AJMC® SUPPLEMENT
THE AMERICAN JOURNAL OF MANAGED CARE®

August 2020
Vol. 26 • No. 8, Sup.

Addressing Unmet Needs in Alzheimer Disease: Implications of Delayed Diagnosis and Examining New and Emerging Therapies

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

Addressing Unmet Needs in Alzheimer Disease: Implications of Delayed Diagnosis and Examining New and Emerging Therapies

Release date: August 7, 2020

Expiration date: August 7, 2021

Estimated time to complete activity: 2.5 hours

Type of activity: Application

Medium: Print with internet-based posttest, evaluation, and request for credit

Fee: Free

This activity is supported by an educational grant from Biogen.

Intended Audience

Pharmacists and managed care professionals

Activity Overview

Alzheimer disease (AD) is the sixth leading cause of death and the most common etiology for dementia. It causes a significant burden to the public health system, patients afflicted with it, and their caregivers. Continuing professional education will increase competency on AD, including the importance of early detection, patient and caregiver education, and the role of new therapeutic targets for the treatment of AD. Application of knowledge will improve clinical decision making, improve quality of life among patients and caregivers, optimize medication therapy, improve outcomes, and decrease costs associated with the treatment of AD.

Statement of Educational Need

Alzheimer disease requires a multispecialty approach to diagnosis and treatment. The estimated cost of Alzheimer disease includes direct medical, indirect, and social care costs. Early diagnosis can improve quality of life for both patients and caregivers. Continuing education on the importance of early diagnosis, current and emerging therapies, and the societal and economic burden of Alzheimer disease will help managed care professionals provide timely and appropriate care to patients.

Educational Objectives

Upon completion of this activity, participants should be able to:

- Explore the impact of Alzheimer disease as it relates to progression, value of early diagnosis, associated comorbidities, and effect on patients and caregivers.
- Analyze current and emerging data for new therapeutic targets for the pharmacologic treatment of Alzheimer disease.
- Examine the importance of medication therapy management and drug utilization reviews for controlling costs and improving outcomes among patients with Alzheimer disease.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will increase their knowledge of the burden of Alzheimer disease, current and emerging therapies, and managed care considerations.

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REPORT

Current and Evolving Treatment Strategies for the Alzheimer Disease Continuum

Richard A. Marasco, BS Pharm, FASCP, BCGP, HRM

Introduction

Alzheimer disease (AD) is the most common cause of dementia, accounting for 60% to 80% of cases.[1] It is a heterogeneous and complex disease that is challenging to differentiate from other forms of dementia, such as vascular dementia, dementia with Lewy bodies, mixed dementia, and frontotemporal dementia. Understanding of AD has evolved over the past 35 years. Before 2011, it was a clinical diagnosis that could only be confirmed by an autopsy.[2] Then, diagnostic criteria were revised to allow a premortem diagnosis based on biomarkers.[3,4] Now, AD is considered to be a long, degenerative process with a preclinical stage in which β-amyloid (Aβ) and tau biomarkers are present while cognition is normal, followed by neurodegeneration and a prodrome of mild cognitive impairment (MCI), which can progress to clinical AD.[5]

Drug therapy that changes the progression of the disease is arguably the greatest unmet need of patients with AD. Despite investing billions of dollars into clinical trials, a new AD drug has not been approved by the FDA since 2003.[6,7] Drugs approved before that do not slow the progression of the disease.[8] In addition, no drugs have been approved to treat MCI.[9] As of May 2020, more than 100 new molecular entities were in clinical development for AD.[10] Although many AD drugs have failed in late-stage clinical trials, there is hope that at least one may receive FDA approval soon. This article explores the current state of biomarker-driven drug development across the AD continuum and reviews current and emerging disease-modifying treatments for AD.

The Epidemiologic Burden of AD

The estimated number of Americans with preclinical AD based on evidence of brain Aβ is expected to rise from almost 47 million in 2017 to over 75 million by 2060.[11] Modeling studies estimate that about 35% of people older than 60 years have preclinical AD.[2] Because the mean time from Aβ appearance to dementia is estimated at more than 20 years, some people are likely to die of other causes before developing AD.[2,12] The lifetime risk of developing AD varies according to age and disease state. For example, the lifetime risk for a 75-year-old woman is approximately 14% with no evidence

ABSTRACT

The burden of Alzheimer disease (AD) on the US healthcare system is substantial and increasing. AD progresses along a continuum from preclinical disease characterized by normal cognition and abnormal brain biomarkers to mild cognitive impairment and then clinically apparent dementia. Diagnosis early in the AD continuum has benefits for patients and caregivers and appears cost-effective, but often, the clinical diagnosis of AD may be delayed. Currently available biomarkers include β-amyloid positron emission tomography and cerebrospinal fluid tests. Collectively, they are expensive, may lead to adverse effects, are not widely available, and are not suited for primary care. Currently available treatment options, cholinesterase inhibitors and memantine, do not alter disease progression, but can help with some symptoms. Benefits of currently available treatments on cognition are difficult to quantify and are offset by a burden of adverse effects that often go unrecognized. More accurate diagnostic biomarkers and disease-modifying drug therapies are critical unmet needs of patients with AD despite decades of clinical research. Because many phase 3 clinical trials that enrolled patients with symptomatic AD have failed, researchers believe that disease-modifying treatment is more likely to demonstrate benefit when utilized early in the disease continuum. Within the past few years, significant achievements that will advance clinical trials in early AD include the Research Framework to define and stage the AD continuum, FDA guidance on study design in early AD, and development of scales to measure cognition that are suitable for early AD. In October 2019, the AD community was re-invigorated by unexpected news that a Biologics License Application will be submitted for aducanumab to treat AD. This article explores the current state of biomarker-driven drug development across the AD continuum and reviews investigational drugs in phase 2/3 clinical development for AD.

***Am J Manag Care*. 2020;26:S167-S176**

For author information and disclosures, see end of text.

of AD pathology, 24% with Aβ, 36% with Aβ and neurodegeneration; and 85% with Aβ, neurodegeneration, and MCI.[12] About 15 million Americans are estimated to have MCI.[13] The prevalence of MCI increases with age, with estimates of 6.7% for ages 60-64 years, 8.4% for 65-69 years, 10.2% for 70-74 years, 14.8% for 75-79 years, 25.2% for 80-84 years, and 37.6% for 85 years and older.[9]

Approximately 10% of Americans aged 65 years or older have AD.[1] Among almost 6 million Americans 65 years or older living with AD, 80% are 75 years or older and more than 60% are women. Prevalence increases progressively with age, with AD estimates of 3% for ages 65-74, 17% for ages 75-84, and 32% for 85 years and older. By 2050, the number of Americans with AD is expected to rise to almost 14 million. The total annual cost of healthcare of patients with dementia, including long-term care and hospice, is projected to increase nearly 4-fold from $305 billion in 2020 to more than $1.1 trillion in 2050.[1] A recent Centers for Disease Control and Prevention study identified 2 key factors that account for the rising prevalence of AD and other forms of dementia in the United States: a doubling in the number of Americans 65 years or older by 2060 and faster growth in minority elder populations who are disproportionately affected by dementia.[14] In 2020, approximately 491,000 Americans 65 years or older are expected to receive an AD diagnosis and 700,000 are expected to die with AD. AD is the fifth leading cause of death in Americans aged 65 years or older.[1]

The AD Continuum

Pathophysiology. AD is characterized by brain tissue abnormalities that are both diagnostic biomarkers and targets for drug development: accumulation of Aβ plaques and oligomers outside of neurons and twisted strands of tau proteins inside neurons.[1,6] In theory, Aβ accumulation contributes to neurodegeneration by interfering with neuron-to-neuron synaptic communication, whereas tau tangles may block the transport of nutrients and other essential molecules within neurons. In addition, Aβ and tau tangles may trigger microglia, which induce inflammation and are associated with abnormal glucose metabolism.[15] AD is associated with distinct abnormalities in glycolysis, the main route of glucose metabolism in the brain.[16] Impaired glycolysis has been correlated with more severe Aβ plaque and tau tangles postmortem.[17]

In 2018, the National Institute on Aging and Alzheimer's Association developed the Alzheimer's Diagnostic Framework to define and classify the AD continuum and distinguish it from non-AD causes of cognitive impairment based on biomarker criteria.[5] The hallmark biomarkers of AD pathology—extracellular deposition of Aβ ("A"), intracellular tau tangles ("T"), and neurodegeneration ("N")—were integrated into the "A/T/N" classification scheme to categorize subjects in AD clinical trials. The preclinical phase of the disease after Aβ deposition is classified as A+T-N-, and the transition to prodromal disease and dementia is characterized by the addition of T and N. Patients with dementia symptoms, tangles, and neurodegeneration biomarkers are classified as A+T+N- or A+T-N+.[5]

