Duke | Robert J. Margolis, MD Center for Health Policy

Exploring Outcomes and Value across the Spectrum of Alzheimer's Disease

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Discussion Guide

Introduction

Alzheimer's diseases (AD) is a neurodegenerative disorder resulting from the formation of plaques and tangles in the brain, which lead to nerve cell death and tissue loss, ultimately causing cognitive damage and physical impairment in patients.

AD is a significant health burden for the elderly population in the U.S. and the world, associated with 60-70 percent of dementia cases and affecting six percent of Americans.[1] The sixth leading cause of death in the U.S. in 2015, this disease is associated with more than 1.9 million annual deaths worldwide.[2] Due to its devastating impact on activities of daily living and the lack of effective treatment options, the costs associated with AD are extremely high. In 2016, the estimated direct cost of AD to the U.S. healthcare system was $226 billion, and the treatment costs of dementia totaled more than $287,000 per capita.[3] Caregivers for AD patients incur an addition $10 billion in total annual healthcare costs due to the physical and emotional burden of care. [4]

There is an unmet medical need for innovative therapies. Currently, there are five drugs for AD on the market, though these only show modest efficacy in improving the disease's symptoms and progression.[5] Ninety-three drugs are under development[6] with a range of mechanisms of action targeted at relieving the symptoms of AD and slowing the progression of the disease. These drug candidates promise improved efficacy and, coupled with scientific discoveries that have enabled the identification and treatment of disease at earlier stages, could significantly lower the cost burden. However, because AD is progressive and requires chronic treatment, and due to high prices for new therapies, stakeholders will need to consider new payment approaches to recognize the full value of these drugs.

This document outlines the symptoms and care requirements for different stages of AD, analyzes the components of AD costs, and outlines key points in the discussion of measuring value for new AD therapies.

Classification of Disease Stages

Measurement criteria of AD clinical stages

The clinical stages of AD are measured through a combination of mental status testing, brain imaging, and examination of a patient's health history. Mental status examinations (MSEs) are designed to estimate the severity of cognitive impairment by using a questionnaire that measures the aspects of cognition, such as language, memory, mood, logical reasoning, and orientation. A quantitative score is calculated based on the patient's answers, which helps physicians determine the stages and progression of the disease.

There are five MSEs commonly used to determine cognitive status in the clinical settings (Table 1),[7] and the Mini-Mental State Examination (MMSE) is considered to be the gold-standard for measuring

cognitive impairment. The test is a 30-point questionnaire; a lower score indicates a higher degree of cognitive impairment.

Table 1. Common Mental Assessment Instruments for AD Diagnosis

Name	Test Time	Goal	Content	Criteria
Mini–Mental State Examination (MMSE)	5-10 minutes	Screening and staging of dementia	12 questions, 30 points; lower score means higher cognitive impairment	A score of less than 25 indicates cognitive impairment; less than 10 indicates severe dementia
General Practitioner Assessment of Cognition (GPAC)	4 minute test; 2 minutes for interview	Diagnosis of dementia in primary care setting	A 9-question cognitive test (9 points); interview (3 points).	Lower score means higher level of cognitive impairment
Abbreviated Mental Test Score (AMTS)	5 minutes	Assess elderly patients for the severity of dementia	10 questions, 10 points;	A score of 7-8 or less suggests cognitive impairment.
Addenbrooke's Cognitive Examination (ACE)	15 minutes	Assessment of cognitive functions in clinical/hospital settings, adapted from MMSE	5 sections, 100 points	Generally, a score lower than 82 indicates a dementia diagnosis.
Mini-Cog	5-10 minutes	Screening for cognitive impairment in older adults; does not substitute for diagnostics	3 items; 5 points	A total score less than 3 points indicates likelihood of dementia

The advantages of MSEs include a short administration time, ease of use, and relative validity and reliability for diagnosis. However, most MSEs lack the sensitivity to detect progressive changes of AD symptoms over time, especially during early stages. Additionally, the accuracy of these tests can be easily affected by the patient's demographic characteristics, as well as the subjective judgment of test administrators.

In addition to MSEs, brain imaging techniques such as MRI and PET are also widely used to confirm the diagnosis of AD. These tests can detect structural changes, such as cortical thinning and grey matter loss, and help rule out other conditions that may cause similar symptoms, such as brain tumors and stroke.[8] However, brain imaging studies are of limited utility in determining the clinical stage of AD patients.

