

# Alzheimer's Disease: A Comprehensive Review of its Causes, Diagnosis, and Treatment

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## ABSTRACT

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that results in the loss of memory, motor function, ability to think, and other basic functions required for day-to-day life. The causes of the disease are still being investigated, but scientists and researchers have mostly agreed on one of the major genetic contributions to the disease. The excess buildup of two proteins, Tau and  $\beta$ -amyloid, limits communication between nerve cells or neurons. The buildup of these proteins only increases with the progression of the disease. This paper will discuss the genetic causes of AD, the process behind the formation of neurofibrillary tangles and amyloid plaques, recent neuroimaging techniques that help diagnose the disease, current symptomatic treatments, and upcoming future treatments that may be able to slow the progression of the disease significantly.

## Introduction

Imagine you're at home, you're going about your day, and you forget to take out the trash, but someone eventually reminds you to do it. Later, you are reading an article, but you must read it again to understand it. The next day at your new job, you forget your boss's name. What you just read was a short description of early-stage symptoms of Alzheimer's Disease, the most common neurodegenerative disease. Patients with Alzheimer's Disease (AD) have normal lives, but they are taken away from them over time. What they experience is referred to as Dementia, a condition which causes progressive loss of brain function in areas like memory and thinking and changes in personality. But what causes AD? As of now, most findings lead us to believe that excess protein buildup between neurons in the brain is one of the most common genetic causes of disease. The proteins in question are Tau and Beta Amyloid ( $A\beta$ ). Tau proteins are proteins that, in AD patients, have an incorrect chemical makeup. This, along with their long, strand-like shape, causes them to be attracted and tangle with each other inside the neurons.  $A\beta$  is a peptide fragment formed by an error in the genetic code. This incorrect code results in the formation of a peptide similar to the correct version but, because of the error, is cut incorrectly by proteins called enzymes, resulting in the  $A\beta$  fragment. These fragments clump together in the extracellular space between neurons and limit communication between them. However, upcoming treatments for AD look promising. Although current drugs like Donepezil and Galantamine only treat symptoms, future treatments aim to attack the disease directly and slow its progression. CAD106 is an  $A\beta$  vaccine that attempts to create antibodies that target and remove  $A\beta$  plaques from the brain. Another drug, Lecanemab, instead directly injects similar antibodies into the patient to target the same clumps of protein. Lecanemab has recently gained approval for accelerated approval by the FDA and has even been approved for medical use in the United States. Another interesting therapy uses audiovisual stimulation methods to induce gamma waves into the brain, which are naturally created in healthy patients but not seen in those with AD. Evidence suggests Gamma Oscillation Therapy could be a non-invasive and affordable way to slow the progression of AD by removing protein buildup and slowing brain matter decay. Millions of people worldwide have no other choice than to live with Alzheimer's and other dementias; however upcoming treatments, like CAD106, Lecanemab, Gamma Oscillation Therapy, and others, maybe the next step in the treatment or even cure of Alzheimer's Disease.

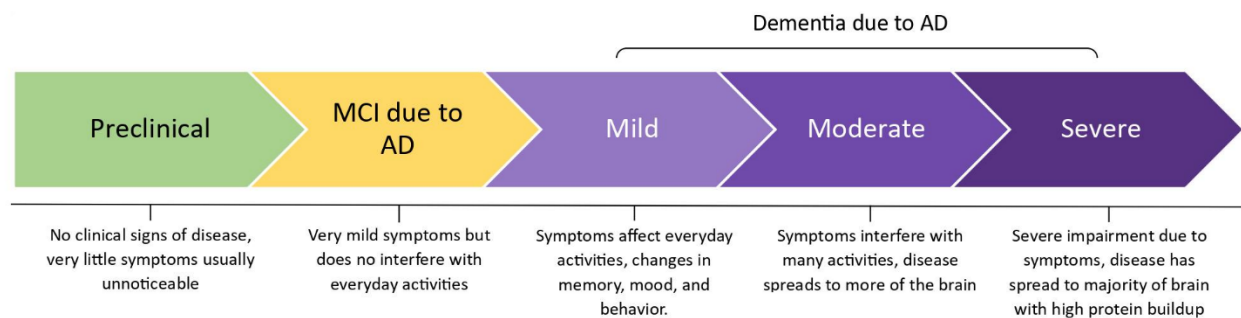
## Alzheimer’s Disease

### Stages and Symptoms

Alzheimer’s Disease (AD), like other progressive diseases, has stages. Each getting worse than the last with different or worsened symptoms. These stages note how far into the disease a patient has progressed and what can be expected in the future. AD does not actually start with symptoms specific to the disease. Instead, it starts off as minor inconveniences that progress into symptoms that are shared between it and other health conditions, then finally into the actual stages of dementia. The category of dementia is then split up further into three substages, which is where the disease occurs (Breijyeh & Karaman, 2020).