Apolipoprotein E (APOE) is a susceptibility gene for AD. The APOE4 allele is linked to a higher risk of AD, while the APOE2 allele is associated with a lower risk of AD. In a recent case-control study in more than 5000 people, the odds ratio for developing AD with the APOE2/2 genotype was 66% less than the APOE2/3 genotype, 87% less than the APOE3/3 genotype, and 99.6% less than the APOE4/4 genotype.[18] Because the relative risk conferred by APOE is impacted by gender and other genetic and environmental factors, the APOE4 allele is neither necessary nor sufficient to cause AD. APOE genotyping for AD risk prediction is not recommended because of limited clinical utility and poor predictive value.[19] The APOE allele is a consideration in clinical trials of monoclonal antibodies and other drugs that target Aβ plaque because they can cause amyloid-related imaging abnormalities (ARIA) that can be accompanied by adverse effects (AEs).[20,21]

Disease course. AD progresses along a continuum with 3 phases: preclinical disease, MCI, and clinically apparent dementia.[1,5,22] Although both cognitive decline and biomarker measurements progress over time, biomarker progression begins before symptom onset.[5]

Preclinical AD. The preclinical phase of the AD continuum is characterized by Aβ pathology that can be detected by neuroimaging and cerebrospinal fluid (CSF) biomarkers in individuals who are not cognitively impaired.[5] In longitudinal observational studies, brain accumulation of Aβ in cognitively normal individuals has been linked to a greater risk of progression to MCI and dementia.[23-25] Although preclinical AD is considered asymptomatic, screening data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) Study recently showed that participants with elevated Aβ had lower Preclinical Alzheimer Cognitive Composite scores and more reports of subtle recent declines in daily cognitive function.[26] It is important to bear in mind that the presence of Aβ plaque does not necessarily predict the development of dementia.[1]

MCI. In addition to the presence of biomarkers, patients with MCI have subtle problems with memory and thinking that may not be readily apparent or interfere with the ability to perform activities of daily living (ADLs).[1] MCI can improve, remain stable, or progress to AD or other conditions. In observational studies, 32% to 38% of patients with MCI progressed to dementia over 5 years of follow-up.[27,28] The American Academy of Neurology recommends evaluating patients for MCI if they or a close contact raise concerns about memory or impaired cognition.[9] Early diagnosis gives patients and significant others more time to address finances and estate planning, take steps to prevent exploitation, plan for care, and address driving safety issues.[29] Early diagnosis can also improve healthcare delivery.[29] For example, patients may need help from a family member and written instructions to maintain medication adherence. Color-coded weekly or monthly adherence packaging prepared by the pharmacy

can also help. Drugs with cognitive AEs that can exacerbate MCI can be avoided. Patients with MCI should be periodically monitored for changes in cognitive status.[9] Documenting the diagnosis in health records alerts other clinicians and may reduce mismanagement.

Alzheimer dementia. AD severity is characterized as mild, moderate, or severe based primarily on the ability to perform ADLs. In mild disease, most patients are able to function independently but are likely to require assistance. These patients may still be able to drive and work. In moderate AD, patients may have difficulties communicating and performing ADLs, such as bathing and dressing. They may exhibit personality and behavior changes. In severe AD, patients need substantial assistance with ADLs and likely require around-the-clock care. These patients may become bedridden due to damage to areas of the brain involved in movement. They may have difficulty swallowing, which can lead to aspiration pneumonia, a contributing cause of death among many patients with AD. In people aged 65 years or older who receive a diagnosis of AD, mean survival is 4 to 8 years, but can reach 20 years.[1] A person living with AD between age 70 and 80 years is expected to have severe dementia for 4 years and reside in a nursing home for most of that time.[1] About 40% of patients with AD have severe dementia that requires care on par with that provided in a nursing home.[11]

Diagnosis

Despite the need for early and accurate diagnosis, an estimated 29% to 76% of patients with dementia in primary care are undiagnosed.[30] Clinical criteria for AD include a history of cognitive decline with a gradual onset and progressive course, exclusion of other causes, and documented cognitive impairment in at least one domain (complex attention, executive function, learning and memory, language, perceptual motor function, and social cognition).[1] The diagnosis should be based on a thorough cognitive and neurologic examination and ideally should include history from close contacts about the patient's cognitive status.[1] The diagnostic evaluation may also include blood tests and magnetic resonance imaging to document neurodegeneration and rule out other forms of dementia and neurodegenerative diseases. Batteries of neuropsychological testing may have value, including to distinguish between dementia subtypes, but they are time consuming and may not be widely available.[31]

Although it has been part of the Medicare Annual Wellness Visit since 2011, a recent Alzheimer's Association survey found that just 47% of primary care physicians routinely assess older patients for cognitive impairment.[1] Evaluation should include direct observation of cognitive function and may include a brief validated, structured cognitive assessment tool. A positive cognitive screening test should lead to additional diagnostic testing to confirm the diagnosis and determine the dementia subtype.[30] Of note, a 2020 US Preventive Services Task Force panel found insufficient evidence to recommend for or against routine cognitive impairment screening in asymptomatic community-dwelling adults 65 years old and older.[30]

Cognitive screening tests. Many standardized mental status scales are used to document the presence and progression of dementia, including the Montreal Cognitive Assessment and the Mini-Mental State Examination (MMSE). Although these scales can accurately differentiate clinically apparent Alzheimer-type disease (CATD) from normal cognition, they are less accurate in distinguishing mild CATD versus normal cognition and CATD versus MCI.[32]

Biomarkers. More accurate diagnostic biomarkers are a critical unmet need because 15% to 30% of patients with CATD do not meet postmortem diagnostic criteria for AD.[1] Current diagnostic biomarkers that differentiate AD from other forms of dementia include brain imaging and CSF biomarkers. FDA-approved Aβ positron emission tomography (PET) scanning agents include florbetapir, flutemetamol, and florbetaben. The Alzheimer's Association and Society of Nuclear Medicine and Molecular Imaging recommend use by dementia experts evaluating patients with cognitive impairment if scan results will improve diagnostic certainty and alter the treatment plan.[33] A recent Agency for Healthcare Research and Quality systematic review found that Aβ PET was highly sensitive and specific for Aβ pathology of AD and may increase classification accuracy.[31] In clinical trials evaluating disease-modifying drugs for AD, biomarkers play a crucial role in identifying eligible patients and contribute to the high cost of AD clinical trials. The out-of-pocket cost per scan is at least $3000.[34] Although commercial insurance coverage varies, Medicare does not cover them unless they are conducted as part of a clinical trial assessing whether Aβ imaging improves patient outcomes or advances patient treatment options.[34]

The Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study is evaluating whether Aβ PET scanning affects the management and outcomes of dementia care in Medicare beneficiaries.[35] In the initial phase of the study, physicians changed treatment based on scan results in greater than 60% of patients. More than a third of patients who were presumed to have AD had a negative PET scan, whereas more than half of patients presumed not to have AD had a positive PET scan. In patients with a positive PET scan, AD drug prescribing increased from 40% to 82% in patients with MCI (P <.001), although no drug has established efficacy to treat MCI.[9] Prescribing increased from 63% to 91% in patients with dementia (P <.001). AD drug prescribing decreased modestly in patients with a negative scan.[35]

The first diagnostic imaging agent that identifies AD-associated tau pathology may be available soon. The FDA is considering approval of flortaucipir, a PET scanning tracer that binds with tau tangles.[36] In a phase 3 postmortem validation study, it had sensitivity of 92% to 100% and specificity of 52% to 92% for predicting tau pathology.[37]

PET and CSF biomarkers for Aβ are invasive, expensive, time consuming, cause AEs, and are not widely available.[13,34] Biomarkers in clinical development may address these limitations. For example, a blood test for plasma phosphorylated-tau181 predicted tau and Aβ pathologies, identified AD across the clinical continuum, and differentiated it from other neurodegenerative diseases in validation studies.[38,39]

AD Management Considerations

Public health burden. AD is a substantial public health burden because patients are disabled and dependent on others for care for a substantial portion of the disease.[1] The disease burden of AD has increased dramatically in the United States over the past few decades. Disability-adjusted life-years (DALYs), the primary measure of disease burden, are calculated by adding the number of years of life lost due to premature mortality (YLLs) and the number of years lived with disability (YLDs) caused by a disease. Based on DALYs, AD rose in the ranking of burdensome diseases from twelfth in 1990 to sixth in 2016. In 2016, it ranked fourth for YLLs and nineteenth for YLDs.[1]

