

The Journey to Alzheimer's Disease Diagnosis and Beyond Through Different Perspectives

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Abstract

Alzheimer's disease (AD) is a prevalent neurodegenerative disease that affects at least 50 million people worldwide and is on the rise to affect about 152 million by 2050. This progressive disease burdens both the patients and their family/caregiver, bringing upon social, emotional, and financial challenges. The pathology of AD involves the build up of amyloid plaques and neurofibrillary tangles years before the onset and diagnosis of the disease. Signs of cognitive decline are often first reported to health care professionals before evaluation and eventual diagnosis and treatment. Initially, these signs are often diagnosed as mild cognitive impairment (MCI), but consistent further testing is required by health care professionals to monitor the progress of the disorder and its possible development into dementia and AD. Health care professionals utilize a combination of cognitive assessment, evidence of AD pathology, and other testing to diagnose the disease and rule out other potential causes of cognitive impairment. An earlier diagnosis of AD is beneficial in planning current and future care management for AD symptoms as well as navigating the limitations for the patient, their families/caregivers, and the health care professionals themselves. In this review article, the current etiology of AD will be discussed in addition to the methods of diagnosis and treatments for the disease. Additionally, the perspectives of health care providers, patients and their family, and society as a whole will be considered in the future of AD.

Introduction

Dementia, including Alzheimer's Disease (AD), which is a progressive neurodegenerative disease most common in adults over the age of 65, currently affects at least 55 million people worldwide, and their incidence is projected to rise to 152 million affected by 2050 (GBD 2019 Dementia Forecasting Collaborators, 2022; World Health Organization, 2023). This projected increase can be attributed to an aging population, aided by the rising life expectancy, forecasted to grow by over four years in both men and women by 2050 (Stein Emil Vollset et al., 2024). AD is the most common type of dementia, with 60-70% of all dementia cases (World Health Organization, 2023). Currently, there is no cure for AD, and the available treatments focus on managing the symptoms of the disease. Some newer treatments, like the drugs lecanemab and aducanumab, have been shown to slow cognitive decline from AD by targeting the disease's underlying pathology (Alzheimer's Association, 2024; FDA, 2023; Sevigny et al., 2016). Such novel developments in AD research are promising, and such interventions can help reduce the prevalence and burden of the disease (Brookmeyer et al., 1998). However, for any such intervention to be effective, it must fit within the emotional, physical, and financial interests of AD patients and their support systems, including health care providers and caregivers.

In this review article, the etiology of AD will be covered, specifically examining the disease's progression from the preclinical stage to the later stages of worsening dementia until death. The current methods and criteria for diagnosing AD and the latest treatment options to manage the disease will be reviewed. Finally, the real-life impact of AD/dementia through the perspectives of health care professionals, affected families, and American society at large will be investigated, which should be considered when developing and implementing new interventions and guidelines for combating AD as the century progresses.

Progression of Alzheimer's Disease

Preclinical Alzheimer's Disease

In the preclinical stage of AD, amyloid beta protein, whose presence is characteristic of AD, can start building up as early as 20-30 years before the onset of dementia (Jansen et al., 2015). Additionally, the levels of phosphorylated tau protein, another hallmark of AD, rise to high levels as amyloid plaques build up in the brain (Barthélemy et al., 2020; Wegmann et al., 2021). Although amyloid buildup to a degree isn't unusual in cognitively normal older adults, amyloid levels can grow to an unhealthy amount in AD patients (Jansen et al., 2015). Cognitive decline is associated with this increase in amyloid plaques, especially in the more advanced stages within preclinical AD with unusual amyloid levels, injury markers, and slight changes in one's cognitive abilities (Vos et al., 2013). Elevated amyloid levels in older individuals have been associated with worse cognitive results on the Preclinical Alzheimer's Cognitive Composite test compared to those without higher amyloid levels (Sperling et al., 2020).

In a study estimating the duration of the different stages of AD considering age, gender, and the APOE4 ϵ 4 carrier status, the preclinical stage of AD in most of the scenarios is estimated to be the longest, especially in a research setting where AD and its progression is studied (Vermunt, 2019). This cohort study of people with amyloid pathology, where participants were studied through their lives, estimates that 20% of those with preclinical AD progress to mild cognitive impairment (MCI) due to AD after a median 3.8 year follow-up (Vermunt, 2019). Because only about a fifth of people with preclinical AD go on to develop Alzheimer's Disease, it can be difficult to diagnose AD with certainty in the early stages. The fact that older adults, who are at the most risk of developing AD, are more likely to have amyloid buildup even without the disease further complicates early diagnosis.

