Alzheimer's Disease Overview

Alzheimer's disease (AD) is a progressive brain disorder and the most common form of dementia. It is thought to be caused by the abnormal buildup of certain proteins. One of the proteins called amyloid deposits and form plaques around brain cells. The other protein called tau deposits and forms tangles within brain cells. These plaques and tangles make it difficult for the cells to communicate with each other and function properly. Over time, different areas of the brain shrink, and brain cells die. The first areas of the brain usually affected are responsible for memories. As a result, early signs of the disease include forgetting recent events or conversations. Over time, it progresses to serious memory problems and loss of the ability to perform everyday tasks. In advanced stages, severe loss of brain function can cause dehydration, malnutrition, or infection. These complications can result in death. Although it is not known exactly what causes this process to begin, scientists now know that it begins many years before symptoms appear.

An estimated 6.7 million Americans aged sixty-five and older are living with Alzheimer's in 2023. Seventy-three percent are aged seventy-five or older. Women are disproportionately affected by Alzheimer's disease, comprising approximately two-thirds of all Alzheimer's patients. Research shows that older Latinos are about one-and-a-half times as likely as older whites to have Alzheimer’s and other dementias, while older African Americans are about twice as likely to have the disease as older whites. The reason for these differences is not well understood, but researchers believe that higher rates of vascular disease in these groups may also put them at greater risk for developing Alzheimer’s. Alzheimer’s is currently ranked as the seventh leading cause of death in the United States.

Experts are not exactly sure why the buildup of proteins occurs, but research suggests genetic, lifestyle, and environmental factors play a role. Age is the biggest risk factor. The condition mainly affects those 65 years of age and older and the chance of developing the disease after this age doubles every five years. Family history of the disease is also believed to play a role as people are more likely to have Alzheimer’s if a first-degree relative had it. Finally, scientists know a few gene mutations that almost guarantee the disease will occur, but these are very rare. More research is needed to better understand the link between genes and Alzheimer’s disease.

While AD cannot entirely be prevented, making modifications to certain lifestyle or environmental factors may decrease the overall risk of developing Alzheimer’s disease or another dementia-related condition. According to a study by the Centers for Disease Control (CDC), there are eight risk factors for Alzheimer’s disease including high blood pressure, physical inactivity, obesity, diabetes, depression, smoking, hearing loss, and binge drinking. In addition, a University of Minnesota study attributed 41% of dementia cases to twelve modifiable lifestyle factors. Among the twelve lifestyle factors, obesity, high blood pressure, and lack of exercise contributed the most to risk of dementia. Reducing these modifiable risk factors could potentially reduce dementia prevalence.

There is no treatment that cures Alzheimer's disease. However, medicines may improve or slow the progression of symptoms. Medications currently available for the management of AD include agents for cognitive symptoms, agents for behavioral and psychological symptoms of dementia, agents for sleep disorders, and more recently, potential disease-modifying agents.

Cholinesterase inhibitors are a group of drugs that prevents acetylcholine, a neurotransmitter, from breaking down. A neurotransmitter carries chemical signals or messages within the body from one nerve cell to the next target cell. Specifically, acetylcholine is a neurotransmitter that supports memory and learning. By stopping the breakdown of acetylcholine, these medications help to maintain more constant acetylcholine levels and enable more effective communication among nerve cells. Some cholinesterase inhibitors include donepezil (Aricept®, Aldarity®) galantamine (Razadyne®), and rivastigmine (Exelon®). Cholinesterase inhibitors may help with symptoms that relate to memory, judgement, language, and thinking. While donepezil is approved for all stages of the disease, galantamine and rivastigmine are approved for use in mild to moderate AD.

Glutamate regulators control glutamate activity. Glutamate is a neurotransmitter that helps the brain process information. The most common glutamate regulator is memantine (Namenda®, Namenda XR). Glutamate regulators may help improve memory, attention, language, reasoning, and the ability to perform basic actions. Memantine is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

Namzaric® is a combination drug product for moderate to severe AD that combines the cholinesterase inhibitor donepezil and the glutamate regulator memantine. Some studies suggest that the combination of memantine plus donepezil has improved effects on cognitive and neuropsychiatric symptoms as well as the ability to perform daily activities when compared to each agent alone, or to placebo. However, the combination medication may be associated with more side effects.

Cognitive issues are not the only troublesome symptoms associated with AD. Insomnia is also a key symptom of dementia. Belsomra® (suvorexant) was approved by the FDA in 2014 to treat insomnia. It is thought to target and inhibit the action of orexin, a neurotransmitter that plays a role in the wake-sleep cycle. In 2020, suvorexant became the first medication approved for treating sleep disorders specifically associated with Alzheimer's disease.