Value of early diagnosis. A recent study commissioned by the Alzheimer's Association estimated the potential cost savings of early diagnosis.[1] Diagnosis in the MCI phase rather than in the dementia phase or not at all could save approximately $7 trillion in medical and long-term care costs. Cost savings would accrue from a lower cost to diagnose MCI versus dementia and lower medical and long-term care costs for diagnosed and managed MCI and dementia versus unmanaged MCI and dementia.[1] Unfortunately, many barriers exist to early diagnosis of MCI in primary care, including a lack of assessment tools, training, time, and infrastructure.[40]

Comorbidities. Medicare beneficiaries with dementia have a higher rate of comorbidities than those without dementia.[1] For example, the prevalence of more than 5 chronic conditions is 26% and 4%, respectively. In 2014, among Medicare beneficiaries with dementia, 38% had comorbid coronary artery disease, 37% had diabetes, 29% had chronic kidney disease, 28% had congestive heart failure, and 25% had chronic obstructive pulmonary disease.[1]

Caregiver burden. As the US population ages, the proportion of younger adults available to provide care for patients with AD is expected to decline.[14] Whereas the ratio of potential younger caregivers to older high-risk adults is currently 7 to 1, it is expected to decline to 4 to 1 by 2030. Negative impacts on caregivers include greater work instability, lower household income and personal savings, increased food insecurity, and less personal medical care. This leads to caregiver health problems, higher rates of depression and psychological stress, and even a higher risk of mortality.[1,14] In 2017, Medicare implemented a billing code to reimburse services related to care planning and coordination for patients with cognitive impairment and their caregivers. This is intended to provide greater caregiver support.[1]

The COVID-19 pandemic has created a cascade of negative effects for patients with dementia and their caregivers. It has amplified the burden of caregiving for patients with dementia. Mortality from COVID-19 is extremely high in patients with dementia due to advanced age, comorbidities, and difficulty complying with safeguarding procedures such as wearing masks, handwashing, and social distancing.[41,42] COVID-19 outbreaks in nursing homes have high attack and case fatality rates.[42,43] Whereas nursing home residents and workers account for 11% of COVID-19 cases in the United States, they account for 35% of deaths.[43] Given this risk, facilities have implemented numerous restrictions. For patients who are cared for at home, social distancing measures and the loss of in-home health aides and adult day care has placed the entire burden of caregiving on immediate family members.[41] Caregivers, whether at home or in nursing homes, are experiencing extreme stress and social isolation during the pandemic.[41,42]

Current Management of the AD Continuum

Patients on the AD continuum often take medications that impair cognition and may accelerate the disease trajectory, including benzodiazepines, anticholinergics, and other psychotropic drugs.[44-46] Because "Do no harm" is a guiding precept in elder care, avoiding these drugs is a crucial strategy to preserve cognition.[47] The Beers list of potentially inappropriate medications acts as a guide to avoiding harmful prescribing in patients with AD.[48] Given that medication nonadherence is endemic in patients with AD, it is important to simplify drug regimens and deprescribe unnecessary drugs.[49] Factors linked to medical nonadherence in patients with dementia include taking more than 4 drugs, use of an anticholinergic, and a pill burden.[49] Caregivers should receive medication management support, with periodic reassessment of the patient's medication needs as AD progresses.[50] A randomized clinical trial is currently evaluating whether deprescribing inappropriate medications and optimizing medication regimens can delay the onset of symptomatic AD and other forms of dementia.[51]

Nonpharmacologic management of AD. A few nondrug modalities have been shown to improve cognition in patients with AD. Exercise has positive effects on cognitive function, and may even slow the rate of cognitive decline in patients with AD.[1] Cognitive stimulation has been found to improve cognitive function, depression, anxiety and quality of life (QOL) in patients with AD. Cognitive training may improve overall cognition that may last for at least a few months in patients with mild to moderate dementia.[1] Nondrug modalities also play an important role in reducing behavioral symptoms, such as sleep disturbances, wandering, depression, agitation, and aggression. Nonpharmacologic interventions for agitation and aggression avoid the potential harms of antipsychotics and may outperform pharmacologic approaches. For example, outdoor activities were found to be more efficacious than antipsychotics

for managing physical aggression.[52] Other beneficial modalities for agitation include multidisciplinary care planning, pet therapy, music, and massage.[52]

Pharmacologic management of AD. As shown in Table 1, FDA-approved drugs for AD include cholinesterase inhibitors and memantine.[53] Cholinesterase inhibitors increase levels of the neurotransmitter acetylcholine while memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that affects glutamatergic transmission. Memantine is used alone or in combination with a cholinesterase inhibitor. Each of these medications is taken orally, once or twice daily. Rivastigmine is also available as a transdermal patch that is applied once daily.[53]

Cholinesterase inhibitors and memantine do not change the progression of AD. In the 1-year AD2000 clinical trial, donepezil demonstrated slight improvements in cognition and function, but failed to delay institutionalization, reduce caregiver burden, or lower costs.[54] Results of a recent Cochrane review of donepezil trials showed a mean reduction of -2.7 points on the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog, range 0-70), but no benefit for behavioral symptoms, QOL, or total healthcare resource utilization.[55] This falls below the 4-point difference on the ADAS-Cog that is generally recognized as clinically meaningful.[56] AEs with donepezil were dose related. In particular, donepezil 23 mg/day did not improve cognitive function more than 10 mg/day, but increased the risk of AEs and premature treatment discontinuation.[55] In another recent Cochrane review, memantine demonstrated a small clinical benefit versus placebo in patients with moderate to severe AD, but had no benefit in patients with mild AD.[57]

In a systematic review that excluded clinical trials with a high risk of bias, cholinesterase inhibitors and memantine slightly reduced short-term cognitive decline.[8] It was unclear if these effects are clinically meaningful. Cholinesterase inhibitors had a small mean improvement in cognition with a median standardized mean difference (SMD) of 0.30 (range, 0.24, 0.52). For function, effects ranged from no difference to a small improvement, with a median SMD of 0.19 (range, -0.10-0.22). Memantine did not demonstrate any benefit in patients with mild to moderate CATD. In moderate to severe CATD, insufficient to low-strength evidence inconsistently suggested that adding memantine to a cholinesterase inhibitor improved cognition, but not function.[8]

As part of the Choose Wisely initiative, the American Geriatrics Society recommends against prescribing cholinesterase inhibitors unless cognitive benefits and gastrointestinal AEs are monitored.[58] A cholinesterase inhibitor should be stopped after 12 weeks if improvements are not observed on practical treatment outcomes reflecting stabilization of cognition that can be easily assessed. Patients and caregivers should be counseled about AEs before beginning a trial of cholinesterase inhibitors. Deprescribing of cholinesterase inhibitors has been linked to a reduction in falls and fractures, but not an increase in the risk of aggressive behaviors and antipsychotic prescribing in nursing home residents with severe dementia.[59,60] Cholinesterase inhibitor AEs are often unrecognized and lead to a "prescribing cascade" that contributes to a treatment burden in patients with AD. For example, observational studies have found that patients receiving a cholinesterase inhibitor had an increased risk of receiving an anticholinergic drug to manage urinary incontinence, which is likely caused or exacerbated by the cholinesterase inhibitor.[61,62]

Treatment Landscape of Emerging Agents for the AD Continuum

Since 2007, more than 50 drugs have failed in phase 3 clinical trials for AD.[63] This includes Aβ-targeting agents (bapineuzumab, crenezumab, semagacestat, solanezumab), β-secretase inhibitors (elenbecestat, lanabecestat, umibecestat, verubecestat), intravenous immunoglobulin, aspirin, ginkgo biloba, idalopirdine, minocycline,

TABLE 1. FDA-approved Drugs for Alzheimer Disease[53]

Drug	AD Indications	Dosing	Common Adverse Effects
Donepezil (Aricept)	All stages	Once daily in the evening	Nausea, vomiting diarrhea, urinary incontinence, vivid dreams, bradycardia, syncope
Galantamine (Razadyne)	Mild to moderate	Tablets: twice daily Extended release capsules: once daily	Nausea, vomiting, diarrhea, dizziness, anorexia, weight loss, bradycardia, syncope
Rivastigmine (Exelon Patch)	All stages	Capsules: twice daily Patches: applied once daily	Oral: nausea, vomiting, diarrhea. Patch: gastrointestinal adverse effects less frequent. Bradycardia, syncope with oral or patch
Memantine (Namenda and Namenda XR)	Moderate to severe	Once daily	Generally, well tolerated; can cause dizziness, confusion, agitation, insomnia, hallucinations, delusions
Memantine + donepezil (Namzaric)	Moderate to severe	Once daily in the evening	See components

nivaldipine, pioglitazone, and others.[6,64-77] Because these failed studies enrolled patients with symptomatic AD, many researchers now believe that clinical trials of disease-modifying drugs should be conducted much earlier, either during the preclinical or MCI phases of the AD continuum.[1] In 2018, the FDA published a draft guidance for drug development in early AD that aligns with this thinking.[78] As shown in **Table 2**, it does away with the preclinical/prodromal definition in favor of 3 stages leading to early AD.[78] It now refers to a "persistent effect on disease course" instead of a disease-modifying effect.[79]