The AD patient will start out in the preclinical phase. In this phase, there are no clinical signs of the disease or impairment of the ability to perform daily activities, but there will be very few symptoms. This phase can last for several years, and as it progresses, it transitions into Mild Cognitive Impairment (MCI). MCI continues off the pre-clinical phase as memory loss gets more noticeable. Finally, the patient enters dementia.

Dementia, as previously stated, can be separated into three different stages: mild, moderate, and severe. In the Mild stage, more symptoms will start to show, including loss of concentration and memory, changes in mood, disorientation, and depression. These are all results of the pathological effects on the brain. In the Moderate stage, the disease will then spread to the cerebral cortex, resulting in increased memory loss. The patient will have trouble recognizing friends and family, they will lose control over impulses and have trouble reading, writing, and speaking. Lastly is the Severe stage. In the final stage of AD, the disease will have spread to a majority of the brain. This also results in high accumulation of plaques and neurofibrillary tangles. These circumstances severely impair the brain further; the patient will not be able to recognize family members at all and may later have trouble completing basic tasks such as eating or using the bathroom. Eventually, this will lead to death as the patient is not able to maintain homeostasis within their bodies (Fig. 1).

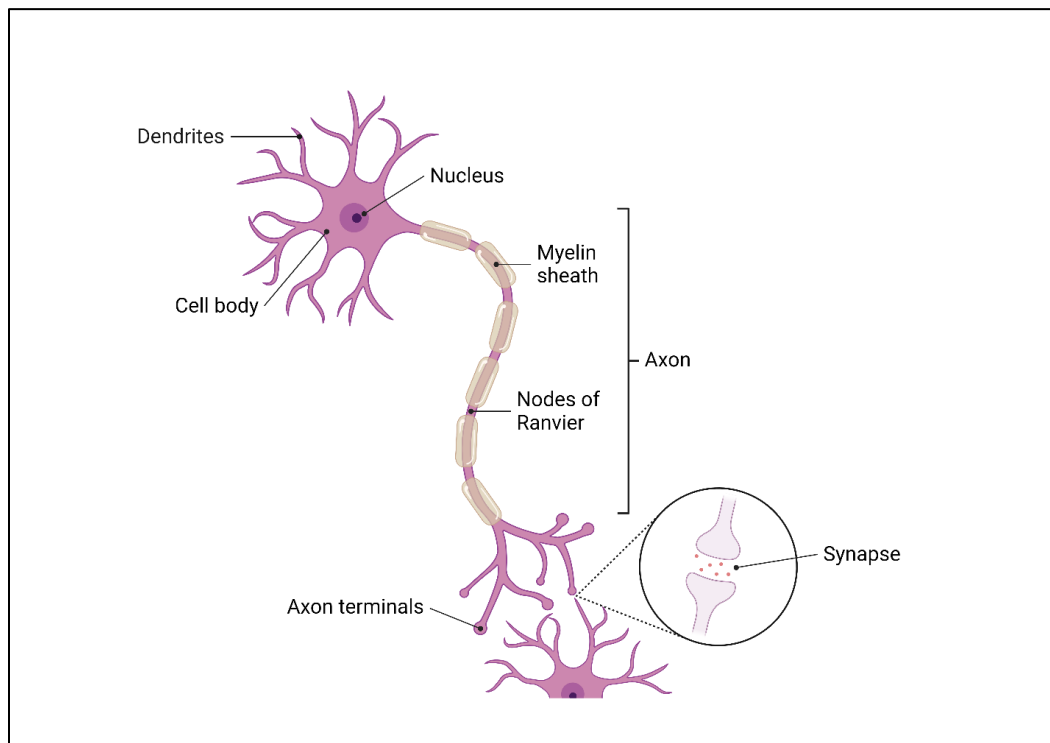


**Figure 1.** A diagram showing the progression of AD and the stages of dementia. AD, Alzheimer’s Disease; MCI, Mild Cognitive Impairment.

### Neurons: The Basis of the Brain

First off, before we look at how the causes of AD interact with the brain, we need to understand how the brain itself functions. One of the most, if not the most, important organs in our bodies is the brain, and it is highly complex. The brain is made up of around 100 billion nerve cells called neurons. These neurons are what allow the brain to communicate within itself and other parts of the body so that we can walk, talk, eat, and so much more. Let’s first get a look at the structure of a neuron to learn how it functions. There are three basic types of neurons throughout the body: efferent or motor neurons, afferent or sensory, and interneurons. The three of them work together to send and receive signals to each other and other parts of the body to keep it running. They also share, for the most part, the same basic structure (Fig. 2). Most neurons are made up of a cell body, which contains the nucleus and is surrounded by dendrites.

