Current Alzheimer's Treatments

"Cholinesterase inhibitors and memantine slightly reduced short-term cognitive decline, and cholinesterase inhibitors slightly reduced reported functional decline, but differences versus placebo were of uncertain clinical importance. Evidence was mostly insufficient on drug treatment of BPSD [behavioral and psychological symptoms of dementia] and on supplements for all outcomes." (Fink et al., 2020, *Annals of Internal Medicine*, p. 1)[1]

List of Current Medications for Memory or Behavioral Symptoms

https://www.nia.nih.gov/health/alzheimers-treatment/how-alzheimers-disease-treated

Dosage and side effects of Alzheimer's disease medications

Doctors usually start patients at low drug doses and gradually increase the dosage based on how well a patient tolerates it. There is some evidence that certain people may benefit from higher doses of Alzheimer's medications. However, the higher the dose, the more likely unwanted side effects will occur.

Patients should be monitored when a drug is started. All of these medicines have possible side effects that may include nausea, vomiting, diarrhea, allergic reactions, loss of appetite, headaches, confusion, dizziness, and falls. Report any unusual symptoms to the prescribing doctor right away.

It is important to follow your doctor's instructions when taking any medication, including vitamins and herbal supplements. Talk with your doctor before adding or changing any medications.

- **Alzheimer's disease medications**
  The following list provides an overview of Alzheimer's medications. Talk with your health care providers about your options and which ones may be most appropriate for you.

  FDA-approved medications to manage symptoms

  - **Brexpiprazole.** *Atypical antipsychotic.* Treats agitation resulting from Alzheimer's. Possible side effects include common cold symptoms, dizziness, high blood sugar, and stroke. Read more about **brexpiprazole** on MedlinePlus.
  - **Donepezil.** *Cholinesterase inhibitor.* Treats symptoms of mild, moderate, and severe Alzheimer's by preventing the breakdown of acetylcholine in the brain. Possible side effects include nausea, vomiting, diarrhea, insomnia, muscle cramps, fatigue, and weight loss. Read more about **donepezil** on MedlinePlus.
  - **Galantamine.** *Cholinesterase inhibitor.* Treats symptoms of mild to moderate Alzheimer's by preventing the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain. Possible side effects include nausea, vomiting, diarrhea, decreased appetite, weight loss, dizziness, and headache. Read more about **galantamine** on MedlinePlus.
  - **Benzgalantamine.** *Cholinesterase inhibitor.* The active component of this compound, galantamine, treats symptoms of mild to moderate Alzheimer's disease. Benzgalantamine was developed to reduce some of the side effects associated with galantamine, including digestive upset. Galantamine prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain. Read more about **benzgalantamine** on MedlinePlus.

[1] Fink, H. A., Linskens, E. J., MacDonald, R., Silverman, P. C., McCarten, J. R., Talley, K. M., ... & Butler, M. (2020). Benefits and harms of prescription drugs and supplements for treatment of clinical Alzheimer-type dementia: A systematic review and meta-analysis. *Annals of internal medicine*, *172*(10), 656-668.

- **Memantine.** *NMDA antagonist.* Treats symptoms of moderate to severe Alzheimer's by blocking the toxic effects associated with excess glutamate and regulates glutamate activation. Possible side effects include dizziness, headache, diarrhea, constipation, and confusion. Read more about **memantine** on MedlinePlus.
- **Memantine and Donepezil (manufactured combination).** *NMDA antagonist.* Treats symptoms of moderate to severe Alzheimer's by blocking the toxic effects associated with excess glutamate and prevents the breakdown of acetylcholine in the brain. Possible side effects include headache, nausea, vomiting, diarrhea, dizziness, anorexia, and ecchymosis (small bruising from leaking blood vessels). Read more about **memantine** and **donepezil** on MedlinePlus.
- **Rivastigmine.** *Cholinesterase inhibitor.* Treats symptoms of mild, moderate, and severe Alzheimer's by preventing the breakdown of acetylcholine and butyrylcholine (a chemical similar to acetylcholine) in the brain. Possible side effects include nausea, vomiting, diarrhea, weight loss, indigestion, decreased appetite, anorexia, and muscle weakness. Read more about the **liquid and capsule forms of rivastigmine** and the **transdermal patch form of rivastigmine** on MedlinePlus.