Many factors may have contributed to the high failure rate of AD phase 3 trials. Because AD is a heterogeneous disease, the inaccuracy of disease biomarkers is a likely factor.[7] In hindsight, some trials may have failed because dose response was poorly understood.[80] Now experts assert that before advancing to phase 3 trials, a drug should demonstrate sufficient brain exposure, strong evidence of target engagement, a clear dose response, and a large effect size in phase 2 trials.[21,80,81] Target engagement is a hot-button issue for investigational anti-Aβ monoclonal antibodies. Some experts theorize that some have failed because they target amyloid monomers or insoluble fibrils or plaques rather than soluble Aβ oligomers, which may be a key mediator of neurodegeneration.[21] Coprimary study end points of cognition and function that were required by the FDA may have also contributed by setting an unachievable standard for efficacy.[7] The draft guidance now suggests an AD biomarker and a cognitive or functional end point could be used to demonstrate efficacy in the earliest stages of AD (FDA stage 1 and 2).[7] It also signals that the agency is willing to grant accelerated approval based on biomarker data with a requirement that a confirmatory clinical trial demonstrates a delay in symptom onset.[7]

Up to now, clinical trials have used the ADAS-cog as an efficacy end point, but it is not very sensitive or reliable in mild dementia.[7] For patients in FDA stage 3 criteria (MCI), the draft guidance suggests an integrated scale that assesses both function and cognitive effects could serve as a single primary efficacy end point. New instruments, such as the integrated AD rating scale or AD Composite Score (ADCOMS), combine cognitive and functional outcomes. ADCOMS combines portions of the ADAS-cog, Clinical Dementia Rating (CDR) scale, and MMSE that have been shown to change the most over time in people who do not have functional impairment yet.[7] As of May 2020, there were 13 drugs in phase 2/3 clinical development for AD.[10,82] They target Aβ, tau, inflammation, neuroprotection, and metabolism.[75]

Aβ-Targeting Investigational Drugs

Aducanumab. This fully-human IgG1 monoclonal antibody binds selectively to aggregated Aβ fibrils and soluble oligomers.[83,84] In March 2019, after an interim futility analysis predicted the phase 3 placebo-controlled EMERGE and ENGAGE trials would not meet their primary end points, the termination of all aducanumab clinical trials was announced. However, in a subsequent analysis of a larger data set from the EMERGE trial, aducanumab met the primary end point, the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score after 18 months of treatment.[85] The highest dose (10 mg/kg) demonstrated a 23% reduction in the CDR-SB ($P = .01$). This translates to an absolute change of –0.4 on an 18-point scale. The high-dose group also declined less on secondary end points, including the ADAS-Cog (–27%; $P = .01$) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL-MCI; –40%; $P = .001$). Although the ENGAGE trial did not meet the primary end point, an exploratory analysis suggested slower decline in patients who received at least 10 doses of the highest aducanumab dose. In sub-studies of EMERGE and ENGAGE, aducanumab caused a dose-dependent reduction in Aβ and some reduction in CSF phosphorylated-tau.[85]

Amyloid-related imaging abnormalities-edema (ARIA-E), the most common AE with aducanumab, occurred in 35% of patients; 74% of cases were asymptomatic and episodes generally resolved within 4 to 16 weeks.[85] In the EMERGE trial, the rate of permanent treatment discontinuation for an AE was 2.9% with placebo versus 7.7% with low-dose and 8.8% with high-dose aducanumab.[86] Respective discontinuation rates because of ARIA were 0.2%, 4.6%, and 6.6%.[86]

What accounts for these divergent results? The initial analysis included about half as many patients as the final data set and was limited to patients who had completed the study by the end of 2018. These patients, early enrollers in the studies, had lower mean aducanumab exposure. The futility analysis was not adjusted to consider the effect of 2 late protocol amendments that led to more patients receiving the highest dose of aducanumab later in the study.[87] Specifically, these protocol amendments increased the dose in APOE4 carriers who are more susceptible to ARIA after data from other studies suggested ARIA is manageable and usually resolves without sequelae. In early July 2020, the manufacturer completed

TABLE 2. FDA-Proposed Stages of Early AD[78]

Stage 1	Stage 2	Stage 3: MCI	Stage 4: Mild Dementia
• AD biomarkers present • No observable cognitive or functional impairment	• Early cognitive decline • No functional impairment on ADLs	• Cognitive decline • Mild detectable functional impairment	• Demonstrable cognitive decline • Demonstrable functional impairment

AD, Alzheimer disease; ADL, activity of daily living; MCI, mild cognitive impairment.

its submission of a Biologics License Application for aducanumab as a treatment for AD.[88,89]

BAN2401. This humanized monoclonal antibody has greater affinity for soluble Aβ protofibrils (ie, large amyloid oligomers) than insoluble fibrils or plaques.[20] In Study 201, a phase 2b trial, there was a significant dose-dependent reduction in Aβ PET burden across all doses in 856 patients with MCI or early AD. At 18 months, 81% of participants on the highest dose had Aβ-negative scans. There was a dose-dependent reduction in cognitive decline on the ADCOMS, starting at 6 months. The highest dose had a 30% reduction in the ADCOM versus placebo (P = .034). Dose-related ARIA-E occurred in fewer than 10% of patients and was more frequent in APOE4-positive patients. It generally occurred within the first 3 months of treatment, resolved within 4 to 12 weeks, and caused headache or confusion in about 10% of cases.[20]

Based on Study 201 results, the phase 3 CLARITY trial is examining BAN2401 in more than 1500 patients with MCI due to AD or mild AD with confirmed Aβ pathology.[90] In this study, BAN2401 will be given at a dose of 10 mg/kg every other week. The primary end point is the change from baseline in the CDR-SB after 18 months of treatment. Initial results are expected in 2022.[90] BAN2401 is also being evaluated for the prevention of AD in the placebo-controlled phase 3 AHEAD 3-45 trial.[91,92] The trial consists of 2 sub-studies: A3 and A45. The A3 sub-study will evaluate low-dose BAN2401 in cognitively normal individuals who are currently below the threshold for Aβ elevation on Aβ PET scanning but are at high risk for further Aβ accumulation. The A45 sub-study will evaluate high-dose BAN2401 in clinically normal participants (ie, little to no cognitive impairment) with elevated levels of Aβ and are at high risk for progression to MCI and AD dementia.[91,92]

Gantenerumab. This IgG1 human monoclonal antibody binds to aggregated forms of Aβ and has been shown to reduce the burden of Aβ plaque in patients with AD.[63,93] Two ongoing phase 3 clinical trials, GRADUATE 1 and 2, are assessing subcutaneous (SC) gantenerumab for the treatment of early AD in more than 2000 patients. Gantenerumab is the only anti-Aβ agent in late-stage clinical trials that is administered by SC injection. In February 2020, it was announced that gantenerumab did not meet its primary end point in the DIAN-TU trial, an international clinical trial evaluating multiple drugs in patients with or at risk for autosomal dominant AD. The GRADUATE studies are evaluating a higher gantenerumab dose that most patients received in the DIAN-TU trial. Results are expected in 2022.[93]

Tau-targeting Investigational Drugs

LMTX. This prodrug of methylene blue, a second-generation tau aggregation inhibitor, is the only tau-specific agent in phase 3 clinical trials.[6,94] Blinding of LMTX in clinical trials is problematic because it discolors urine. Two phase 3 clinical trials of LMTX for mild to moderate AD (TRX-005 and TRX-015) were completed in 2016. Based on phase 2 clinical trial results, these studies compared LMTX doses of 150-250 mg/day with 8 mg/day as an intended control that would maintain blinding. In TRX-015, 8 mg/day appeared to show the same benefit as the higher doses, and LMTX monotherapy appeared more effective than coadministration with cholinesterase inhibitors and/or memantine. These findings led to changes in the design of the ongoing TRX-005 study. That study met modified primary prespecified outcomes and confirmed the results seen in Study TRx-015.[95] A third phase 3 clinical trial, LUCIDITY, is currently underway to confirm whether low-dose monotherapy is effective.[96] Top-line results are expected by the end of 2021. To maintain blinding, a urine discolorant has been added to some placebo pills in this study.[96] AEs with LMTX included diarrhea, dysuria, and decreased hemoglobin. It does not appear to cause ARIA.[6]

