Insightsfeature

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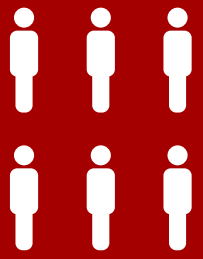
Alzheimer's Treatments on the Horizon

Potential New Drugs Offer Hope Amid Past Failures

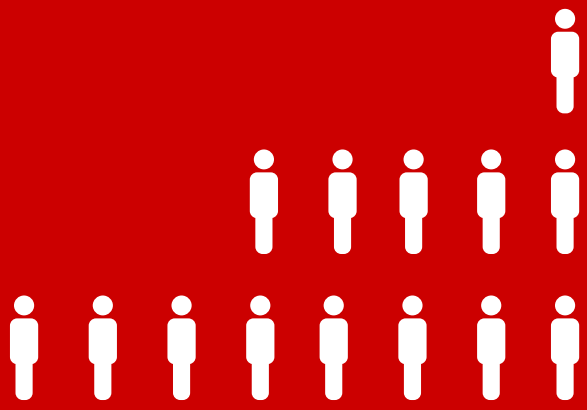
CVSHealth®

As the number of people affected by Alzheimer's disease (AD) and other dementias grows, anticipation for effective treatment also increases. Nearly six million Americans are living with Alzheimer's and that number is projected to rise to nearly 14 million by 2050.[1]

There is no cure for Alzheimer's disease, which is the sixth leading cause of death in the U.S.[1] Available medications can treat symptoms, but there is no approved medication that can mitigate its progression. However, at least one new drug nearing the end of clinical trials — and others in different trial phases — may offer the first viable treatments to slow the advance of Alzheimer's.



6M Americans currently living with Alzheimer's[1]



14M projected Alzheimer's cases in 2050[1]

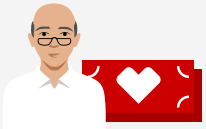
Complexity and Costs

AD was first documented in 1901 by German psychiatrist Alois Alzheimer.[2] What makes the condition so devastating are its symptoms, which include impaired memory, agitation, incontinence, difficulty sleeping, inability to recognize family or friends, and in late stages, inability to sit or walk, seizures, and vulnerability to infections, ultimately leading to death.[3] AD primarily affects people aged 65 and older, but some 200,000 Americans are diagnosed at younger ages.[1]

The toll on caregivers is also tremendous. An estimated 18.5 billion hours of care valued at $234 billion are provided by family and other caregivers. Two-thirds of caregivers are women and a third are over age 65.[1]

Among 70 year olds with AD, 61 percent are expected to die before the age of 80 — more than double the rate of those without Alzheimer's.[1] People aged 65 and older survive an average of four to eight years after a diagnosis of Alzheimer's dementia.[1]

The costs of living with AD and associated conditions reached an estimated $290 billion in 2019 and are expected to jump to $1.2 trillion by 2050.[1] Those costs include a doubled incidence of hospital stays each year compared with other older people.[1]



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Currently Available Treatments

The five drugs approved for AD treatment in the U.S. only have symptom reducing effects and are not disease modifying agents — drugs that slow or reverse the disease's progression. Two classes of drugs temporarily treat AD's cognitive symptoms: cholinesterase inhibitors (CI) and memantine, a N-methyl D-aspartate (NMDA) antagonist. CIs increase the volume and activity of neurotransmitters and NMDA blocks the transfer of oversupplies of calcium to cells, which can damage them.[4] They treat issues with memory, thinking, language, judgment, and other thought processes.[5]

Current therapy options include:

Drug[6]	Mechanism	Treatment Use	Modality
Aricept (donepezil)	CI	Mild to severe cases	Oral
Exelon (rivastigmine)	CI	Mild to moderate cases or a patch for severe cases	Oral or transdermal patch
Namenda (memantine)	NMDA	Moderate to severe cases	Oral
Namzaric (memantine and donepezil)	NMDA and CI	Moderate to severe cases	Oral
Razadyne (galantamine)	CI	Mild to moderate cases	Oral

Other non-pharmacological therapies like nutrition, cognitive rehabilitation, and exercise programs are often used to mitigate the symptoms or slow progression.