From the cell body extends the axon, which is a long arm that transmits signals from the dendrites to the axon terminals. The axons are also insulated using a myelin sheath made up of Schwann cells, which helps keep the signal strong as it passes through. The axon terminals of one neuron meet the dendrites of another with a small gap in between, the synapse, in order to communicate. Neurons use both electricity and chemicals in the form of neurotransmitters to send signals. For example, the neurotransmitter dopamine will bind to the receptors on the dendrites. The receptors will now trigger an exchange of ions throughout the inside and outside of the neuron, causing an electrical signal to be sent through the cell body and down the axon all the way to the terminals, where more neurotransmitters will be released across the synapse and onto the receptors of other dendrites.



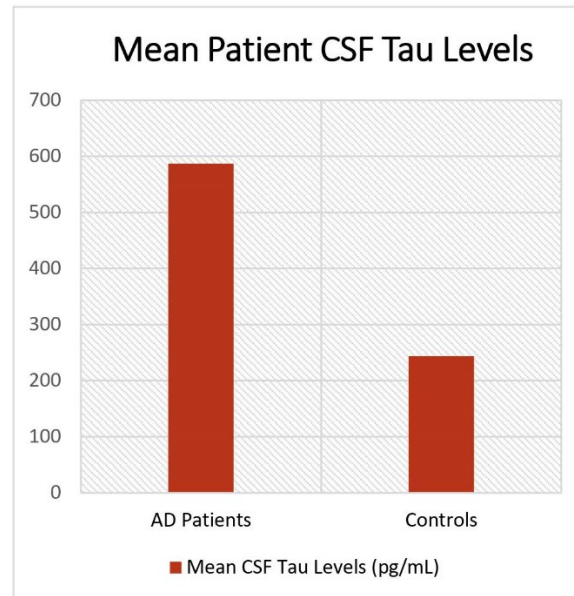
**Figure 2.** Diagram depicting the anatomy of a generic neuron. Created with BioRender.com.

### Causes: Neurofibrillary Tangles

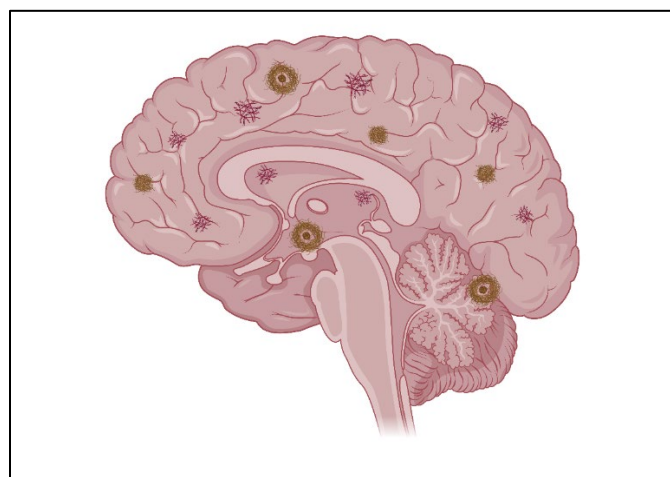
Now that we know how the basis of the brain works, we can look at the main causes of AD and see how they restrict neuronal communication.

One of the most discussed and accepted reasons for the cause of AD is the aggregation of proteins. One of the two is Tau. Tau is a group of proteins that help keep the cytoskeleton of neurons stable. The cytoskeleton of a cell is a category that contains all organelles that help retain the structure of the cell. In a neuron, microtubules are polymers of tubulin, which are tube-shaped structures that help retain the shape of neurons, especially in parts like the axon, which are long and otherwise unstable. Tau is a microtubule-associated protein that helps to add to this structure by binding to the microtubules and suppressing microtubule shortening and other deformations (Kadavath et al., 2015). On its own, Tau is very helpful and necessary to keep up the stability of cells. However, in some cases, it can be damaging. In a patient with AD, the cerebrospinal fluid (CSF) contains significantly more Tau proteins than a normal adult, as can be seen in (Fig. 3). This occurs due to the neurofibrillary tangles (NFTs) caused by the proteins inside the neurons. Over the progression of AD, more and more Tau begin to detach from microtubules, weakening their structure and binding to themselves, forming clumps of Tau within the neurons themselves. These tangles restrict the