Preclinical stage (asymptomatic disease)

The preclinical stage of disease is defined as an early period without observable symptoms, but the presence of specific biomarkers suggest a high risk of future AD development. Amyloid-beta (Aβ) is a known precursor for disease, and it may start to accumulate in the brain many years before symptoms appear.[9] The two commonly used methods for identifying this biomarker are positron emission tomography (PET) and assays to measure Aβ levels in the cerebrospinal fluid (CSF).[10] Eleven percent of asymptomatic patients with abnormal amyloid levels will develop AD symptoms within 5 years, compared to only 2 percent of individuals without the presence of biomarkers.[11]

While Aβ is the primary biomarker used as evidence of preclinical AD, certain genetic mutations can also help clinicians estimate the risk of AD progression later in life. A high-risk variant of the apolipoprotein E (APOE) gene, called APOE-ε4, is associated with an increased risk of Alzheimer's disease. This gene mutation is present in 13.7% of the entire population, but its frequency is as high as 40% in AD patients.[12] Individuals who carry the APOE-ε4 gene are 20 times more likely than non-carriers to develop AD symptoms after the age of 65.[13]

Some additional factors can also increase the probability of AD: studies have shown that vascular conditions, including heart disease, stroke, and high blood pressure, as well as metabolic conditions such as diabetes and obesity, are associated with a higher risk of AD.[14] However, the way these factors affect the development of AD is still unclear.

Early stage (mild to moderate Alzheimer's disease)

Early Alzheimer's disease is characterized by a mild or moderate decline in memory and thinking coupled with primary biomarkers for disease.[15] Common symptoms at this stage include short-term memory loss, challenges in planning or solving problems, increasing difficulty completing familiar tasks, and mood changes. These symptoms can advance as the disease progresses, but they are typically not severe enough to disrupt a person's daily life. Early-stage AD can span for 2-10 years before more severe symptoms develop.[16]

In most cases, patients living with early Alzheimer's can function independently and do not require full-time assistance from caregivers. At this stage, the primary goal of caregivers is to help the patient develop new strategies to cope with everyday tasks.[17] Caregivers will often need to provide memory support, assist with the patient's daily schedule and household budget, and offer emotional support and companionship. [18]

Late stage (severe Alzheimer's disease and dementia)

The late stage of AD is characterized by a severe decline in cognitive and physical functions, and most patients lose their ability to live independently and respond to the external environment. At this stage, patients experience a breakdown of many physical functions, and many are often confined to a wheelchair or bed. Due to this physical deterioration, late-stage AD patients are increasingly vulnerable to various infections, such as pneumonia and UTIs. In addition to these physical symptoms, there is a severe accumulation of plaques and tangles in the brain, and a significant reduction in the size of the brain. The life expectancy at this stage of disease is one to five years.[19]

Due to the loss of independent functioning, late-stage AD patients require intensive, full-time care to complete basic activities, including bathing and feeding.[20] Since late-stage AD is a terminal condition, the main goal of caregivers is to maintain the quality of life and dignity of the patients. During the end stage of life, nursing home and hospice are favored because they can provide palliative care options that focus on relieving the physical suffering of patients.[21]

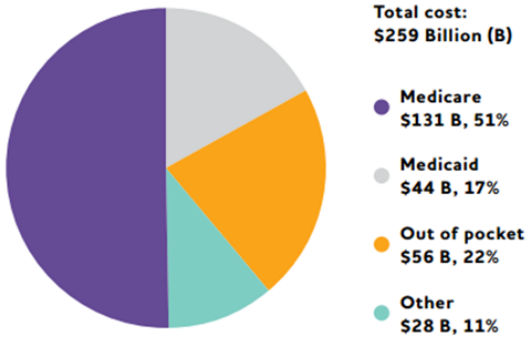
The Costs of Alzheimer's Disease

Direct healthcare costs

Alzheimer's disease is devastating for both patients and their families, and as the population ages, this disease also places a disproportionate financial burden on society. In the coming decades, AD-associated costs are expected to soar to $1.1 trillion,[22] and some estimate that these costs could bankrupt Medicare.[23] Currently, the estimated annual aggregate cost of care for American AD patients over 65 is $259 billion, and these costs are primarily covered by federally-supported health care programs, including Medicare, Medicaid, and State Health Insurance Programs (SHIPs) (Chart 1).[24] Drivers of

expenses include nursing home care, hospital stays, medical visits, home health care, outpatient rehabilitation, and prescription drugs.[25]