FDA-approved medications to treat Alzheimer's

- **Lecanemab.** *Disease-modifying immunotherapy.* Treats mild cognitive impairment or mild Alzheimer's by removing abnormal beta-amyloid to help reduce the number of plaques in the brain. Possible side effects include brain swelling and bleeding, headache, cough, diarrhea, nausea, vomiting, fever, chills, body aches, fatigue, high blood pressure, low blood pressure, and low oxygen. Read more about **lecanemab** on MedlinePlus.
- **Donanemab.** *Disease-modifying immunotherapy.* Treats mild cognitive impairment or mild Alzheimer's by removing abnormal beta-amyloid to help reduce the number of plaques in the brain. Possible side effects include brain swelling and bleeding, headache, confusion, dizziness, vision changes, nausea, seizures, and difficulty walking. Read more about **donanemab** on MedlinePlus.

Managing Behavioral Symptoms of Alzheimer's disease

Common behavioral symptoms of Alzheimer's include sleeplessness, wandering, agitation, anxiety, aggression, restlessness, and depression. Scientists are learning why these symptoms occur and are studying new treatments — drug and non-drug — to manage them. Research has shown that treating behavioral symptoms can provide comfort for people with Alzheimer's and make things easier for caregivers.

Experts agree that medicines to treat these behavior problems should be used only after other non-drug strategies have been tried. Learn more about behavioral changes in people with Alzheimer's disease and ways to cope.

Medicines to be used with caution in people with Alzheimer's disease

Some medicines, such as sleep aids, anti-anxiety drugs, anticonvulsants, and antipsychotics warrant extra caution for people living with Alzheimer's. These drugs should only be considered as options after:

- A doctor has explained all the risks and side effects of the medicine
- Other, safer non-drug options have not helped treat the problem

People living with Alzheimer's and their caregivers must watch for side effects from these medications.

Sleep aids are used to help people get to sleep and stay asleep. People with Alzheimer's should *not* use these drugs regularly because they make the person more confused and more likely to fall. There are lifestyle changes people can make to improve their sleep. Learn more about getting a good night's sleep.

Anti-anxiety drugs are used to treat agitation. Certain types of anti-anxiety drugs, such as benzodiazepines, can cause sleepiness, dizziness, falls, and confusion. For this reason, doctors recommend they only be used for short periods of time, if at all.

Anticonvulsants are drugs sometimes used to treat severe aggression. Side effects may cause sleepiness, dizziness, mood swings, and confusion.

Antipsychotics are drugs used to treat hallucinations, delusions, and paranoia, and agitation and aggression. Their side effects can be serious, including increased risk of death in some older people with dementia. These medications should only be given to people with Alzheimer's when the doctor agrees the symptoms are severe.

Alzheimer's treatments: What's on the horizon?

https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-treatments/art-20047780

Taking aim at plaques

Some of the new Alzheimer's treatments target clumps of the protein beta-amyloid, known as plaques, in the brain. Plaques are a characteristic sign of Alzheimer's disease.

Strategies aimed at beta-amyloid include:

- **Recruiting the immune system.** Medicines known as monoclonal antibodies may prevent beta-amyloid from clumping into plaques. They also may remove beta-amyloid plaques that have formed. They do this by helping the body clear them from the brain. These medicines mimic the antibodies your body naturally produces as part of your immune system's response to foreign invaders or vaccines.

  The U.S. Food and Drug Administration (FDA) has approved lecanemab (Leqembi) and donanemab (Kisunla) for people with mild Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease.

  Clinical trials found that the medicines slowed declines in thinking and functioning in people with early Alzheimer's disease. The medicines prevent amyloid plaques in the brain from clumping.

  Lecanemab is given as an IV infusion every two weeks. Your care team likely will watch for side effects and ask you or your caregiver how your body reacts to the drug. Side effects of lecanemab include infusion-related reactions such as fever, flu-like symptoms, nausea, vomiting, dizziness, changes in heart rate and shortness of breath.

  Donanemab is given as an IV infusion every four weeks. Side effects of the medicine may include flu-like symptoms, nausea, vomiting, headache and changes in blood pressure. Rarely, donanemab can cause a life-threatening allergic reaction and swelling.

