

Alzheimer's disease treatment horizons

Current drugs to treat symptoms

The U.S. Food and Drug Administration (FDA) has approved five drugs to treat the symptoms of Alzheimer's disease:

- Donepezil (Aricept®)
- Galantamine (Razadyne®)
- Rivastigmine (Exelon®)
- Memantine (Namenda®)
- Memantine + Donepezil (Namzaric®)

These drugs work by increasing the amount of chemicals in the brain called neurotransmitters, which help nerve cells in the brain (neurons) communicate with each other. While these drugs may temporarily help with symptoms, they do not treat the underlying causes of Alzheimer's or slow its progression.

Targets for future drugs

Many drugs in development aim to interrupt the disease process itself by impacting one or more of the brain changes associated with Alzheimer's. These changes offer potential "targets" for new drugs to slow or stop the progress of the disease. Researchers believe successful treatment will eventually involve a combination of medications aimed at several targets, similar to current treatments for many cancers and AIDS.

The following are examples of promising targets for next-generation drug therapies under investigation in current research studies.

Target: Beta-amyloid

Beta-amyloid is the chief component of plaques, one hallmark Alzheimer's brain abnormality. Scientists have a detailed understanding of how this protein fragment is clipped from its parent compound, amyloid precursor protein (APP), by two enzymes — beta-secretase and gamma-secretase — to form the beta-amyloid protein that is present in abnormally high levels in the brains of people with Alzheimer's.

Researchers are developing medications aimed at almost every point in the amyloid processing pathway. This includes blocking activity of the beta-secretase enzyme; preventing the beta-amyloid fragments from clumping into plaques; and even using antibodies against beta-amyloid to clear it from the brain. Several clinical trials of investigational drugs targeting beta-amyloid are underway.

Current drug in research that targets beta-amyloid: Posiphen

Posiphen is a selective inhibitor of the production of amyloid precursor protein (APP) that may delay the onset of Alzheimer's disease or slow the progression of brain damage due to amyloid buildup. In small early-phase clinical studies, posiphen was determined to readily enter the brain and in cerebrospinal fluid tests, scientists found that the drug lowered levels of amyloid, tau and inflammation — all key targets in the effort to find therapies for Alzheimer's. The Posiphen in Early Alzheimer's Disease (Discover Study) clinical study is recruiting volunteers to evaluate the safety, pharmacokinetics and efficacy of three different doses of posiphen in older adults living with early-stage Alzheimer's disease. The study will conclude in December 2019. Researchers think this drug could be used as a disease-modifying treatment.

Target: Beta-secretase

Beta-secretase (BACE) is one of the enzymes that clips APP and makes it possible for beta-amyloid to form. Therapies that interrupt this process may reduce the amount of beta-amyloid in the brain and ultimately intervene in the development of Alzheimer's disease.

Current drug in research that targets beta-secretase: CNP520

CNP520 is a BACE1 inhibitor designed to prevent the BACE1 enzyme from cutting up APP, a move that should curb amyloid-beta accumulation. CNP520 is being investigated in two trials within the Alzheimer's Prevention Initiative's Generation Program. The Generation Study 1 includes cognitively healthy older adults who are at high risk of developing Alzheimer's based on their age and having two copies of the Alzheimer's risk gene apolipoprotein (APOE)-e4. This study focuses on whether two investigational drugs — an active immunotherapy (CAD106) and a BACE inhibitor (CNP520) — can prevent or delay the onset of Alzheimer's symptoms. The Generation Study 2, started in 2017, will compare CNP520 and a placebo's ability to slow cognitive decline in people at risk for the onset of clinical Alzheimer's symptoms based on their age, APOE genotype and elevated amyloid. Both trials will run five to eight years and are expected to conclude by 2025. (Drug is still in research; not available to the public.)

Target: Tau protein

Tau is a protein that helps stabilize the internal skeleton of nerve cells (neurons) in the brain. This internal skeleton has a tube-like shape through which nutrients and other essential substances travel to reach different parts of the neuron. In Alzheimer's disease, an abnormal form of tau builds up and causes the internal skeleton to fall apart. These abnormal forms of tau protein cling to other tau proteins inside the neuron and form "tau tangles." Large accumulations of these tangles are one of the hallmarks of Alzheimer's disease. Researchers are investigating mechanisms to prevent tau protein from collapsing and twisting into tangles.

Current drug in research that targets tau protein: AADvac1

AADvac1 is a vaccine that stimulates the body's immune system to attack an abnormal form of tau protein that destabilizes the structure of neurons. If successful, it has the potential to help slow or stop the progression of Alzheimer's disease. The phase I safety study concluded in March 2015. A phase II clinical trial, called ADAMANT, enrolled 208 volunteers with mild Alzheimer's disease in March 2016. The study was expected to be completed in June 2019. (Drug is still in research; not available to the public.)