Chart 1. The aggregate cost of Alzheimer's disease in 2017 Dollars



(Source: The Alzheimer's Association, Facts and Figures in 2017)

The healthcare costs associated with AD patients is much higher than for those with other chronic medical conditions.[26] Individual patients with AD incur an average of $46,786 per year in expenses, which is almost four times higher than the expenses for an elderly individual without AD.[27] Most of these expenses go towards nursing homes or assisted living facilities, which account for 46 percent of total healthcare costs. On average, a person with dementia spends 22.5 days in a hospital or skilled nursing facility every year, compared to 4.6 days for the Medicare population as a whole.

The cost of care for AD patients varies by stage of disease, with costs increasing significantly as the disease progresses. During the first two years after diagnosis, the annual cost of care is not significantly different from other therapeutic categories. However, the total cost of care can reach $341,651 during each of the last five years of a patient's life,[28] which can be primarily attributed to life sustaining and palliative care services.[29]

Unfortunately, the medical costs associated with AD extend beyond treatment of the disease itself. Injuries and medical conditions that result from cognitive impairment can also result in medical expenses. The leading causes of hospitalization for AD patients include fainting, falls and trauma, gastrointestinal problems, and delirium.[30] Many patients also suffer from a variety of comorbidities, including arthritis, diabetes, or cancer. In addition to negatively impacting the health outcomes of AD patients, these conditions can increase the economic burden to patients and their families.[31]

Indirect cost of caregiving

Due to the decline in memory, mobility, and independent functioning, most AD patients will ultimately require some level of assistance in their day-to-day activities, which can range from paying bills and helping run errands, to bathing and grooming as well as managing behavioral changes. More than 75 percent of the caregiving provided to AD patients is unpaid, and is often performed by family members.[32] Nationwide, it is estimated that there are 15.9 million unpaid family caregivers for AD and dementia patients, who provided over 18.2 billion hours of unpaid care in 2016. With an hour of care valued at $12.50, the total cost of uncompensated care for AD is estimated to be $230.1 billion a year in U.S.[33]

Caregiving is a demanding job, and it can take a financial, emotional, and physical toll on caregivers. Many take on the caregiving role to delay or prevent their loved one from needing to move to a nursing facility, but the expense of care in a facility may also lead some to become unpaid caregivers themselves. The estimated cost of full time care for someone with AD is $60,000 a year, and the average cost for unskilled home-care assistance can be as high as $21 per hour, which can be unaffordable for many.[34] Caring for individuals with AD may mean that caregivers have to sacrifice their paid occupations;

a 2015 study indicated that 17 percent of caregivers quit their jobs either before or after assuming caregiving responsibilities, nine percent quit their jobs in order to continue providing care, 54 percent arrived to their place of work late or left early, and 15 percent took a leave of absence.[35]

In addition to the financial burden that caregivers face, the emotional and physical demands of caregiving result additional healthcare costs, estimated at more than $10 billion in the U.S. in 2016. [36] Caregivers spend eight percent more on healthcare than non-caregivers. This increased burden disproportionately affects women, who constitute 63 percent of Alzheimer's and dementia caregivers. Half of all female caregivers experience severe emotional and physical strain, and approximately 40 percent of family caregivers suffer from varying degrees of depression.[37]

Caregiver burden is usually not factored into the cost of disease or treatment, but the financial and health impacts are substantial. As result, therapies that improve the symptoms of AD or that can delay the progression of disease would have a high value not only for patients, but also for caregivers.

Pharmaceutical Development for the Treatment of Alzheimer's Disease

Current treatment options

There are currently five drugs used to treat AD and dementia, approved between 1996 and 2014 (Table 2). Three of the drugs – donepezil, galantamine and rivastigmine – are cholinesterase inhibitors that aim to prevent the breakdown of acetylcholine in neurons. Acetylcholine is a neurotransmitter that is important for memory, and drugs that prevent its breakdown aim to improve thinking and memory functions. Another drug, memantine, is an NMDA (N-methyl-D-aspartate receptor) inhibitor that blocks the activities of the neurotransmitter glutamate, which also plays a role in learning and memory. The last drug, donepezil + memantine, is a combination therapy.