Inflammation-targeting Investigational Drugs

ALZT-OP1. This combination regimen consists of nasally inhaled cromolyn, a mast cell stabilizer, and oral ibuprofen, a nonsteroidal anti-inflammatory agent. In theory, it could reduce neuroinflammation and promote clearance of Aβ by converting microglia from a proinflammatory to a phagocytic state.[94] The phase 3 COGNITE trial is evaluating whether ALZT-OP1 slows or reverses cognitive and functional decline on the CDR-SB in patients with early AD.[97]

COR388. This oral small-molecule agent irreversibly inhibits gingipains.[98] These are virulence factor proteases from *Porphyromonas gingivalis*, a periodontal pathogen that has been found in the brain of patients with AD. COR388 is being evaluated in the phase 2/3 GAIN clinical trial.[99] It is evaluating COR388 given twice daily in 570 patients with mild to moderate AD. An interim analysis is expected by the end of 2020, and top-line results are expected by the end of 2021.[99]

Masitinib. This selective tyrosine kinase inhibitor acts on mast cells and modulates neuroinflammation.[100] Potential mechanisms of action in AD include modulating neuroinflammation mediated by mast cells and inhibition of Fyn, a protein kinase involved in Aβ signaling and tau phosphorylation. In June 2019, interim analysis of the phase 3 AB09004 clinical trial indicated that the study should continue. The study is comparing masitinib 4.5 or 6 mg/kg/day with placebo in 720 patients with confirmed mild to moderate AD receiving a cholinesterase inhibitor and/or memantine.[100] The study is expected to complete in 2020.[101]

Other Investigational Drugs

AGB101. Levetiracetam is being repurposed as a synaptic vesicle glycoprotein 2A (SV2A) modulator that is hypothesized to decrease Aβ-induced hippocampal hyperactivity.[75] The phase 3 HOPE4MCI clinical trial is evaluating low-dose extended-release levetiracetam at a dose 220 mg once daily to slow cognitive and functional impairment,

as in patients with MCI.[102] The primary outcome is change in the CDR-SB. Top-line results are expected in September 2022.[102]

Blarcamesine (ANAVEX2-73). This sigma-1 receptor agonist targets protein misfolding, and may reduce tau hyperphosphorylation, oxidative stress, and neurodegeneration in AD.[103] In a phase 2a study, it demonstrated dose-dependent improvement in MMSE ADCS-ADL. A 48-week phase 2b/3 study in 450 patients with early AD is ongoing. Top-line results are expected in September 2023.[104]

CAD106. This second-generation active Aβ vaccine contains multiple copies of the $A\beta_{1-6}$ peptide linked to a carrier containing many copies of bacteriophage Qb coat protein.[105] In animal studies, it induced Aβ antibodies without triggering an Aβ-specific T-cell response. It is under evaluation in a 5-year phase 2/3 trial in individuals aged 60 to 75 years who are asymptomatic APOE4 carriers with elevated Aβ in CSF or on PET scan.[106] CAD106 is given by intramuscular injection every 6 weeks for the first 3 injections and then every 3 months thereafter. The CAD106 trial is expected to yield top-line results by the end of 2024.[107] In a phase 2b clinical trial, serious AEs more frequent with CAD106 than placebo included headache, hypertension, and fever. Several cases of ARIA occurred in CAD106-treated patients.[105]

Icosapent ethyl. The phase 2/3 BRAVE-EPA study is evaluating the effect of icosapent ethyl in 150 cognitively-normal APOE4-positive veterans aged 50 to 75 years. Initial results are expected in late 2021.[108]

Plasma exchange. The phase 2/3 Alzheimer's Management by Albumin Replacement (AMBAR) trial assessed whether plasma exchange and infusions of albumin ± intravenous immunoglobulin (IVIG) would delay progression of mild to moderate AD.[109] Plasma exchange may remove albumin-bound Aβ circulating in plasma. Albumin and IVIG have immunomodulatory and anti-inflammatory properties. In top-line data, plasma exchange did not significantly affect the coprimary end point of ADAS-Cog and ADCS-ADL scores compared with placebo at 14 months but had significant benefits on some individual end points. The sponsor intends to meet with the FDA to discuss the design of a successive AMBAR II trial to confirm whether the protocol has benefit.[110] The feasibility of plasma exchange, an invasive and expensive procedure, to manage progression of AD is questionable.[111]

Troriluzole (BHV-4157). This once-daily oral drug is a prodrug conjugate of riluzole that may reduce glutamate-mediated excitotoxicity and nerve cell deterioration by promoting nerve cell glutamate reuptake.[75] It is being evaluated in the T2 Protect AD phase 3 clinical trial, which could have preliminary results by late 2020.[112]

The Future of AD Drug Development

More than 1000 clinical trials have been put on hold because of the COVID-19 pandemic.[113] This includes clinical trials in AD that have enrolled participants who are especially vulnerable to COVID-19 complications.[114] Researchers are concerned that data collection in ongoing AD clinical trials may be harmed. Because conducting clinical trials in AD is already a daunting undertaking, there is also concern that some pharmaceutical companies may abandon a challenging drug development area such as AD in this time of crisis.[42]

What does the future hold if a drug receives FDA approval to prevent progression of preclinical or prodromal AD? A RAND Corporation analysis suggests that a paradigm shift to preventing progression in people with preclinical or prodromal disease could create enormous challenges for the US healthcare system, especially managed care.[13] Necessary resources such as dementia specialists, PET imaging facilities, and infusion centers are in short supply. Between 2020 and 2040, 2.1 million patients might develop AD while on a waiting list for treatment.[13] Considering the large number of individuals with preclinical AD, the cost of preventive therapy could be enormous.[115] Assessing the value of treatment will likely be a complex undertaking if a drug is approved based on a surrogate measure (eg, cognitive test score improvement) that does not guarantee prevention of dementia. For the first time in almost 20 years, the FDA is evaluating whether to approve a drug for AD that could modify its course. This exciting news has broad implications in managed care. ■

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Funding source: This activity is supported by an educational grant from Biogen MA, Inc.

Author disclosure: Dr Marasco has no relevant financial relationships with commercial interests to disclose.

Authorship information: Substantial contributions to the concept and design; drafting of the manuscript; overall supervision; and critical revision of the manuscript for important intellectual content.

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REPORT

Economic Burden of Alzheimer Disease and Managed Care Considerations

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Introduction

Dementia is a term for any disease causing a change in memory that impairs a person's daily functioning.[1] Alzheimer disease (AD), the most common type of dementia, is a degenerative disease characterized by loss of memory, loss of cognitive function, and functional impairment, with associated neuropsychological symptoms. As AD is a progressive disease, patients can be classified as having preclinical AD, mild cognitive impairment (MCI) due to AD, and mild, moderate, or severe dementia due to AD along the disease continuum. MCI is defined as deficits in memory with no significant impact on daily functioning, whereas MCI due to AD is defined as evidence of AD pathology and impairment in one or more cognitive domains that does not interfere with daily functioning. MCI can be a result of several conditions including, but not limited to, AD, cerebrovascular disease, Parkinson disease, frontotemporal degeneration, or traumatic brain injury. However, patients with MCI are more likely to develop AD than those who do not have MCI, suggesting that MCI may be an early sign of AD.[2-7] Evaluation of patients with MCI and other risk factors for AD may help in early identification and diagnosis of AD.

AD has been identified as the sixth leading cause of death among adults in the United States, and the fifth leading cause of death among adults over 65 years.[8] In 2018, more than 122,000 people died from AD, an increase of 146% from the year 2000. An estimated 5.8 million adults over 65 years are living with AD, with the number expected to more than double by the year 2050 to approximately 14 million individuals. A diagnosis of AD is typically not made until the patient has progressed to mild or moderate dementia. Many patients with AD go undiagnosed, and about 50% of Medicare patients are unaware they have a documented diagnosis of AD.

When evaluating the economic burden of AD, it is important to consider direct costs, such as skilled nursing care, home healthcare, and long-term care, and indirect costs, such as quality of life and the impact on the caregiver. Indirect costs of care have been shown to be higher than the costs of direct care for patients with AD and should not be overlooked when evaluating the cost of care for patients with AD.[9] Many patients living with AD are undiagnosed;

ABSTRACT

Alzheimer disease is the most common cause of dementia and the fifth leading cause of death in adults older than 65 years. The estimated total healthcare costs for the treatment of Alzheimer disease in 2020 is estimated at $305 billion, with the cost expected to increase to more than $1 trillion as the population ages. Most of the direct costs of care for Alzheimer disease are attributed to skilled nursing care, home healthcare, and hospice care. Indirect costs of care, including quality of life and informal caregiving, are likely underestimated and are associated with significant negative societal and personal burden. Managed care organizations are in a unique position to develop utilization strategies that would positively impact early diagnosis and treatment to lead to better outcomes and lower costs for patients, caregivers, and the healthcare system. Additionally, the recent inclusion of Alzheimer disease diagnoses into risk corridor calculations by the Centers for Medicare & Medicaid Services may encourage Medicare Advantage organizations to invest in programs that aid in its early detection and diagnosis.