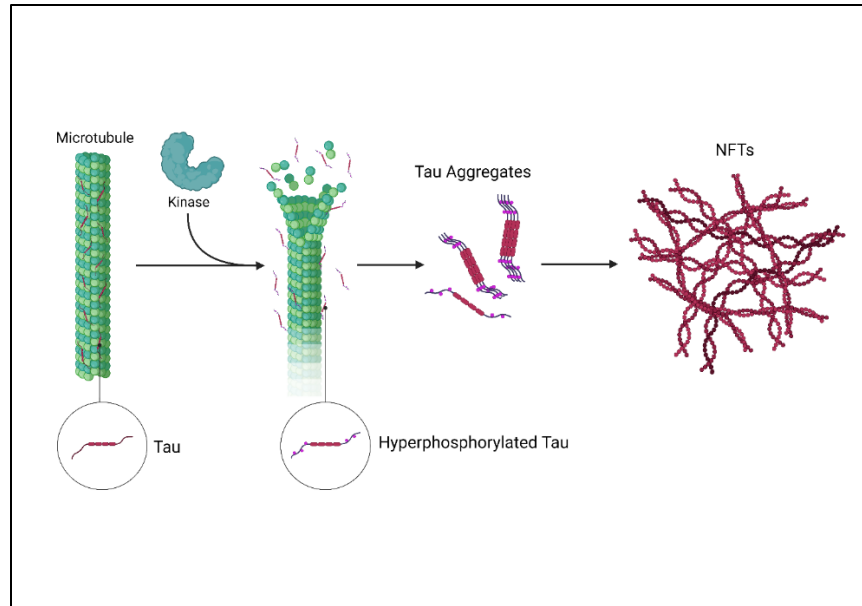
ability of neurons to carry signals from their dendrites to their axons (Fig. 4). Now, the reason tangles form is due to their chemical abnormality. Unlike normal Tau proteins, the Tau associated with AD are hyperphosphorylated. This means that the proteins have a few extra phosphate groups bonded to them. Tau is regularly phosphorylated and dephosphorylated throughout the body by an enzyme group known as kinase. Kinases are responsible for catalyzing the transfer of phosphate groups between ATP and other molecules. However, when an imbalance favors phosphorylation, Tau tends to bond with itself rather than the microtubules it is supposed to bond with (Fig. 5) (Zhang et al., 2021). Along with these chemical imbalances, the basic structure of Tau also helps with the formation of NFTs. Tau resembles a long “rope-like” structure which, when paired with hyperphosphorylation, allows it to not only bind with itself but also form complicated tangles like balls of lint.



**Figure 3.** Chart displaying the average CSF Tau levels found in AD patients versus control patients. Data sourced from Sunderland et al. (2003).



**Figure 4.** Digital illustration depicting the accumulation of Tau NFTs and Aβ plaques throughout the human brain. NFTs, Neurofibrillary Tangles; Aβ, Beta Amyloid. Created with BioRender.com.



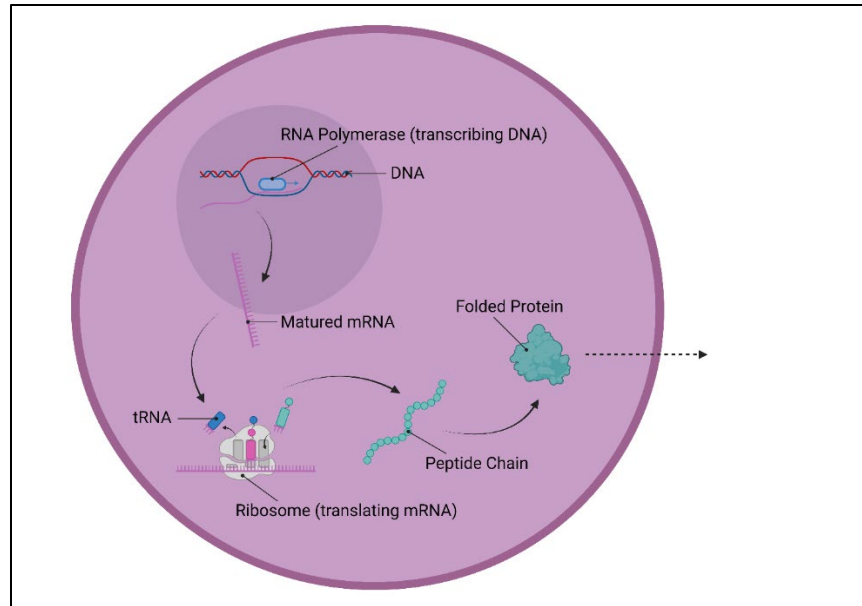
**Figure 5.** Diagram displaying the process of Tau phosphorylation by kinases, breakdown of microtubule structure, and formation of Tau aggregates and NFTs. NFTs, Neurofibrillary Tangles. Created with BioRender.com.

### Causes: Amyloid Plaques

On the other hand, there is another protein that plays an important role in the progression of AD: Amyloid  $\beta$  ( $A\beta$ ).  $A\beta$  is a peptide chain created from the breakdown of its parent protein, Amyloid Precursor Protein (APP). Although a normal protein, APP's function is still being researched today, but some speculate it may be used in neural growth and maturation (Coronel et al., 2018). But, to fully understand APP processing and  $A\beta$  formation, we need to understand the basics of protein formation.