Mild Cognitive Impairment

MCI, a stage of cognitive decline not normal for one's age but not classified as dementia, is clinically diagnosed due to an observed change in cognition, impairment in at least one cognitive domain, and struggle to perform certain complex tasks efficiently yet able to maintain their independence (Albert et al., 2011). The cognitive domains that can be impacted include language, executive function, visuospatial processing, and memory, with impairments in episodic memory being commonly observed in those who progress further to dementia due to AD (*A Healthcare Provider's Guide to Mild Cognitive Impairment (MCI): Diagnosis, Pharmacologic Management, Non-Pharmacologic Management, and Other Considerations*, n.d.; Chehrehnegar et al., 2021; McCullough et al., 2019). It is estimated that 45% of MCI patients progress to AD mild dementia, according to a median 3.9-year follow-up (Vermunt, 2019). Therefore, at the MCI stage, it is twice as likely that the patient progresses to the next stage in the next few years than patients with preclinical AD to MCI. The MCI stage of AD may be a more optimal stage for AD intervention due to the greater certainty of AD in addition to the observation that those with MCI are still able to retain their independence despite some cognitive challenges.

Mild Dementia

In this early stage of AD dementia, the patient has progressed to dementia. Although affected individuals may face difficulties in higher-level tasks like personal financial management and act slower in general while completing other tasks, they are still able to maintain their

independence and manage most of their lives on their own (Alzheimer's Association, 2024). Individuals may need some support at this stage from trusted close people to keep up with some responsibilities, including financial as the person affected is likely dealing with retirement and now planning for their future with AD. An estimated 30% of mild dementia patients progress further to moderate and severe dementia due to AD after a median two-year follow-up (Vermunt, 2019). The follow up period being shorter compared to the preclinical and MCI stages can be attributed to the shorter durations of later AD stages compared to early stages of the disease (Vermunt, 2019). Since the individual has dementia at this point that can be disruptive to the flow of their lives, the current patient quality of life should become more of a focus when planning disease treatment and management.

Moderate/Severe Dementia

As AD progresses and further damage accumulates in the brain, impacted individuals greatly lose their independence from not being able to do daily self-care tasks such as going to the bathroom or bathing, placing the burden on their caregivers to provide around-the-clock care as their brain and body functions progressively shut down in their final stretch of life (Alzheimer's Association, 2024). The whole body is now impacted and vulnerable as it prepares for death. Important body processes like swallowing become more difficult and hazardous, a dysfunction known as dysphagia for late-stage AD patients in particular (Homer et al., 1994; Johns Hopkins Medicine, 2024). Dysphagia contributes to the development of the most frequent cause of death in AD patients, aspiration pneumonia (Kalia, 2003). Overall, Alzheimer's disease is a major cause of death and was the 7th leading cause of death in the United States in years following the start of the COVID pandemic (Centers for Disease Control and Prevention, 2021).

Diagnosis

Clinical Diagnosis

Through a combination of different tests and evaluations conducted over a period of time, a diagnosis of AD can be made. Health care providers may conduct various cognitive tests, order blood tests, analyze cerebral spinal fluid (CSF), perform psychiatric evaluations, and conduct supportive brain scans on patients with reported cognitive symptoms (National Institute on Aging, 2022). In an updated version of the 1984 NINCDS-ADRDA criteria for AD dementia diagnosis by a workgroup established by the National Institute on Aging and the Alzheimer's Association, the characteristics of a probable or possible AD dementia diagnosis are outlined for consideration in a clinical setting (McKhann et al., 2011). For a patient to be diagnosed with probable AD dementia, the criteria include the gradual onset of symptoms, short term memory loss, cognitive impairment in one other cognitive domain besides learning and memory, and the absence of events like strokes from cerebrovascular disease that can also be responsible for cognitive impairment (McKhann et al., 2011). The differential diagnosis of possible AD dementia includes the characteristics of either a more sudden change in cognitive impairment or the presence of other contributing factors, such as a history of stroke or other neurological diseases (McKhann et al., 2011). Due to the many factors that must be considered when diagnosing AD with a certain degree of certainty, the diagnosis journey can be lengthy and costly with the amount of tools and testing used in evaluation for diagnosis. Some of the criteria for diagnosis like the gradual onset of symptoms needs to be observed by patients, their family, and health providers and noted as time passes to demonstrate the criteria. If the patient isn't able to notice these changes and doesn't have family that interact with them daily, meeting such criteria can

become more difficult and the initial visit to the doctor with concern to the developing symptoms may be delayed, further slowing down the diagnosis of AD.

Treatments

At present, there are several FDA-approved drugs that either target the disease progression of AD or manage its cognitive and behavioral symptoms (*FDA-Approved Treatments for Alzheimer's*, n.d.). Additionally, non-drug interventions, such as orientation training, which help improve a patient's sense of space and time, and various mental exercises, may also be utilized if deemed suitable (National Library of Medicine, 2022).