***Am J Manag Care*. 2020;26:S177-S183**

For author information and disclosures, see end of text.

therefore, estimating true costs of AD care is difficult. The incorporation of medication therapy management (MTM) into AD care is an important strategy to optimize early medication initiation. Early detection and diagnosis of AD, leading to early initiation of current AD therapies, is associated with improved quality of care and quality of life, and economic and caregiver outcomes. Barriers to early diagnosis of AD include healthcare provider time restraints regarding testing and counseling, hesitancy of patient and caregiver reporting of symptoms, and lack of diagnostic resources in primary care.[3-6,10,11]

Direct and Indirect Costs of AD

As the prevalence of AD continues to rise with the aging "baby boomer" population, so do the costs of care associated with AD. The total cost of care for the treatment of AD in 2020 is estimated to be $305 billion. Medicare and Medicaid cover the largest proportion of these costs, estimated to be around $206 billion (≈68%), while patient out-of-pocket (OOP) costs are estimated to be around $66 billion (≈22%)[2,12] (**Table**[2]).

Total costs for AD care are estimated to increase to more than $1 trillion by 2050. Direct medical costs associated with the treatment of AD include physician visits, emergency department and hospital admissions, long-term care or skilled nursing facility care, and medications. Direct nonmedical costs include home healthcare, transportation to medical visits, and modifications to adapt to changes in physical function. Long-term care and nursing home care costs account for the majority of direct costs associated with AD care.[13]

Direct costs of care reported for AD may vary depending on the time frame being evaluated, and may include analysis of end-of-life costs, lifetime costs, pre- and postdiagnosis costs, and prevalence-based costs.[13] Total Medicare costs in 2019 for patients 65 years and older with AD or other dementias have been estimated to be $25,213 per person, about 3 times higher than those without AD ($7750). Medicaid pays for nursing home and long-term care services for patients with low income who meet certain criteria. The average annual Medicaid payments for beneficiaries with AD are estimated to be 23 times higher than those without AD (average $8779 vs $374).[2]

TABLE. Estimated Total Cost of Care for the Treatment of Alzheimer Disease in 2020

Payment Source	Cost in Billions (B)
Medicare	$155 B
Medicaid	$51 B
Out of pocket	$66 B
Other	$33 B
Total cost	$305 B

Three studies evaluated the direct costs of care for patients with AD around the time of death. A retrospective analysis evaluated 338,288 beneficiaries older than 69 years. Of these beneficiaries, 21% were classified as having AD. Beneficiaries with AD had costs on average of at least $18,000 more than those who did not have AD in the 8 years before death plus the year of death (P <.01), with most of these costs associated with skilled nursing care, home healthcare, and hospice care as compared with intensive medical treatments, such as Medicare Part B drugs (P <.01). Additionally, patients with AD had used 11% higher costs over the last 8 years of life compared to those who did not have AD.[14] Kelley et al showed the mean adjusted total healthcare spending in the last 5 years of life was $287,038 in patients with dementia, compared with $183,001 in other disease groups (eg, cancer, heart disease).[15] Another study estimated the cost of dementia to Medicare and Medicaid by analyzing the 1997 to 2005 Medicare Current Beneficiary Survey. Using cohort-based simulation models, the costs of dementia were estimated from the time of diagnosis until death. Patients with dementia had significantly higher annual Medicare and Medicaid expenditures at $10,814 and $6234 compared with those without dementia at $5953 and $1962, respectively ($P$ <.05).[16]

One study evaluated direct costs of care for patients with AD around the time of diagnosis. A retrospective, observational cohort study using a 5% sample of the 2009 to 2013 Medicare claims files evaluated Medicare expenditures during the 24 months before and after the diagnosis of AD and related dementia (ADRD) or MCI, each with propensity score-matched controls. Patients in the ADRD group were older and had more comorbidities when compared with those in the MCI or control groups. During months 13 to 24 before diagnosis, the average Medicare costs for patients in the ADRD group were $10,533. Costs increased to an average of $15,091 in the 12 months before diagnosis. The 12 months after diagnosis were found to be the most costly, totaling on average $27,126, and decreased during months 13 to 24 after diagnosis to an average of $17,257 due to a decrease in inpatient and acute care. Utilization of inpatient care, home healthcare, and post-acute skilled nursing facility care significantly increased in the 12 months before and after diagnosis. Patients in the MCI group experienced similar trends as patients in the ADRD group when compared with the control group.[17]

As skilled nursing care, home healthcare, and hospice care have been identified as major drivers of direct costs of care in AD, it is important to review healthcare utilization in these settings. It is estimated that 32% of patients using home healthcare services, 42% of patients in residential care facilities, and 48% of nursing home residents have AD.[2] Goldfeld and colleagues evaluated 323 nursing home residents over 18 months with advanced dementia in a prospective, cohort study to examine the factors associated with increased Medicare costs. The average total Medicare expense over 18 months was $8522 per resident. Medicare expenditures

were highest for hospice care (45.6%), followed by hospitalizations (30.2%). Medicare spending was found to be highest in the last 90 days before death.[18] Additionally, OOP costs for patients with AD are estimated to be higher than OOP costs for patients without AD. A retrospective, cross-sectional study using data from the 2012 Medicare Current Beneficiary Study aimed to estimate the OOP healthcare spending associated with ADRD. The average annual per-capita OOP spending was $3285 in patients with ADRD and $1895 in patients without ADRD. The majority of OOP spending in patients with ADRD was for prescription drugs and home healthcare services.[19]

Indirect costs of care associated with AD include caregiver burden and associated healthcare utilization and costs.[13] Family and friends may take on the burden of caregiving due to a sense of obligation and love, and desire to keep their loved ones comfortable in their own homes. This desire to keep loved ones at home is supported by the observation that patients with AD and dementia will be less agitated and more comfortable in surroundings that they recognize and are familiar with. Informal caregiving is the unpaid care that is provided to a patient with AD by their family and friends. It has been estimated that 75% of caregiving for a patient with AD is informal care.[13] Providing care to a patient with AD is financially, physically, and emotionally burdensome to the caregiver. Caregiving for patients with AD is unique compared with caregiving in other disease states due to the long duration of disease, and the progressive, unrelenting decline in cognitive and physical functioning.[2] The majority of AD care consists of assisting with activities of daily living (ADLs), but many more AD caregivers report also handling finances and advocating in terms of healthcare than non-AD caregivers. Other caregiver tasks for patients with AD include ensuring medication compliance, managing behavioral symptoms of the disease, finding and participating in support services such as adult day programs, and organizing in-home care.[2,20]

Several studies have examined the impact of AD on the caregiver. When evaluating the financial impact of informal caregiving in AD, researchers have typically expressed these costs as either replacement cost of hiring formal care or forgone wages. In 2019, 16.3 million informal caregivers provided an estimated 18.6 billion hours of unpaid care. When evaluating the cost using replacement costs of care valued at $13.11 per hour, the estimated value of informal care provided in 2019 was $244 billion.[2] A retrospective cohort study evaluated social costs and financial risks in Medicare fee-for-service beneficiaries older than 70 years from the Health and Retirement Study in the 5 years before their death between 2010 and 2015. This study found that costs of informal care for patients with AD were significantly higher than those with other conditions, including cancer and heart disease. The costs of informal care, measured in this study by replacement costs, were found to be $83,022 for patients with AD versus $38,272 for other diseases.[15] A large, multicenter, prospective cohort study used bivariate probit models to estimate home health and informal care utilization and costs in patients with AD from the Predictors Study over a span of 7 years. This study estimated informal caregiving costs by using the national average hourly earning for all private industries for each year. The majority of patients received informal care (80.6%), which increased from 4 hours of care per day at baseline to 7.6 hours per day at year 4. The costs of informal care were estimated to be $20,590 for the baseline year, and increased to $43,031 in year 4.[21] It is estimated that informal caregiver costs increase 18% per year as symptoms of AD progress.[22] Lastly, one study estimated the "welfare cost," a more comprehensive cost estimate of informal caregiving that takes into account the value of time, implications for future employability, and intrinsic benefits that accrue to daughters caring for mothers with AD, and the cost of forgone wages in the same population. When comparing cost estimates of informal caregiving over 2 years, the average cost in forgone wages was estimated to be $24,500 over all health states (needing assistance with ADLs only, memory only, both, or cannot be left alone) compared with welfare cost of $180,000. This study highlights that the financial impact on the informal caregiver may be much greater than other current estimates, and estimating by forgone wage or replacement costs, provide underestimates of informal care costs.[23]