### *Protein Synthesis*

Without proteins, we would not be able to do anything. One good example of this is the proteins that allow us to digest the molecules that make up the food we eat, such as lipases for fats and amylases for starches. Proteins also allow us to move things around our body, like sodium/potassium pumps, which allow for the exchange of ions into and out of neurons. But how are these proteins formed? It all starts with your DNA, the "blueprint" for everything your body needs to run itself. The DNA molecule carries genetic instructions on how to build everything in your body, mostly proteins. When DNA is "read" by RNA polymerase and transcribed into mRNA, this mRNA, after maturing, travels from the nucleus into the cytoplasm of the cell and is translated by ribosomes. The ribosomes read the RNA, each set of 3 nucleotides called codons. Once a codon is "read," it is translated into its respective peptide molecule, which is delivered to the ribosome by tRNA. As the ribosome works its way down the mRNA molecule, it forms a chain of peptides or a peptide chain. After the mRNA is fully translated (with the correct mRNA sequence), the peptide chain forms bonds between its own molecules, folding itself into a functional protein. (Fig. 6)



**Figure 6.** Diagram displaying the process of protein synthesis. DNA, Deoxyribonucleic Acid; RNA, Ribonucleic Acid; mRNA, Messenger RNA; tRNA, Transfer RNA. Created with BioRender.com.

### Causes: Amyloid Plaques (cont.)

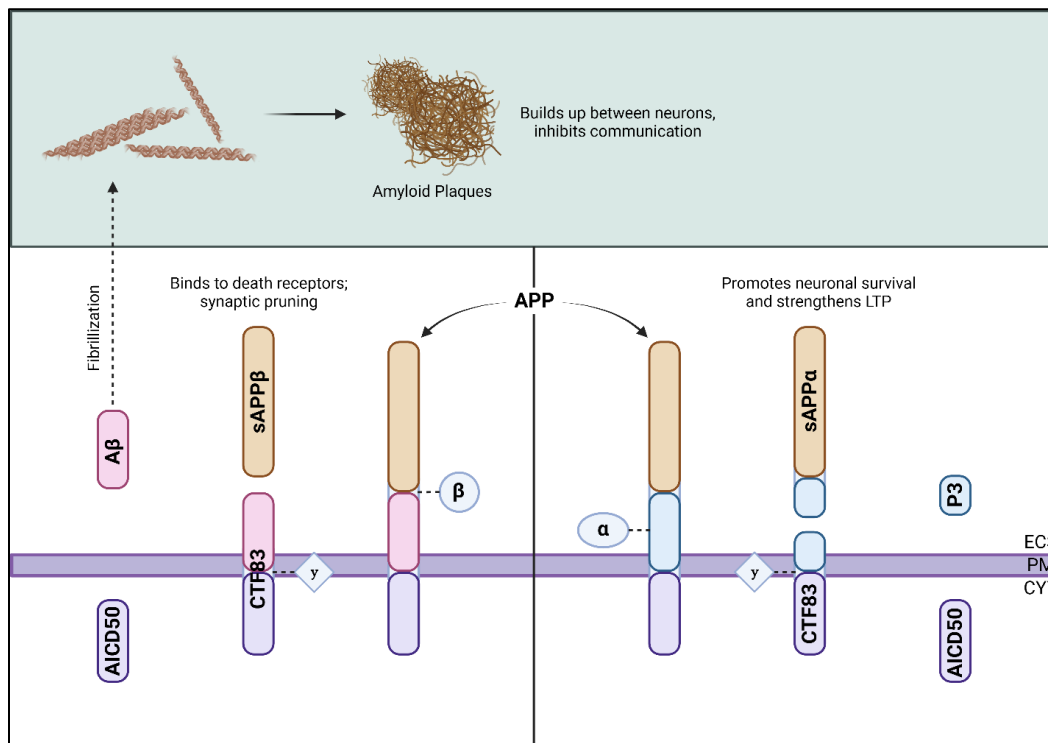
Now that we know how proteins like APP are formed, we can look at what can go wrong during this process and how genetic mistakes can result in deadly outcomes like Alzheimer's Disease. The formation of APP is like any other protein; DNA is transcribed, matured, and translated into peptide chains. However, this time, the peptide needs to be edited slightly before leaving the cell.