Disease Modifying Therapies

Currently, many therapies target AD pathology, classified as disease-modifying therapies, in phases 2 and 3 of clinical testing (Cummings et al., 2019). In July 2024, the U.S. Food and Drug Administration approved Lilly's Kisunla™ (donanemab-azbt) injection as a treatment for patients with mild cognitive impairment (MCI) or mild dementia (Research, 2024). In a randomized clinical trial conducted by Eli Lilly and Company on those with early symptomatic AD, the participants with early symptomatic AD who received the donanemab had lower levels of cognitive impairment than those who received placebo (Sims et al., 2023). The side effects of Kisunla include amyloid-related imaging abnormalities (ARIA), which can lead to temporary brain swelling that resolves on its own without major complications in most cases and was seen to be 10x more common in those who received donanemab in the Lilly clinical trial (Research, 2024; Sims et al., 2023). Lecanemab, sold as Leqembi™ by Eisai, was approved by the FDA a year earlier, is another treatment that targets the underlying AD pathology and was confirmed in a randomized phase 3 clinical trial to benefit recipients of the treatment by reducing amyloid plaque build up in the brain, particularly in those with MCI or mild dementia (CTG Labs - NCBI, n.d.; FDA, 2023; "LEQEMBI®" (Lecanemab) Approved for the Treatment of Alzheimer's Disease in China | News Release: 2024, n.d.; Van Dyck et al., 2022). A third drug that targets AD pathology, aducanumab, is set to be discontinued in 2024 for management reasons by the company Biogen, the drug manufacturer, without any concerns to safety (Alzheimer's Association, 2024; Research, 2023; U.S. Food and Drug Administration, 2021). This factor of the drug industry and the role of business is important to consider due to the capitalized health care system. In the case of aducanumab, the drug was discontinued for business-related reasons rather than health-related reasons, demonstrating the significance of money in AD disease care not only for those directly and personally affected, but also for the healthcare industry whose aim is to sell health care at a favorable profit. Focusing on the new treatments, in order to maximize the effectiveness of these newer disease modifying treatments, an earlier diagnosis of AD is necessary to target and manage the disease before its symptoms and damage permanently worsen as AD progresses to the later stages.

Treating Symptoms

The drugs approved by the FDA for the management of the symptoms of Alzheimer's disease include donepezil, galantamine, memantine, and rivastigmine (*FDA-Approved Treatments for Alzheimer's*, n.d.; Howard et al., 2012; Raskind et al., 2004). Three of the drugs, donepezil, galantamine, and rivastigmine, are the cholinesterase inhibitors that stop acetylcholine, an important messenger involved in nerve cell communication, from breaking down (*FDA-Approved Treatments for Alzheimer's*, n.d.). The exposure to cholinesterase

inhibitors have been shown to reduce the mortality among dementia-prone groups, particularly nursing home residents (Havreng-Théry et al., 2024).

Additionally, the drugs brexpiprazole and suvorexant are FDA-approved to manage the behavioral and psychological symptoms of AD (*FDA-Approved Treatments for Alzheimer's*, n.d.; Grossberg et al., 2024; Herring et al., 2020). Brexpiprazole has been approved as the Rexulti™ supplement and has been shown to manage the higher prevalence of agitation in AD patients, which includes restlessness, hostile language, and physical aggression (Commissioner, 2023; Lee et al., 2023; Van der Mussele et al., 2014). The other drug used to treat the non-cognitive symptoms of AD is suvorexant, which is administered through Belsomra™'s tablets and is utilized to manage the sleep disturbance of insomnia in patients whose AD disease progression is in the mild to moderate stages (Herring et al., 2020; *HIGHLIGHTS of PRESCRIBING INFORMATION*, n.d.; *Merck Receives Approval for BELSOMRA® (Suvorexant) C-IV Label Update to Include Findings from Study of Insomnia in Patients with Mild-To-Moderate Alzheimer's Disease*, n.d.). Suvorexant is an orexin receptor antagonist that blocks OX1R and OX2R, which both contribute to wakefulness (Bennett et al., 2014).