Patients with AD and dementia also often have behavioral and psychological disturbances. Agitation is among the most persistent, complex, and stressful aspects of care among patients with behavioral and psychological symptoms of AD. It is reported in approximately half of people with Alzheimer’s and is associated with earlier nursing home placement. In May 2023, the FDA announced the supplemental approval of Rexulti® (brexiprazole) for the treatment of agitation associated with dementia due to Alzheimer’s disease. Rexulti works to rebalance dopamine and serotonin in the brain to improve thinking, mood, and behavior. In two Phase 3 randomized clinical trials, the drug was shown to reduce agitation symptoms by 31% compared to placebo. This is the first FDA-approved treatment option for this indication. Rexulti was originally approved by the FDA in 2015 for treatment of schizophrenia and as an add-on treatment for major depressive disorder in adults.

Medications like cholinesterase inhibitors and glutamate antagonists are safe but have limited benefit for most patients, offering symptomatic relief without a successful cure of the disease. In the last couple of years, two agents with potential disease-modifying activity have been approved by the FDA for early AD. Both Aduhelm® (aducanumab) and Leqembi™ (lecanemab-irmb) work by targeting aggregated forms of amyloid beta found in the brains of AD patients in the hopes of reducing its buildup. Amyloid beta is a protein that occurs naturally in healthy brains but forms clumps or tangles between the brain cells of people with AD, causing brain-cell death that leads to symptoms including memory loss.

Aduhelm was approved by the FDA in 2021 and is administered once monthly via IV infusion. It was approved under the accelerated approval pathway. This allows patients suffering from a serious disease earlier access to drugs despite some uncertainty about the drug's clinical benefit. Aduhelm is indicated for use in patients with mild cognitive impairment or mild dementia stage of disease, the population studied in clinical trials. Aduhelm's approval was controversial in that the efficacy is based upon reduction in amyloid plaques in the brain, but there is no direct correlation with AD progression and amyloid plaques. In clinical trials, success was measured not by cognitive improvement but by slowing in the rate of cognitive and functional decline. The accelerated approval pathway requires Biogen, the manufacturer, to verify clinical benefit in a post-approval trial. If the clinical benefit is not verified within a few years, the FDA may initiate proceedings to withdraw the approval of the drug.

On July 6, 2023, the FDA gave full approval to Eisai/Biogen's Leqembi for the mild cognitive impairment or mild dementia due to AD. It is administered every other week via IV infusion and originally received accelerated approval in January 2023. The FDA converted Leqembi's accelerated approval into a traditional approval, following results of the Clarity AD trial, where a modest clinical benefit was verified. Eisai, the manufacturer, studied the medication in people with early or mild disease. Specifically, the trial's primary end point was the change from baseline at 18 months in score on the Clinical Dementia Rating-Sum of Boxes (CDR-SB). The range of rating is 0 to 18 with higher scores indicating greater impairment. The mean CDR-SB score at baseline was approximately 3.2 in both groups. Lecanemab reduced clinical decline on the CDR-SB scale compared with placebo at 18 months by 27%, which represents a treatment difference in the score change of -0.45 ($p=0.00005$). Some Alzheimer's experts say that delay is likely too subtle for patients or their families to notice. Like Aduhelm, success of Leqembi was measured not by cognitive improvement but by the decreased rate of clinical decline. Brain impairment still occurs despite the modest decrease in amyloid plaque.

Safety concerns with both Aduhelm and Leqembi should be considered by prescribers and patients before initiating therapy. Both medications have warnings for Amyloid Related Imaging Abnormalities (ARIA). ARIA is most commonly observed as temporary swelling in areas of the brain that usually resolves over time. Some patients may also have small spots of bleeding in or on the surface of the brain, and infrequently, larger areas of bleeding in the brain can occur. Most people with this type of swelling in the brain do not get symptoms. As a result, the labeling for both treatments recommend confirming the presence of amyloid beta pathology prior to initiating treatment. Currently, to demonstrate amyloid pathology a patient must undergo a positron emission tomography (PET) scan or cerebrospinal fluid (CSF) analysis. In addition, both medications recommend three to four additional MRIs to be completed before future infusions to check for ARIA.

A third amyloid-targeting monoclonal antibody, donanemab, could be approved by the end of 2023. Similar to Aduhelm and Leqembi, donanemab's effectiveness is measured by reduction in clinical decline. Clinical trials results on amyloid-positive early symptomatic participants indicated a reduced decline on the Integrated Alzheimer's Disease Rating Scale (iADRS) by 22% and on the (CDR-SB by 29% compared to placebo. When comparing phase 3 trials of donanemab and Leqembi, donanemab may be associated with a higher incidence of ARIA.

Treatment of Alzheimer's disease has always been a highly challenging area. While some progress has been made with the availability of newer medications like Aduhelm and Leqembi, opportunities still exist for medications that not only slow decline but improve disease symptoms without significant and dangerous side effects. Cost is another consideration. Despite their

modest benefit, these new therapies are expensive. Aduhelm costs approximately $28,000 per year while Leqembi is $26,500 annually. These prices are above the Institute for Clinical and Economic Review's (ICER's) suggested cost-effective annual list price of $8,500 to $20,600. According to the World Health Organization, the number of persons suffering from AD will rise by at least 14% by 2025 as a result of the increased number of adults over age 65. Therefore, the high demand for improved, cost-effective treatment options from patients, caregivers, and their providers will continue into the foreseeable future for this devasting and deadly disease.

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