Target: Inflammation

Inflammation in the brain has long been known to play a role in the changes that occur in Alzheimer's disease. Both beta-amyloid plaques and tau tangles cause an immune response in the brain and microglia cells act as the first form of immune defense against them. However, while microglia help clear beta-amyloid in the brain, they can become overactive in the presence of plaques and produce compounds that damage nearby cells.

Current drug in research that targets inflammation: Sargramostim

Approved by the FDA for bone marrow stimulation in people with leukemia, Sargramostim stimulates the innate immune system. It is being tested in Alzheimer's because it may stimulate immune processes that could protect neurons in the brain from toxic proteins. A phase II study of Sargramostim is underway and is expected to be completed in May 2020 (Drug is still in research; not available to the public.)

Target: 5HT6 receptor

The **5HT6 receptor** found on some brain cells can lock in chemicals called neurotransmitters. This decreases the amount of neurotransmitters available for the brain to use for communication between nerve cells (neurons). Only

through neuron-to-neuron communication can an individual think and function normally. Acetylcholine is one of these neurotransmitters. People with Alzheimer's disease have low levels of acetylcholine. Blocking the 5HT6 receptor may increase the amount of acetylcholine and help nerve cells to maintain normal communication.

Current drug in research that targets 5-HT2A: Pimavanserin

Pimavanserin is an inverse agonist for the 5-HT2A receptor. This means that pimavanserin mimics the shape of the serotonin 'key' and fits into the 5-HT2A 'lock'. However, pimavanserin has the opposite effect of serotonin: it reduces communication between neurons. This may have the effect of reducing the symptoms of dementia-related psychosis. A phase III clinical trial of pimavanserin is underway. The study is expected to be completed in March 2020. (Drug is still in research; not available to the public.)

Alzheimer's Disease Prevention Trials

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Trial

The A4 trial is studying the effectiveness of solanezumab, a drug targeting beta-amyloid, in 1,150 symptom-free volunteers whose PET scans show abnormally high levels of beta-amyloid in the brain. High levels of beta-amyloid in the brain increase the risk for developing Alzheimer's disease. Researchers hope that early intervention in individuals at increased risk of developing Alzheimer's will prevent the cognitive decline of this devastating and ultimately fatal disease. Due to results of a different study on solanezumab, the A4 researchers decided to quadruple the dose of solanezumab from 400 to 1,600 mg and add 72 weeks to the study period. They believe that by increasing the dose and extending the study, they will be able to provide more definitive answers on solanezumab as a therapy for Alzheimer's.

Dominantly Inherited Alzheimer Network Trial Unit (DIAN-TU)

Mutations on three genes are known to cause a rare form of Alzheimer's disease that accounts for less than 1% of cases. When a person has one of these mutations, he or she has a 95% to 100% chance of developing Alzheimer's. DIAN-TU hopes to slow or stop the development of Alzheimer's in these individuals with experimental drugs. Two drugs, gantenerumab and solanezumab, are currently being tested. Both are designed to help remove excess beta-amyloid in the brain. The brain changes of people with this form of Alzheimer's are very similar to the brain changes of those with the more common sporadic form of Alzheimer's disease. It's possible that a drug that slows or stop Alzheimer's in DIAN-TU participants will also slow or stop Alzheimer's in people with or at high risk of sporadic Alzheimer's. The DIAN-TU trial of solanezumab and gantenerumab is scheduled to conclude at the end of 2019.

The Alzheimer's Prevention Initiative (API)

API includes both the Autosomal Dominant Alzheimer's Disease (ADAD) trial and the Generation Study. Like DIAN-TU, API tests therapies in people who have a gene mutation that causes Alzheimer's, but have not yet developed symptoms. Drugs that delay or prevent symptoms in people with genetic mutations for Alzheimer's may potentially delay or prevent symptoms in people with the brain changes of Alzheimer's who do not have these genetic mutations. The ADAD trial is studying the effects of crenezumab, an immune-based therapy. Crenezumab delivers antibodies against beta-amyloid in an effort to reduce the negative cognitive effects of excess beta-amyloid. The ADAD is expected to conclude in February 2022.

The Generation Program, described above under "beta-secretase," includes cognitively healthy older adults who are at high risk of developing Alzheimer's based on their age and having two copies of the Alzheimer's risk gene apolipoprotein (APOE)-e4.

TS-0043 | Updated October 2019