1.[27]

Moderate dementia. More functional impairments emerge during moderate dementia, such as worse short-term memory, difficulty with simple household appliances, and particularly driving impairment. Patients could potentially have mild difficulty with bathing or dressing. The MMSE score during this stage typically ranges from 11 to 17, and the CDR is a 2.[27]

Severe dementia. In this stage, patients will begin to have difficulty with long-term memory, executive function and language abilities and with basic functions such as getting dressed, bathing, eating, and toileting. The MMSE score is generally below a 10, the MoCA also below a 10, and the CDR a 3.9.[27]

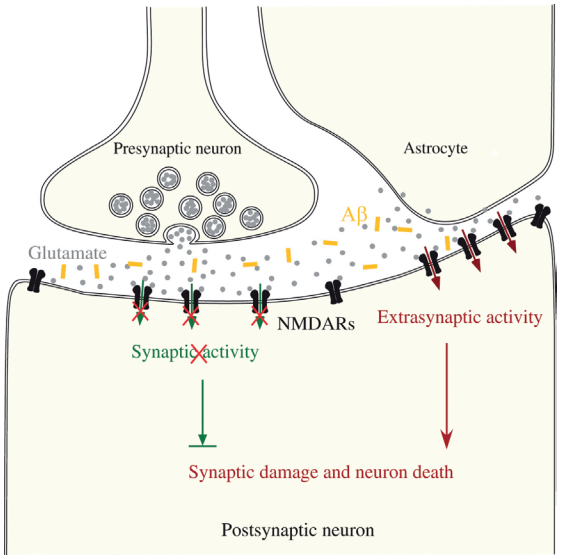
Symptomatic Treatments

Symptomatic treatments are used to slow the progression of cognitive symptoms. The available symptomatic treatments do not alter the underlying biologic course of the disease[3] but target neurotransmitters in the brain and modify their function. Clinical trials have demonstrated that these agents improve cognitive measures, such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) by 1.5 to 3 points out of 70, with corresponding changes on the Mini-Mental Status Examination (MMSE). However, while cognition slightly improves, the disease course continues.[5] Symptomatic treatments have also been shown to ameliorate neuropsychiatric symptoms.[4–6] Two groups of symptomatic treatments are available, cholinesterase inhibitors and NMDA antagonists.

Cholinesterase inhibitors. In patients with Alzheimer disease, the occurrence of reduced cerebral content of choline acetyltransferase leads to a decrease in acetylcholine synthesis as well as impairment in acetylcholine function.[5,28] Cholinesterase inhibitors (ChEIs) increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft, thereby providing a modest symptomatic benefit in patients with Alzheimer disease.[5,6,28]

Recent reviews and meta-analyses on ChEIs showed that they delay the decline in cognitive function as measured by the ADAS-Cog, global clinical rating, behavior, and activities of daily living (ADL) over 6- to 12-month periods.[28] These benefits seem to be applicable to mild, moderate, and severe Alzheimer disease.[6] Symptoms that were improved included attention,

Figure 3. Regionalized NMDAR Activity Determines Cell Fate[a]



[a]Reprinted with permission from Wang and Reddy.[19] Glutamate activates extrasynaptic NMDARs that overcome synaptic NMDAR-mediated survival signaling, leading to neuronal death.
Abbreviation: NMDAR = *N*-methyl-D-aspartate receptor.

thinking, memory, praxis, language comprehension, and communication.[29]

ChEIs include donepezil, rivastigmine, and galantamine and are typically the first-line therapy for mild to advanced dementia. Side effects can include gastrointestinal issues and dizziness and, less commonly, muscle cramping, rhinorrhea, or bradycardia.[30] ChEIs exacerbate urinary incontinence, but because these side effects are dose-related, slow up-titration to the desired maintenance dose can mitigate them. Different formulations of ChEIs allow for switching between them to address side effects.[30] No current evidence supports the use of more than 1 ChEI at a time, and the risk of side effects increases.

NMDA antagonists. The partial *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine is a potentially neuroprotective agent, unlike ChEIs.[29] Memantine targets the neurochemical glutamate, the principal excitatory amino acid neurotransmitter in cortical and hippocampal neurons. Glutamate activates the NMDA receptor, which is involved in learning and memory.[19] Excessive stimulation of the NMDA receptor can lead to excitotoxicity. It is suggested that agents like memantine block these pathological stimulations or overstimulations, which may protect against additional neuronal atrophy[19] (Figure 3).

Memantine appears to benefit individuals in the moderate to severe stages more effectively. It has shown significant benefit on cognition, function, language, and ADL, as well as behaviors and global state,[31] particularly when combined with a ChEI such as donepezil. Several trials have shown little to no improvement in mild Alzheimer disease or MCI.[32] However, there may be a subset of patients who could potentially benefit. Clinical specialists like Dr Burke have seen improvements in mood, focus, and engagement. Memantine is well tolerated[31] but can cause dizziness, headaches,[30] and in certain cases confusion or agitation.[33]

Disease-Modifying Treatments

Instead of targeting neurotransmitters, disease-modifying therapies target factors that lead to neuronal atrophy and therefore brain cell death. Reducing neuronal degeneration has the potential to slow damage to the brain and therefore slow disease and symptom onset and progression.