Perspectives

Health Care Provider

Health care providers, who are responsible for maintaining the health of their patients through diagnosis, prevention, and treatment, are an important party to consider in improving the outcomes of people with AD, especially in the early diagnosis and treatment of AD (Monica Zigman Suchsland et al., 2023; World Health Organization, 2013). In interviews with ten health care providers to gather their insight and opinion on the KAER (Kickstart, Assess, Evaluate, Refer) toolkit, which aims to improve the process of diagnosing AD, although they found the toolkit to be useful, they also emphasized how such methods of cognitive assessment must be easy to use and efficient within their means (Monica Zigman Suchsland et al., 2023). Although health care providers have a critical role in the outcomes of their patients, they are often restricted by the health care systems they work in and may not always be able to provide the necessary level or type of care (Sideman et al., 2023). For instance, 69% of health care professionals acknowledge that in medical school, the condition of dementia was taught to a very limited degree or not at all despite older patients' interest on that topic as they are getting older (Alzheimer's Impact Movement, 2024). Coupled with the general lack of teaching of dementia in standard medical education, is the shortage of dementia specialists, impacting U.S. states like Kansas (Alzheimer's Association, 2024; Alzheimer's Impact Movement, 2024).

Patient and Family

The journey through AD and the major life changes associated with its occurrence affects both patients and their families significantly, particularly women, who consist of two-thirds of caregivers for people with AD (Alzheimer's Association, 2024). Additionally, according to a case-control study in Northern Italy, women were shown to have a higher risk of developing AD compared to men, although the risk of developing dementia was similar among both genders (Adani et al., 2020). On average, caregivers provide 31 hours of care to dementia patients per week, dedicating about a fifth of their lives to caregiving (Alzheimer's Association, 2024). Such long hours and the trauma of witnessing the progressive mental decline of loved ones have been shown to drastically affect the mental health of dementia caregivers, with 32.3% of caregivers experiencing suicide ideation compared to the 4.3% of adults annually on average in

the United States (Ivey-Stephenson et al., 2022; Solimando et al., 2022). Therefore, it is important to consider family, the main support system of a patient, when designing and implementing new treatments and caregiving practices. Prioritizing the health of the loved ones who stand by and support their sick family member is necessary to maximize human health and emotional well-being as well as promote the bonds of relationships in times of sickness.

Society

According to the Alzheimer's Association's *2024 Alzheimer's Disease Facts and Figures* report, a projected \$360 billion will be spent on the healthcare and long-term care of those with Alzheimer's or other dementias in the United States in 2024 (Alzheimer's Association, 2024). \$231 billion of that sum will be spent by the government programs of Medicare and Medicaid (Alzheimer's Impact Movement, 2024). If there are no major developments in dementia care or treatment, costs of this disease will increase to almost \$1 trillion in 2050, increasing both out-of-pocket and government spending under Medicare and Medicaid (Alzheimer's Association, 2024). These staggering costs could potentially bankrupt Medicare and Medicaid, especially with the projected increase in AD and other dementias in the next few decades (Alzheimer's Association, 2014; GBD 2019 Dementia Forecasting Collaborators, 2022). This increase in dementia can be attributed to the aging world population, which is caused by a greater life spans due to medical advancements and in the coming decades, will lead to a greater proportion of older, retired individuals compared to young, working people (GBD 2019 Dementia Forecasting Collaborators, 2022; United Nations, 2019). A demographic shift to older population from younger population could mean decreased government tax revenues that are utilized to fund public health care services like Medicare and Medicaid. This is particularly problematic when the need for such services will likely go up with the coming rise in AD prevalence.

However, focusing on the early diagnosis of AD has been predicted to lead to a better prognosis of the disease from an economic standpoint for health care costs. In the scenario where AD is diagnosed with greater frequency in the mild cognitive impairment (MCI) stage, it is projected that there will be \$7 trillion in cumulative savings in the United States which \$5.6 trillion would be saved in Medicare and Medicaid costs from the early diagnosis among those alive in 2018 who go on to develop AD (Alzheimer's Association, 2018). This includes medical, pharmaceutical, and long-term care costs (Alzheimer's Association, 2018; Medicare.gov, 2019; *Prescription Drug Coverage*, 2019). Therefore, working towards earlier diagnoses of AD is essential for lowering health care costs for Americans with AD and reducing the cost burden on crucial American health insurance programs. Early AD diagnosis can promote a more controlled and sustainable health care system that is better able to manage and take care of the health needs of people with AD and others in need of care in the future.

Conclusion

In this review article, the perspectives and interests ranging from that of healthcare providers to American society as a whole on Alzheimer's Disease were covered. Additionally, the fact that the current number of health care providers, who already face burnout, who diagnose and treat AD patients aren't sufficient was highlighted, especially with the doubling and tripling of dementia cases in the US and worldwide in the coming decades (Centers for Disease Control and Prevention, 2023). The importance of diagnosing and treating AD earlier on in prognosis was also emphasized because the ability of certain novel treatments to slow down disease progression is particularly more effective in the earlier stages of prognosis. Therefore,



despite current dementia medical provider limitations, it is essential that steps are taken for the timely diagnosis and treatment of AD, especially as new treatments gain traction and are utilized.

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