The impact on physical health of the caregiver and the associated healthcare utilization and costs are often overlooked. Caregivers to patients with AD have been shown to have higher rates of stress, depression, anxiety, physical ailments, increased cardiovascular disease, and weakened immune systems. One study showed that as the comorbid diseases in patients with AD progressed and dependence on the caregiver increased, healthcare utilization and costs of the caregiver increased.[24] A retrospective cohort study using Medicare Advantage Prescription Drug Plan members with a diagnosis of AD and their household members compared with those without AD evaluated the medical condition burden, healthcare usage, and healthcare costs of the caregiver. Rheumatoid arthritis, mood and anxiety disorders, insomnia, and substance use/abuse were significantly more prevalent in household members caring for patients with AD. Household members caring for patients with AD had significantly higher average annual healthcare costs ($7168 ± $10,050 vs $6301 ± $8311; $P < .001$).[25] Therefore, it is imperative to support and treat the caregiver as much as the patient. Caregiver interventions include case management, educational and psychotherapeutic approaches, respite care options, and support groups. Education on the progression of the disease, how to find and access help, and optimal usage of resources to assist in providing AD care have shown to have a positive impact on AD caregivers.

The quality of life (QOL) in patients with AD is also significantly negatively impacted. Dementia interferes with daily functioning and independence, and places not only an economic burden, but also

a heavy personal burden on the patient and their caregivers. The symptoms of dementia are disabling, the degree to which depend largely on the stage of AD. Symptoms include loss of memory, difficulty speaking, psychological and psychiatric changes, and the inability to perform ADLs.[2] According to Lawton's model of QOL in AD, physiological well-being, behavioral competence (eg, cognitive and functional ability), and objective environment (eg, caretakers and living situation) are the 3 main factors that contribute to QOL in patients with AD.[26] The long duration of AD contributes to the negative impact it has on public health and decreases in QOL. To quantify this, disability-adjusted life-years (DALYs) assess the number of years of life lost due to a disease. DALYs are calculated as the number of years of life lost (YLLs) due to premature mortality plus the number of years lived with disability (YLDs), totaled across all those with the disease or injury.[2] According to The State of US Health, 1990-2016: Burden of Diseases, Injuries, and Risk Factors Among US States, AD ranked number 4 in YLLs and 19 in YLDs, indicating the high burden of disease to the patient and the caregiver.[27] Although it is known that QOL is negatively impacted in individuals with AD, there is a paucity in data quantifying the cost of decreased QOL in the patient.

Early Treatment Optimization Strategies

The overall goals of treatment for patients with AD are to maintain QOL; maximize function in daily activities; enhance cognition, mood, and behavior; foster a safe environment; and promote social engagement. These goals are achieved by regular monitoring of health and cognition in patients with AD, providing education and support to patients and their caregivers, and initiation of pharmacologic and nonpharmacologic interventions.[28] The National Plan to Address Alzheimer's Disease was established in 2012 to fulfill the 2011 National Alzheimer's Project Act (NAPA), which established a set of goals to address the current needs of patients with AD and prevent future cases of AD and ADRD. These goals include prevention and effective treatment of AD by 2025, optimizing care quality and efficiency, expanding support for patients with AD and their families and caregivers, enhancing public awareness and engagement, and tracking progress to drive improvement.[29]

Unfortunately, most patients with AD are diagnosed in the late stages of the disease when the symptoms are noticeable, with very few patients being diagnosed in the preclinical stages. As a response to the detrimental impacts and costs of misdiagnosed or undiagnosed AD, new practice guidelines for the clinical evaluation of AD in primary and specialty care settings were released at the 2018 Alzheimer's Association International Conference. These guidelines sought to improve and coordinate efforts for more timely and accurate AD diagnosis and evaluation of symptoms, as well as providing continued care and support for the affected individual and their caregivers. The guidelines focus on recommendations for appropriate, timely evaluation and assessment, and highlight the importance of including the caregiver in all aspects of AD care.[30]

In its recent practice recommendations, the Alzheimer's Association renewed the focus of care on the individual with dementia and their caregiver in a person-centered care delivery model that focuses more on the individual's unique needs, personal experiences, and strengths rather than the loss of abilities.[2] The Alzheimer Association guidelines for the treatment of dementia-related behaviors indicate that nonpharmacologic psychosocial interventions should be used as first-line interventions. For the treatment of cognitive symptoms of AD, current pharmacologic agents approved for use in the treatment of patients with AD at various stages of the disease include cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and memantine.[31] These current pharmacologic therapies for AD provide symptomatic relief by improving cognitive symptoms of memory loss and confusion, but do not stop AD progression.[32] Promising disease-modifying therapies that target inflammatory processes, tau proteins, and β-amyloid proteins are currently in development.

In the preclinical stages of AD, patients do not show signs of MCI or dementia, but may have measurable changes in the brain that can be detected on positron emission tomography scans, by specific biomarkers, possibly by retinal nerve fiber layer thickness as detected on optical coherence tomography, or other changes that may be detected through varying laboratory and genetic tests that are in development.[2,33] Patients with MCI are more likely to have AD than those who do not have MCI, suggesting that MCI may be an early sign of AD. If MCI is properly detected and diagnosed, this may lead to an earlier diagnosis of AD.[34,35]

Early diagnosis of AD can lead to earlier interventions, both pharmacologic and nonpharmacologic, to help maintain and improve physical and cognitive functioning.[36] Early diagnosis may lead to earlier interventions, such as coordinated care planning involving the affected individual, better management of symptoms, reduced costs, and better QOL for the patient and caregiver.[37] One study evaluated the costs and benefits of early identification and treatment of patients with AD using a Monte Carlo cost-benefit analysis. This analysis showed that early diagnosis and management of patients with AD with pharmacologic and nonpharmacologic measures would lead to cost savings, with cost savings being greatest when AD cases were diagnosed earlier. Cost savings were greatest when drug treatment in combination with caregiver interventions (eg, increased counseling and support) were initiated when cognitive impairment was lower. For example, a Monte Carlo cost-benefit analysis predicted that the net savings for a 70-year-old woman with MCI (defined as a Mini-Mental State Examination score of 28) may be estimated at $125,000 in social benefits, $16,000 in state fiscal benefits, and $34,000 in federal fiscal benefits.[38] De Vugt and colleagues argue that early diagnosis of AD allows the informal

caregiver to have more time to adjust to their role in providing care for their loved one with AD, but highlight the importance of the caregiver finding the support they need in caring for a patient with AD. While stress levels may be lower in the preclinical stages of AD, early interventions and support can help the caregiver anticipate and plan for future care needs and allow the patient to be involved in the decision-making process.[39] More studies assessing the impact of early diagnosis and early intervention on quality of life, caregiver burden, and economic burden are needed as more patients receive a diagnosis earlier.

Managed care organizations (MCOs) have a unique opportunity in developing medication utilization strategies that support the goals of the National Plan and have an impact on early diagnosis and treatment that can lead to better outcomes and lower costs for patients, caregivers, and the healthcare system. While there is promise in the various emerging treatment options to modify the progression of AD, the current pharmacologic therapies that provide temporary, symptomatic relief are associated with significant adverse effects that often lead to noncompliance. Appropriate utilization of current pharmacotherapy options and care coordination is important for managing costs of AD, as well as optimizing QOL and care for patients with AD and their caregivers.