The gene that codes for APP forms a peptide chain regularly cut by enzymes  $\alpha$ -secretase and  $\gamma$ -secretase. These enzymes look for specific sections to cleave or cut the peptide chain at. In a normally coded APP gene, the  $\alpha$ - and  $\gamma$ -secretases cut at two different points on the chain, forming the amino terminal fragments and the carboxyterminal fragments (CTFs). When the APP peptide is cleaved by  $\alpha$ -secretase, it results in CTF83 and sAPP $\alpha$ . sAPP $\alpha$  is sent out of the cell, and CTF83 is cleaved again by  $\gamma$ -secretase to form fragments AICD50 and P3.

However, in the case that the APP gene is mutated, the initial polypeptide chain will be altered. As such,  $\alpha$ -secretase will no longer be able to cleave the peptide as it normally would. Instead, another enzyme called  $\beta$ -secretase will cleave the chain where it is able to. This results in CTF99 and sAPP $\beta$ . sAPP $\beta$  will once again be shipped out of the cell, but because it was not cleaved correctly, it will bond with death receptors in the brain, causing synaptic pruning, a process in which extra neurons and synapses are eliminated to promote efficiency. Ironically, its counterpart, sAPP $\alpha$ , promotes neuronal survival and enhances memory by strengthening long-term potentiation (LTP), a process that develops the connection between neurons and makes communication between them easier. On the other hand, CTF99 will be cleaved normally by  $\gamma$ -secretase, again forming fragments AICD50, but this time also A $\beta$ . These unusual A $\beta$  fragments also enter the extracellular space and form amyloid plaques (Fig. 7), filling up spaces between neurons and disrupting connections further (Chow et al., 2010). Other findings also confirm that APP gene mutations accelerate A $\beta$  generation (Li et al., 2019).

But why do these A $\beta$  clump together or aggregate? One reason is that because the A $\beta$  fragments were not formed correctly, they tend to be "stickier" than other peptides, especially to each other. Another reason is their environmental pH levels. pH is a measure of how acidic or basic something is; anything with a pH level less than 7 is acid, and anything with a pH greater than 7 is a base. But what does this have to do with peptides and proteins? Proteins are pH-dependent, meaning to function properly, they need to be in an environment that suits them best. This need is

caused by their isoelectric point (pI), which is the point at which the proteins carry no net electrical charge; they are neutral relative to their environment. The closer a pH is to a protein's pI, the more stable that protein or peptide will be. In the case of A $\beta$ , its pI is 5.3, or acidic. So, when the pH of A $\beta$ 's surroundings is lowered to around 5.3, the peptide is more stable. However, this makes it easier for it to bind with other A $\beta$  fragments, which results in the formation of amyloid plaques. Other studies show how acidic – or low pH – environments can promote the aggregation of A $\beta$  fragments, further progressing AD.



**Figure 7.** Diagram displaying healthy APP Processing (right) and incorrect processing following an amyloidogenic pathway (left). A $\beta$ , Beta Amyloid; APP, Amyloid Precursor Protein; CTF, carboxyterminal fragments;  $\beta$ ,  $\beta$ -Secretase;  $\alpha$ ,  $\alpha$ -Secretase;  $\gamma$ ,  $\gamma$ -secretase; ECS, Extracellular Space; PM, Plasma Membrane; CYT, Cytoplasm. Created with BioRender.com.

## Prevention and Treatment of AD

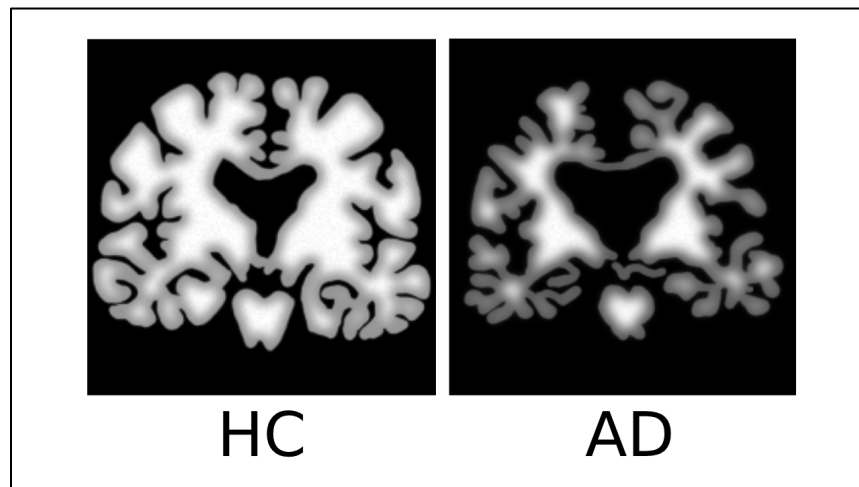
Before discussing the treatments that may benefit AD patients, it is important to know how the disease can be identified and diagnosed. After which, we will compare two major treatment options for AD by what they do, how they work, and which seems better overall.

