

Alzheimer's disease treatment horizons

Current drugs to treat Alzheimer's symptoms

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

- Galantamine (Razadyne®)
- Rivastigmine (Exelon®)
- Donepezil (Aricept®)
- 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 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 living 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 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: Aducanumab.

Aducanumab is a recombinant monoclonal antibody targeting aggregated forms of beta-amyloid, such as oligomers and fibrils, that can develop into amyloid plaque in the brains of people living with Alzheimer's disease. Early studies showed decreased levels of beta-amyloid in the brains of study volunteers. Two Phase 3 studies are underway to test whether monthly doses of Aducanumab can slow cognitive and functional decline in people with early Alzheimer's disease. The studies are expected to be completed in late 2019. (Drug is still in research; not available to the public.)

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: JNJ-54861911.

JNJ-54861911 inhibits the ability of the beta-secretase enzyme to make beta-amyloid. It is currently in a Phase 3 study to determine if it slows cognitive decline in people who do not have Alzheimer's symptoms but have elevated levels of beta-amyloid in the brain. The study is expected to be completed in 2024. JNJ-54861911 is administered in pill form. (Drug is still in research; not available to the public.)

Target: Tau protein

Tau protein is the chief component of tangles, the other hallmark brain abnormality of Alzheimer's disease. Tau protein helps maintain the structure of a neuron, including tiny tube-like structures called microtubules that deliver nutrients throughout the neuron. Researchers are investigating mechanisms to prevent tau protein from collapsing and twisting into tangles, a process that destroys microtubules and, ultimately, the neuron itself.

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. A Phase 2 clinical trial enrolling 185 volunteers living with mild Alzheimer's disease began in March 2015 and is expected to be completed in February 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 2 study of Sargramostim is underway. It is expected to be completed in late 2018. (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 living 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 3 clinical trial of pimavanserin is underway. The study is expected to be completed in September 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.

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 percent of cases. When a person has one of these mutations, he or she has a 95 to 100 percent 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 living with the more common sporadic form of the disease. It's possible that a drug that slows or stops Alzheimer's in DIAN-TU participants will also slow or stop the in people living with, or who are at high risk of, sporadic Alzheimer's.

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 who have the brain changes of Alzheimer's but not 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 Generation Study 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.

Resources

Alzheimer's Association Research Center

alz.org/research

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