To achieve this, MCOs must first prioritize and encourage appropriate, timely testing for cognitive status earlier in the disease process. MCOs can prioritize review of emerging treatment options that target inflammatory processes, tau proteins, and β-amyloid proteins as they become available. One study suggests that the maximum effective price of these potential disease-modifying therapies per patient per year is $10,000 from a payer perspective under the willingness-to-pay threshold of $150,000 per quality-adjusted life-year, assuming 20% reduction relative to standard of care.[40] Care planning should be initiated for all patients with AD, as it provides individuals with cognitive impairment and their caregivers information on medical and nonmedical treatments, and helps to coordinate care among clinicians vital to the care of patients with AD.[41]

MCOs can also use MTM approaches to help initiate and maintain patients on currently approved pharmacologic agents in the treatment of AD early in the disease process. MTM is a process of collecting patient-specific information, assessing medication therapies to identify medication-related issues, and creating a plan to resolve these issues. The core elements of MTM services include medication therapy review, personal medication record, medication-related action planning, intervention/referral, and documentation and follow-up. MTM is especially important in chronic disease states with several comorbidities. Disease management programs that incorporate MTM have been developed for AD, as patients with AD and their caregivers manage this complex, progressive disease and associated comorbidities at home. Disease management programs that incorporate MTM services have been shown to reduce healthcare costs and improve QOL of the patient and caregiver.[42] Additionally, caregiver coaching can help to educate, prepare, and train the caregiver to minimize caregiver burden. Caregiver coaching includes, but is not limited to, education on AD, how to manage changes in behavior and communication, personal care and hygiene tips, home safety and fall prevention strategies, medication management, how to manage financial and legal matters, and emergency procedures. There are many resources and support groups available for caregivers of patients with AD, and it is imperative for the caregiver to have a support team while caring for their loved one with AD.[43]

The Centers for Medicare & Medicaid Services (CMS) uses a risk-adjustment mechanism, currently the Hierarchical Condition Category (HCC) risk adjuster, to calculate revenue payments made to Medicare Advantage organizations (MAOs) for their Part C Medicare Advantage (MA) plans. This is done so that MAOs do not select their members by their risk score, but allows for a market where quality and efficiency of service is optimized. Risk scores are calculated by patient medical diagnoses submitted to CMS from the prior year, which are then used to calculate member-specific revenue payments, which make up most of the revenue of the plan. Thorough diagnosis coding and submission, and retention of members, directly impacts the ability of the MAO to maintain and increase their revenue.[44] CMS released its proposed risk score methodology for MA plans for 2020 in December 2018. In January 2020, CMS included 2 additional HCC risk adjusters for patients with dementia, which includes patients with AD to the risk score calculation methodology. Therefore, it is in the MAO's best interest to actively identify and track costs for patients with AD and dementia to be included in their risk-adjustment calculations. MAOs are encouraged to provide care to patients with AD and dementia because the costs are already included in their risk-adjustment calculations and are being paid to provide the services.[45] This will also encourage MAOs to invest in programs that aid in early detection and diagnosis of AD.

In addition to pharmacologic therapy, early nonpharmacologic interventions, such as learning basic strengthening exercises and learning how to use basic self-help assistive devices while patients with AD have the capacity to learn them, can help patients maintain autonomy in ADLs and physical and cognitive functioning. The American Academy of Neurology recommends that patients with MCI exercise regularly as part of an overall approach to managing their symptoms and to consider cognitive training.[46] Physical and occupational therapy for learning and maintaining fine and gross motor function skills are important aspects of nonpharmacologic management to help maintain ADLs. Physical therapists are well trained to assist in exercising by using specific methods, techniques, and approaches to help maintain physical functioning in patients with AD, including sight, sound, and touch cues for

walking, mirroring movements, task breakdown to safely get out of bed, hand-over-hand guidance to learn different motions, and muscle training to help patients walk safely.[47] Occupational therapists can evaluate the home for safety to prevent falls or injuries, create safety plans to keep the patient safe while at home when the caregiver is unavailable, and observe the patient at home to recommend changes to foster independence.[48] Various cognitive training programs, including cognitive stimulation therapy (CST), are being considered for coverage by MA plans under supplement benefit funds from CMS.[49,50] CST has been shown to be a cost-effective early intervention in patients with dementia, and is typically delivered in a group setting consisting of cognitive-based tasks and activities, such as word games and puzzles. A multicenter, single-blind, randomized control trial evaluated the effect of CST on cognition using the AD assessment scale-cognition (ADAS-Cog) in patients with AD. CST showed a significant impact in improving the ability to follow commands and spoken language ability in patients with AD ($P < .05$).[51] The use of assistive devices for ADLs can help patients with AD maintain their independence, and includes devices such as button, zipper, and sock aids to help get dressed, and modified utensils, plates, and bowls to assist in eating.[52,53] Technological advances in medical equipment for patients with dementia who have several comorbidities with high pill burden, such as automated pill dispensers that remind patients with AD to take their medications, may have a positive impact on medication management and reduce healthcare utilization for comorbid disease states. MCOs should consider coverage of nonpharmacologic therapies and tools that have shown to be cost-effective, and increase QOL in patients with AD and their caregivers.

Conclusions

AD is prevalent among adults older than 65 years and is often misdiagnosed or underdiagnosed. The economic burden from treating patients with AD is overwhelming, and estimated to increase in the coming years as the population ages. The direct costs of care for patients with AD are largely attributed to skilled nursing care, home healthcare, and hospice care, and have been shown to be significantly more costly for patients with AD as compared with other diseases. The costs of informal care and QOL burden have also been shown to be significantly higher in patients with AD and their caregivers than other disease states. The financial and personal burden experienced by caregivers to patients with AD is immense and often underestimated. It is important to treat and support the caregiver of patients with AD just as much as the patient with AD. MCOs can have a profound impact on the QOL of the patient with AD, caregiver burden, and economic and healthcare burden of AD by supporting early diagnosis of AD with MTM strategies, early review of emerging therapies, care coordination, and providing covered nonpharmacologic interventions. ■

Author affiliation: Winston Wong, PharmD, is president of W-Squared Group, Longboat Key, FL.

Funding source: This activity is supported by an educational grant from Biogen MA, Inc.

Author disclosure: Dr Wong has no relevant financial relationships with commercial interests to disclose.

Authorship information: Substantial contributions to the concept and design; drafting of the manuscript; overall supervision; and critical revision of the manuscript for important intellectual content.

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Medical writing and editorial support: Elenna M. Smalley, PharmD, BCPS

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POSTTEST

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Sample of Online Posttest

Choose the best answer for each of the following:

1. Which of the following are currently available biomarkers used in the diagnosis and monitoring of the Alzheimer disease (AD) continuum?

A. Aβ positron emission tomography (PET) scanning, neurodegeneration on magnetic resonance imaging (MRI), and the Mini-Mental Status Exam (MMSE)
B. Aβ PET scanning, Aβ cerebrospinal fluid testing, and neurodegeneration on MRI
C. Aβ PET scanning, neurodegeneration on MRI, and apolipoprotein E (APOE) genotyping
D. Aβ PET scanning, APOE genotyping, and the MMSE

2. In observational studies, up to what percentage of patients with mild cognitive impairment progressed to dementia over 5 years of follow-up?

A. 21%
B. 26%
C. 38%
D. 57%

3. Which of the following statements most accurately reflects the effects of cholinesterase inhibitors and memantine on the course of the AD continuum?

A. Although cholinesterase inhibitors do not change the course of AD, memantine slows the progression of dementia.
B. Cholinesterase inhibitors slow the course of AD, but memantine does not.
C. Cholinesterase inhibitors and memantine do not slow the progression of AD.
D. Cholinesterase inhibitors and memantine slow the course of AD.

4. Which phase 3 investigational drug for AD targets inflammation?

A. ALZT-OP1
B. AGB101
C. CAD106
D. BAN2401

5. Which phase 3 investigational drug for AD is a monoclonal antibody that targets aggregated Aβ fibrils and soluble oligomers?

A. LMTX
B. COR388
C. CAD106
D. Aducanumab

6. Which statement is true?

A. Early diagnosis of AD is associated with improved quality of life.
B. It is estimated that informal caregiver costs increase 5% per year as symptoms of AD progress.
C. Early intervention is not associated with improvements in cognitive function.
D. Long-term care is not a major driver of cost of care in AD.

7. Which of the following is true about the economic impact of direct costs of care for patients with AD?

A. As the prevalence of AD increases, costs of care are estimated to decrease.
B. Total costs of care for patients with AD are estimated to increase to more than $1 trillion by 2050.
C. Total Medicare payments in 2019 for patients with AD were similar to those without AD.
D. Patient out-of-pocket costs were similar in patients with AD compared with those without AD.

8. **Informal caregiving for patients with AD _____**
   A. Is associated with poor economic outcomes for the caregiver.
   B. Is similar to informal caregiving for patients with other diseases.
   C. Is not associated with increased healthcare utilization by the caregiver.
   D. Does not pose a significant financial burden on the caregiver.

9. **Which of the following has been shown to reduce healthcare costs and improve quality of life of patients with AD and their caregivers?**
   A. Speech therapy
   B. Medication therapy management
   C. Physical therapy
   D. Assistive devices for activities of daily living

10. **Outcomes associated with early diagnosis of AD include all of the following, except:**
   A. Increased costs
   B. Early pharmacologic and nonpharmacologic interventions
   C. Increased patient and caregiver quality of life
   D. Inclusion of the patient in the planning of future care needs

NOTES

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