### Identification and Diagnosis of Alzheimer's Disease

The brain of an Alzheimer's patient looks vastly different from that of someone without the disease. But how can we see these differences? There are many types of neuroimaging technologies that help us observe and analyze the human brain, like CT and PET scans. Each method helps to show something else about the brain that you may not see using a single technique; however using these methods in combination gives us a lot of information that we can use to diagnose diseases like Alzheimer's.

### *Computed Tomography*

A Computed Tomography scan, otherwise known as a CT scan, is one of the most common imaging technologies throughout the medical field. In the case of neuroimaging, the process of essentially making a “map” of the brain, CT scans are used to look at the shape and structure of the brain. The images resulting from a CT scan can be compared to control images to look for abnormalities. A CT scan works by having a patient lie down on a bed. This bed moves through the loop of the CT machine while the X-ray mechanism inside rotates around the patient while shooting beams of X-rays through the body. This can be done to any part of the body. After the X-rays pass through the body, they are captured by X-ray detectors that rotate with and opposite to the X-ray source. After being captured, the computer is able to convert these X-rays into slices of the body, which are presented on the screen as flat images. CT scans can show detailed images of body parts, including bones, muscles, organs, blood vessels, and fat (Fig. 8).



**Figure 8.** Digital representative illustration depicting the expected results of a CT scan of an AD patient (right) and a healthy control (left). AD, Alzheimer’s Disease; HC, Healthy Control.

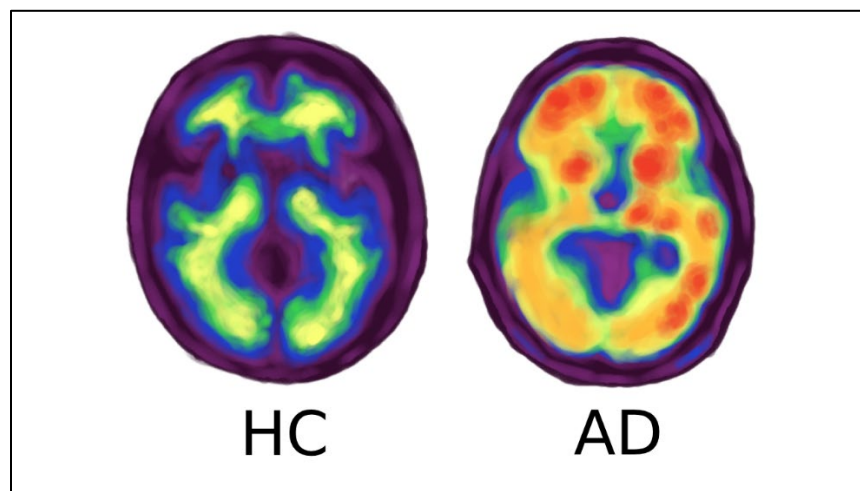
### *Positron Emission Tomography*

A Positron Emission Tomography scan, or PET, is another common imaging technique that can detect the movement of a particular substance to show the substance’s usage in the brain, which in turn locates the occurrence of specific activity. The previously discussed CT scans show the overall structure of tissues in the body/brain, whereas a PET scan will show the activation of certain regions of the brain. Also, in the form of two-dimensional images, PET scans can be compared with healthy controls to show any abnormalities in brain activity or substance movement. In order to perform a PET scan, the patient first needs to be injected with a small amount of radioactive tracer – like a sugar, for example – intravenously. The tracer needs to be left to flow throughout the patient’s body and collect in different areas of the brain. It mimics the movement of other molecules used in the brain. After about an hour, the patient is laid down on a bed and passed through the scanning machine. The machine, like the CT machine, has a circular tube the patient is passed through, which detects where the radioactivity emitted by the tracer is coming from. The location information of the tracer is passed through a computer, which then outputs a flat image showing which parts of the brain have accumulated what amount of tracer. The amounts of tracer are also color-coded so that brain activity can be visualized.

However, PET scans are not only used to view brain activity, but they are also used to see how, where, and in what quantity different substances are used in the brain. In the case of AD, PET scans can be specified to look for the buildup of substances specific to AD pathology. For example, 2-deoxy-2-[18F]fluorodeoxyglucose ([18F]FDG)



is a glucose-based radiopharmaceutical that is eagerly taken up by healthy brain cells to be metabolized. Unhealthy or dead cells are less likely to take up the same amounts of the substance. In previous processes of AD diagnosis, [18F]FDG has been used to detect the location of healthy and unhealthy cells. However, the accuracy of the tracer reduces when used in older patients where there are fewer healthy cells simply due to age and not disease. This is where Amyloid- and Tau-PET scans come in. As discussed earlier, two of the most important biomarkers that indicate genetically caused AD are the A $\beta$  and Tau peptides. The plaques and tangles caused by these two malformed peptides are one of the main reasons for the progression of AD. It would be extremely helpful to know if the aggregation of these peptides is present in the brain to diagnose AD and even track its progress. These scans are also much more specific and accurate because they focus on the specific pathologies of the disease. Amyloid-PET scans work similarly to normal PET scans. Amyloid-PET scans use radiotracers that target A $\beta$  aggregates to record the movement and location of the plaques (Fig. 9). Tracers like Pittsburgh Compound B ([11C]PiB), selectively bind to A $\beta$  plaques, which helps to more accurately show AD pathologies of A $\beta$  (Suppiah et al., 2019).