Past Failures, but Hope for the Future

The search for an effective treatment or cure for AD has been littered with failure after failure over the last two decades. The most recent among them was Dominantly Inherited Alzheimer's Network Trials of gantenerumab, by Roche and Genentech, and solanezumab, by Eli Lilly.[7] The five-year investigation of a rare genetic AD strain was halted earlier this year for poor performance, shocking and disappointing researchers. However, there are more than 500 other active drug research projects around the world.[7]

In March 2019, two phase 3 clinical trials of the investigational intravenous infusion treatment aducanumab by Biogen were halted because they failed to reduce brain cell death in patients with mild cognitive impairment due to AD.[8]

However, Biogen re-analyzed its trial data and discovered that aducanumab administered at higher doses of 10 milligrams per kilogram of body weight and over a longer period was effective in delaying dementia decline by approximately 30 percent compared to placebo.[9] This positive effect was only seen in a small subset of patients and was only demonstrated in one of the two phase 3 trials.[10] Because the positive results were based on a small subset, some researchers suggested that additional trials were needed before the drug was submitted to the U.S. Food and Drug Administration (FDA).[11]

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If approved, aducanumab will be the first therapy to slow disease progression.

In clinical trials, aducanumab caused serious side effects in some users. Biogen reported that the higher dose treatment produced signs of brain swelling or bleeding in up to 40 percent of participants, brain scans showed.[9]

Biogen resubmitted its clinical trial data to the FDA and sought permission to restart clinical trials of the human monoclonal antibody at the higher dose. If approved, the drug will be the first to slow the advance of AD and the first to confirm that treating the build-up of the sticky protein beta-amyloid is an effective modality against the build-up of plaques, which interfere with cognition.[12]

If aducanumab is approved by the FDA, the more important outcome may be that it will create momentum for next-generation drug research on the role of beta-amyloid oligomers, which some believe are the underlying cause of neurodegeneration and cognitive impairment, and could lead to more effective and safer therapies.[13]

If approved as the first disease modifying treatment, aducanumab will likely have a significant cost impact for payors. Biogen estimates that 10 million Americans would be eligible for treatment.[11] The list price of the drug hasn't been released. While the drug was once estimated to be approved as early as this fall, the company now expects to resubmit their application in the third quarter.[14] This means approval is likely to be delayed and the COVID-19 pandemic could further create uncertainty. When approved, the drug will fall under the medical benefit given its intravenous mode of administration.[15]

Other Therapies in Development

Researchers are also pursuing multiple new avenues of treatment that offer even greater hope for AD treatments over the next few years. Of 46 trials in process, 30 target disease processes other than beta-amyloid.[7] Drugs in development focus on a range of modalities, including stimulating the immune system to protect neurons from toxic proteins and vaccines targeting tau protein tangles, which are the brain nerve-cell destroyers that are a hallmark of Alzheimer's.

Several drugs have reached phase 3 trials and many others are in earlier stages of testing.[16] Some researchers believe successful treatment most likely will require a combination of drugs aimed at several targets.[16]

Drug maker Novartis has taken a unique approach in trying to develop a vaccine for Alzheimer's rather than a treatment. CAD106, an injectable vaccine in phase 2/3 trials, stimulates the immune system against beta-amyloid formulation. Its side effects include headache, muscle pain, fatigue, and inflammation of the nose and throat.[17] CAD106 trials are expected to be completed in 2023.

Compounds in phase 3 trials include:

- **BAN2401:**

  In joint development by Biogen and Japanese drug maker Eisai Co., is an intravenous anti-amyloid monoclonal antibody.[18] Earlier results showed that the drug reduced clinical signs of AD and improved cognition, reducing amyloid clusters by up to 70 percent.[18]

- **Nuplazid** (primavanserin):

  A symptomatic therapy, is an oral selective serotonin receptor inverse agonist that received Breakthrough Therapy designation from the FDA to treat dementia-related psychosis in Parkinson's disease. In a phase 3 trial that was halted early due to positive outcomes, it showed promise in treating similar symptoms in Alzheimer's and other conditions that cause psychosis. [19] Developer Acadia Pharmaceuticals plans to meet with the FDA in the first half of 2020 to discuss a supplemental new drug application submission.[16]

Improving Diagnosis, Ensuring Capacity

If the FDA approves a disease modifying treatment, one of the most pressing needs will be accurate diagnostic AD screening of the population so that treatment can begin as early as possible and before brain cell damage has occurred. About 15 million Americans have mild cognitive impairment, which could be an early sign of the disease, and they will have to be evaluated, and receive diagnostic testing — and potentially treated.[20] As Baby Boomers and Gen Xers age, the demand to quickly and easily screen will grow, and unfortunately there are a limited number of specialists available to evaluate and diagnose patients. One analysis predicts an average 18.6-month wait time for treatment in 2020.[20] In addition, about 2.1 million patients would develop the condition, while on wait lists, between now and 2040.

Aducanumab and at least one other treatment in development will need to be administered as an infusion. This means ensuring there is sufficient infusion capacity available to treat the patients that are diagnosed and are eligible for treatments, will also be critical.

CVS Health will continue to develop strategies to help patients access the right treatment at the right time, and support their condition journey, while helping payors manage care for their plan members and balance cost and appropriate access.

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