Aducanumab is the first FDA-approved disease-modifying therapy to treat mild Alzheimer disease or MCI.[34,35] Amyloid buildup in the brain can draw in reactive cells and is involved in inflammation and the full cascade that leads to neuronal atrophy. Aducanumab is a recombinant monoclonal antibody directed against amyloid β, dissolving and therefore eliminating it from the brain.[36]

In June 2021, aducanumab was granted an accelerated approval pathway from the FDA based on its effects on a surrogate endpoint of reducing amyloid β plaques on the brain but not on an endpoint of improving cognition. The FDA has required additional studies to show clinical efficacy and safety within 9 years.[35] However, in April 2022, Centers for Medicare & Medicaid Services voted to deny coverage for antiamyloid monoclonal antibody treatments for Alzheimer disease that pursued that accelerated approval pathway and/or until there is greater evidence of clinically meaningful benefit.[37] Since then, other antiamyloid monoclonal antibody treatments for AD have been granted access to the FDA accelerated approval pathway, including lecanemab and donanemab.

Aducanumab appropriate use recommendations were published to provide more comprehensive guidance to prescribing clinicians.[8,38] The expert group defined eligible patients, including individuals with MCI or mild dementia, and testing cutoffs such as MMSE ≥ 21, MoCA ≥ 17, or CDR 0.5 to 1. Only those with confirmed amyloid plaque should be considered. Patients with contraindications like Lewy body disease or vascular dementia and patients with Down syndrome should not be treated with aducanumab. Populations at high risk for hemorrhagic side effects also should not be offered aducanumab.[8,37]

Most patients in clinical trials tolerated aducanumab well; however, 40% developed amyloid-related imaging abnormalities (ARIA), either ARIA-E—vasogenic edema—or ARIA-H, essentially microhemorrhages. The symptoms resolved once treatment stopped in the majority of patients, and when treatment was restarted, only 10% had more than 1 ARIA event.[34]

It was found that the genetic presence of 1 or 2 copies of apolipoprotein epsilon 4 (ApoE ε4) puts patients at greater risk for developing ARIA-H or ARIA-E, so clinicians are instructed to discuss the risk with patients and then test for

this allele prior to starting a patient on this medication.[8]

Dr Burke closed her session with a discussion with Dr Goldfarb, offering a summary of the care required for diagnosing Alzheimer disease early. Considering the revolution that detecting the disease even several years before cognitive symptoms occur offers, this provides a window of opportunity to prevent Alzheimer disease from becoming symptomatic.

Primary care providers make up the majority of clinicians who diagnose Alzheimer disease, so it is important for specialists such as Dr Burke and Dr Goldfarb to support these health care providers with the proper tools for early diagnosis and treatment. This includes the delivery of personalized medicine, learning about the individual and their family and infusing treatment plans with what is important to them. A partnered approach creates buy-in to the recommended pharmacologic and lifestyle changes. Recognizing and addressing problems with health equity should also be included as an area of focus moving forward.

"If you put all of us as cognitive disorder specialists together around the country, we're able to cover maybe 10% of the dementia population," Dr Burke said. "Supporting our primary care colleagues with appropriate tools to help them diagnose and manage patients in that setting is going to be key. It will really need to be one of the areas of focus of our advocacy."

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Clinical Points

- With the presence of new technologies in the arena of dementia, it is now possible to detect amyloid deposits in the brain up to 20 years before cognitive symptoms manifest, offering a window of opportunity to diagnose Alzheimer disease early.
- New therapies available now and in the future can slow the progression of Alzheimer disease or improve symptoms.
- The majority of care for patients with Alzheimer disease takes place in the primary care setting, so partnering with dementia specialists is key to delivering personalized treatment.

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1. **What is one of the methods used to detect the newly added preclinical stage of Alzheimer disease in patients?**
   a. Identifying changes in the brain with neuroimaging techniques
   b. Detecting cognitive changes that are impacting the patient's life
   c. Conducting a Mini Mental State Examination (MMSE)
   d. Conducting a Montreal Cognitive Assessment (MoCA)
2. **Aducanumab can be considered for patients in which stage of Alzheimer disease?**
   a. Severe dementia
   b. Mild cognitive impairment
   c. MMSE scores of 11 to 17
   d. MoCA scores below 10
3. **Which of the following targets neurochemical glutamate and is a potentially neuroprotective agent?**
   a. Aducanumab
   b. Memantine
   c. Galantamine
   d. Rivastigmine
4. **Diana and her mother, Louise, a 71-year-old female, inform you that Louise has been experiencing episodic memory problems and irritability in mood. What is your next step?**
   a. Diagnose her with Lewy body disease
   b. Run a PET scan to detect amyloid or tau
   c. Prescribe aducanumab to target amyloid beta
5. **71-year-old Louise also discusses with you that she has been having episodes of leaving the stovetop on, leaving the refrigerator door open, and other difficulty in the kitchen, as well as anxiety and agitation, which is confirmed by her daughter, Diana. Which medication would best be suited for Louise?**
   a. Memantine
   b. Aducanumab
   c. Quetiapine
   d. Aducanumab plus memantine
   e. Aducanumab plus quetiapine

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