Table 2. Currently Available AD Drugs

Drug name	Year Approved	Indication
Donepezil	1996	All stages
Rivastigmine	2000	All Stages
Galantamine	2001	Mild to moderate
Memantine	2003	Moderate to severe
Donepezil+ memantine	2014	Moderate to severe

Both classes of drugs are available as generics. While the resulting low cost for medication is beneficial for patients, it also reflects the difficulty in finding new, effective drugs for this disease. While the effects of these drugs vary by individual, they do not slow the progression of disease, and in many cases, their efficacy at relieving symptoms is moderate at best,[38] leaving AD patients and their families with few options for treatment.[39]

Current drug pipeline

The lack of effective treatments for AD is a clear unmet medical need, and there are a number of companies working to develop viable drug candidates. As of November 2016, there were 93 drug candidates in the development pipeline, with 24 in Phase I, 45 in Phase II, and 24 in Phase III clinical trials.[40] There are two categories of drug candidates: symptomatic and disease-modifying**.** Symptomatic drugs are designed to relieve the symptoms of AD, but do not slow the progression of disease. Disease-modifying drugs are designed to halt or slow the progression of disease, but may not address the primary symptoms. There are currently 25 symptomatic agents and 68 disease-modifying agents in development pipeline.

Across all areas of drug development, many therapeutic candidates fail to gain approval by the FDA, either due to lack of efficacy or due to severe adverse reactions. However, the failure rate of drugs for Alzheimer's is considerably higher than that for other categories. One study estimated that less than one percent of potential Alzheimer's treatments ultimately gain approval.[41] These failures have been largely due to lack of efficacy in achieving the primary endpoints, cognition and a global functional assessment.[42] Amyloid beta reduction is one target for many new therapies, with the goal of eliminating the accumulated proteins thought to contribute to the symptoms of advanced-state patients. However, Aβ has proved a challenging target, with large manufacturers, including Lilly, Pfizer and J&J, suffering setbacks due to unsatisfactory clinical trial results.

Scientists hypothesize that targeting the disease at too advanced a stage contributes to these setbacks; instead, the focus should be on preventing amyloid and tau buildup in the earlier stages of AD. As a result, a growing number of developers are now shifting their clinical trials to target early-stage patients,[43] which has been facilitated through progress on biomarker identification.[44] To support these efforts, the U.S. Food and Drug Administration (FDA), through a guidance document that was released in 2013, clarified the clinical trial design, clinical endpoint selection, and outcome measurement issues associated with early-stage AD drug development.[45]

Innovative new drug candidates that are more effective in treating AD symptoms or delaying disease progression are likely to come at significantly higher prices, reflecting their potential to truly change how AD is treated. A recent report from RTI International estimated the cost for developing a new Alzheimer's drug to be $5.7 billion dollars, which is significantly more than the estimated industry average of $1.2-$2.6 billion.[46]

Coverage and payment issues

Using a pharmaceutical treatment to address Alzheimer's development before the full onset of disease could be extremely beneficial for patients, but given uncertainties in clinical diagnosis and staging, could raise concerns for payer coverage and reimbursement decisions. These concerns can include determination of the appropriate population for treatment, evidence of incremental improvement, and the cost/benefit equation for each patient.

Early-stage treatment depends on clinician access to validated biomarkers that will give a strong indication of whether the patient will go on to develop AD. For current trials, the presence of amyloid is used as a selection criteria for enrollment because those who are amyloid positive are more likely to progress to Alzheimer's than those who are amyloid negative.[47] Payers will need to consider the probability of a particular patient developing disease when making a coverage decision for a drug that is designed to delay or prevent onset of disease, and uncertainty may make it more difficult for manufacturers to secure reimbursement for these treatments.

Treatments that reduce symptoms of disease or that slow the progression of disease would undoubtedly be valuable to patients suffering from Alzheimer's, but the heterogeneity of the disease means that both symptoms and progression vary across stages of disease and from patient to patient. Therefore, it will be difficult to make generalizations about the effect of a medication on a given patient. Further, patients and caregivers will assign value to outcomes differently.