Also, people taking lecanemab or donanemab may have swelling in the brain or may get small bleeds in the brain. Rarely, brain swelling can be serious enough to cause seizures and other symptoms. Also in rare instances, bleeding in the brain can cause death. The FDA recommends getting a brain MRI before starting treatment. The FDA also recommends periodic brain MRIs during treatment for symptoms of brain swelling or bleeding.

People who carry a certain form of a gene known as APOE e4 appear to have a higher risk of these serious complications. The FDA recommends testing for this gene before starting treatment.

If you take a blood thinner or have other risk factors for brain bleeding, talk to your healthcare professional before taking lecanemab or donanemab. Blood-thinning medicines may increase the risk of bleeds in the brain.

More research is being done on the potential risks of taking lecanemab and donanemab. Other research is looking at how effective the medicines may be for people at risk of Alzheimer's disease, including people who have a first-degree relative, such as a parent or sibling, with the disease.

The monoclonal antibody solanezumab did not show benefits for individuals with preclinical, mild or moderate Alzheimer's disease. Solanezumab did not lower beta-amyloid in the brain, which may be why it wasn't effective.

- **Preventing destruction.** A medicine initially developed as a possible cancer treatment — saracatinib — is now being tested in Alzheimer's disease.

  In mice, saracatinib turned off a protein that allowed synapses to start working again. Synapses are the tiny spaces between brain cells through which the cells communicate. The animals in the study experienced a reversal of some memory loss. Human trials for saracatinib as a possible Alzheimer's treatment are now underway.

- **Production blockers.** These therapies may reduce the amount of beta-amyloid formed in the brain. Research has shown that beta-amyloid is produced from a "parent protein" in two steps performed by different enzymes.

  Several experimental medicines aim to block the activity of these enzymes. They're known as beta- and gamma-secretase inhibitors. Recent studies showed that the beta-secretase inhibitors did not slow cognitive decline. They also were associated with significant side effects in those with mild or moderate Alzheimer's. This has decreased enthusiasm for the medicines.

Keeping tau from tangling

A vital brain cell transport system collapses when a protein called tau twists into tiny fibers. These fibers are called tangles. They are another common change in the brains of people with Alzheimer's. Researchers are looking at a way to prevent tau from forming tangles.

Tau aggregation inhibitors and tau vaccines are currently being studied in clinical trials.

Reducing inflammation

Alzheimer's causes chronic, low-level brain cell inflammation. Researchers are studying ways to treat the processes that lead to inflammation in Alzheimer's disease. The medicine sargramostim

(Leukine) is currently in research. The medicine may stimulate the immune system to protect the brain from harmful proteins.

Researching insulin resistance

Studies are looking into how insulin may affect the brain and brain cell function. Researchers are studying how insulin changes in the brain may be related to Alzheimer's. However, a trial testing of an insulin nasal spray determined that the medicine wasn't effective in slowing the progression of Alzheimer's.

Studying the heart-head connection

Growing evidence suggests that brain health is closely linked to heart and blood vessel health. The risk of developing dementia appears to increase as a result of many conditions that damage the heart or arteries. These include high blood pressure, heart disease, stroke, diabetes and high cholesterol.

A number of studies are exploring how best to build on this connection. Strategies being researched include:

- **Current medicines for heart disease risk factors.** Researchers are looking into whether blood pressure medicines may benefit people with Alzheimer's. They're also studying whether the medicines may reduce the risk of dementia.
- **Medicines aimed at new targets.** Other studies are looking more closely at how the connection between heart disease and Alzheimer's works at the molecular level. The goal is to find new potential medicines for Alzheimer's.
- **Lifestyle choices.** Research suggests that lifestyle choices with known heart benefits may help prevent Alzheimer's disease or delay its onset. Those lifestyle choices include exercising on most days and eating a heart-healthy diet.

Hormones

Studies during the 1990s suggested that taking hormone replacement therapy during perimenopause and menopause lowered the risk of Alzheimer's disease. But further research has been mixed. Some studies found no cognitive benefit of taking hormone replacement therapy. More research and a better understanding of the relationship between estrogen and cognitive function are needed.