Alzheimer’s disease treatment horizons

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

- Galantamine (Razadyne®)
- Rivastigmine (Exelon®)
- Donepezil (Aricept®)
- Tacrine (Cognex®)
- 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 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: Solanezumab**

Solanezumab is a monoclonal antibody designed to lower the level of beta-amyloid in the brain. The antibody binds to beta-amyloid, preventing the formation of plaques; solanezumab may also help carry excess beta-amyloid away from the brain. Several studies of this drug are underway with the goal determining if solanezumab improves participants’ cognition (thinking and memory) and functioning. Some participants will undergo a brain scan called positron emission tomography (PET) to determine levels of beta-amyloid in the brain. (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: Verubecestat**

Verubecestat is a BACE inhibitor — it inhibits the ability of the beta-secretase enzyme to make beta-amyloid. At the Alzheimer’s Association International Conference® (AAIC®), researchers reported that the drug significantly lowered beta-amyloid levels in people with mild-to-moderate Alzheimer’s. Verubecestat is being tested in two phase 3 clinical trials. One is testing it in more than 2,000 people with mild-to-moderate Alzheimer’s, and the other is testing it in 1,500 individuals with prodromal Alzheimer’s and mild cognitive impairment (MCI). These individuals are at high risk of Alzheimer’s, but still able to function normally. (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 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: CSP-1103**

CSP-1103 (also known as CHF 5074) is a microglial modulator that aims to reduce inflammation in the brain. At AAIC, researchers presented the results of a 90-week phase 2 clinical trial in which CSP-1103 was given to people who had MCI. In MCI, people have subtle memory and thinking problems, but these problems don’t interfere with their ability to carry out everyday activities. Many, but not all, people with MCI go on to develop Alzheimer’s. Preliminary results of the phase 2 study showed that CSP-1103 prevented beta-amyloid from being deposited on neurons. It also reduced problems with thinking and memory (cognition). The cognitive tests of people who had participated for at least 64 weeks showed statistically significant improvements in participants’ cognitive abilities. A phase 3 study of CSP-1103 is planned. (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 5HT6: Intepirdine**
Intepirdine is a 5HT6 receptor antagonist that blocks the receptor’s ability to decrease acetylcholine levels. A phase 3 clinical trial of Intepirdine began in October 2015 with a goal of recruiting 1,150 people with mild-to-moderate Alzheimer’s disease. The trial is expected to be completed in October 2017, at which time researchers compare the thinking and functioning abilities of study participants who received Intepirdine with those who received an identical but inactive pill. (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.

TOMMORROW Trial
The TOMMORROW Trial includes 3,500 asymptomatic individuals, including some who have the Alzheimer’s risk gene apolipoprotein E e4 (APOE-e4) or the TOMM40 risk gene. The trial will explore whether the anti-diabetes drug pioglitazone can prevent MCI due to Alzheimer’s disease. Studies suggest that pioglitazone may decrease inflammation and beta-amyloid levels in the brain, improve blood flow to the brain and increase the brain’s ability to use glucose to fuel nerve cells.

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 with the more common sporadic form of Alzheimer’s disease. It’s possible that a drug that slows or stops 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 Alzheimer’s Prevention Initiative (API)
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 API 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.

**Resources**

**Alzheimer’s Association Research Center**
alz.org/research