Payers also may consider the cost-benefit trade-off of new Alzheimer's treatments. Drugs that can relieve symptoms or slow the progression of disease have great potential to reduce the significant long term costs of care for AD patients. However, patients often change payers or transition from coverage

by a private payer to a public payer, meaning that the accrued benefits and cost-savings may not be realized by the payer that initially reimbursed the treatments. As a result, justifications for coverage and reimbursement based on future cost-savings may not be a strong argument for payers. Further, payments by payers are counted in the short-term (quarterly or annually). By contrast, benefits from effective therapies for Alzheimer's will be likely be realized through healthcare saving years in the future.

The current payment system presents a challenge to maintaining a sustainable reimbursement mechanism for high-price, chronic therapies. In parallel to these issues, the U.S. healthcare system is undergoing a transformation in the way that medical services are reimbursed, shifting away from payment models that reimburse on a fee-for-service basis to payments that are dependent on quality and outcomes. New payment approaches are needed for Alzheimer's treatments to promote drug accessibility and sustainable pricing while also encouraging innovation. Recent examples of outcomes- or value-based payment approaches for pharmaceutical products and medical devices reflect an increased interest among payers and developers to re-think traditional payment arrangements in ways that support and incentivize better outcomes for patients. For AD in particular, new high-priced innovations may come with high degrees of uncertainty as to which patients should receive them and durability of effectiveness. These uncertainties may serve as an opportunity for exploring value-based payment arrangements, giving rise to questions about how to define and measure value and outcomes across the stages of AD.

Exploring Outcomes and Value Across the Spectrum of Alzheimer's Disease

Before these payment approaches can be applied, stakeholders must begin to define the evidence and outcomes that could be used to support any type of new value-based arrangement. This workshop is being convened to discuss these issues, as well as to evaluate new payment approaches that could be used to better distribute the costs and benefits across stakeholders.

Session I: The spectrum of Alzheimer's disease and impact on society

Alzheimer's is a complicated and long lasting disease that negatively impacts not only the patient, but the patients' caregivers and society as a whole. In order to evaluate the potential benefits that a therapeutic treatment could provide, there must be an understanding of the disease progression, direct costs to the healthcare system, and indirect costs to society. This session will explore these issues, and some key questions include:

- What are the current gaps in diagnosing and treating patients?
- What factors are included in the total cost burden of disease?
- What are the clinical endpoints used in evaluating new drugs and technology?
- How does Alzheimer's disease impact caregivers and the patients' families?

Session II: Current payment models and approaches for treating AD

Current treatments for Alzheimer's are low-cost generic drugs that are designed to treat the symptoms of disease, but do not affect progression. Upcoming symptomatic drugs promise to bring increased efficacy to the treatment of symptoms, but will likely also come with a higher price. As a result, payers will need to weigh the potential benefits that a patient might experience against the cost and longevity of treatment. This session aims to understand the value of reducing symptoms of Alzheimer's disease,

and what gaps exist in the current payment system when it comes to rewarding desired outcomes at all stages of disease. Some key questions include:

- What evidence should manufacturers provide to demonstrate the clinical utility and value of their drug?
- What type of outcomes are most valuable to each stakeholder group?
- What value can symptomatic drugs provide?
- How long should symptomatic drugs be used, and when should they be discontinued?

Session III: Defining value – identifying clinical outcomes and economic impact of disease modifying treatments

Recent evidence has indicated that disease modifying drugs might be most effective if utilized at the earliest stages of disease onset. However, the progression of AD takes many years, and the strongest evidence will likely be generated outside of the clinical trial setting. Further, since disease onset will vary between patients, it may be difficult to assess the value of incremental improvement or delayed disease progression. This session aims to identify the outcomes and evidence that could be used to assess the value of a drug to patients, clinicians, and payers. Some key questions include:

- What does a successful treatment look like? What is important to patients?
- What are achievable outcomes?
- What models should be used to assess the cost?
- How should incremental value be measured?

Session IV: Approaches for rewarding AD treatments that provide long-term value

Current payment models reimburse drugs on a fee-for-service basis, but this system may become unsustainable as effective, expensive drugs enter the market to treat a condition that can stretch more than a decade. New payment approaches need to consider the long-term outcomes for patients as well as the impact that these drugs could have on the healthcare system as a whole. This session aims to understand payment approaches that could be used to reward innovation and that benefits are aligned with payments. Some key questions include:

- How can outcomes identified to represent value be utilized during payment?
- What are the gaps in evidence needed to determine the value of a therapy?
- What type of payment approaches could fit with AD treatments and identified value?
- What evidence would a payer need to better inform payment decisions during each stage of disease?

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