**Figure 9.** Digital representative illustration depicting the expected results of an Amyloid-PET scan of an AD patient (right) and a healthy control (left). Low A $\beta$  concentration is noted by cooler colors (eg. blue, green, etc.). High A $\beta$  concentration is noted by warmer colors (eg. orange, red, etc.). AD, Alzheimer's Disease; HC, Healthy Control.

## Current Treatments

Unfortunately, as of now, there is no cure for Alzheimer's disease. It is an extremely complicated condition that we have yet to understand fully. In the meantime, however, the FDA has approved many different treatments, some better and more available than others. Receiving a treatment for AD is based on which stage the patient is in; there are therapies for early-stage patients and other drugs for mild/moderate-stage patients. Donepezil and Galantamine are two leading drugs in the treatment of AD. However, the way these drugs work only provides symptomatic treatment and does not affect the disease itself. They help slightly increase cognitive abilities for patients to continue with their daily lives, but they will not slow the progression of AD.

Both drugs and many others like them, work by following the cholinergic hypothesis, which says that AD is caused by a reduction in acetylcholine (ACh) synthesis. ACh plays an important role in the brain as a neurotransmitter and drives the brain's state of attention and arousal, but ACh is lacking in AD. An enzyme called acetylcholinesterase (AChE) usually breaks down excess ACh so that its levels stay normal. Donepezil, Galantamine, and others are AChE inhibitors (AChEIs) and stop AChE from breaking down ACh (Breijyeh & Karaman, 2020).

### *Current Treatments: Donepezil*

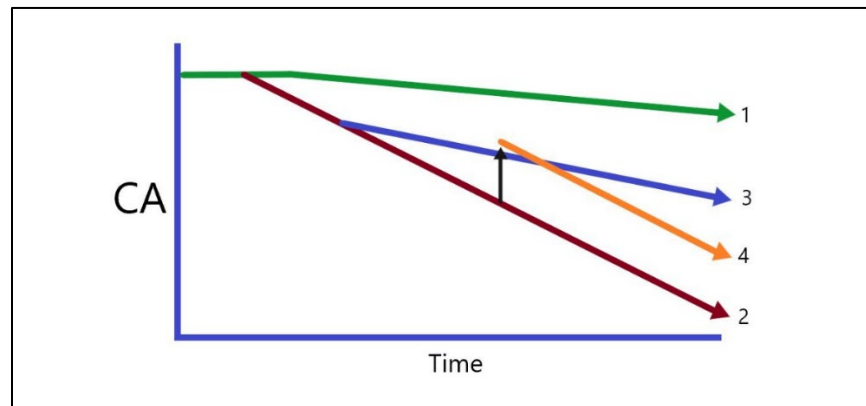
Donepezil is a second-generation AChEI and is a leading drug for AD treatment. The drug is first orally consumed as a tablet. It works by binding to the AChE enzyme and inhibiting it from breaking down ACh. When there is less ACh processed, there is a higher concentration left at the synapses. This compensates for the lack of neurotransmitters and brings the levels closer to normal. However, like other similar drugs, Donepezil induces side effects related to the gastrointestinal and nervous systems (Breijyeh & Karaman, 2020).

### *Current Treatments: Galantamine*

Another drug, Galantamine (GAL), is considered one of the first-line drugs to treat mild/moderate AD. GAL works just like other acetylcholinesterase inhibitors; it binds to AChEs and stops them from interacting with acetylcholine. But, unlike other AChEIs, GAL also acts as a neurotransmitter agonist, meaning it can bind to ACh receptors and activate them, essentially “pretending” to be an ACh molecule itself. This extra function boosts cognitive function by raising ACh activeness without needing as much of it (Breijyeh & Karaman, 2020). Like Donepezil, GAL is also ingested orally as a tablet.

### Future Treatments

Currently, existing drugs and treatments only target symptoms and not the disease itself. They increase cognitive function without changing its rate of decline. Although not yet approved by the FDA for distribution, future treatments like CAD106, Lecanemab, and 40hz therapy may prove to be useful in reducing the rate of cognitive decline or returning it to a normal state altogether (Fig. 10).

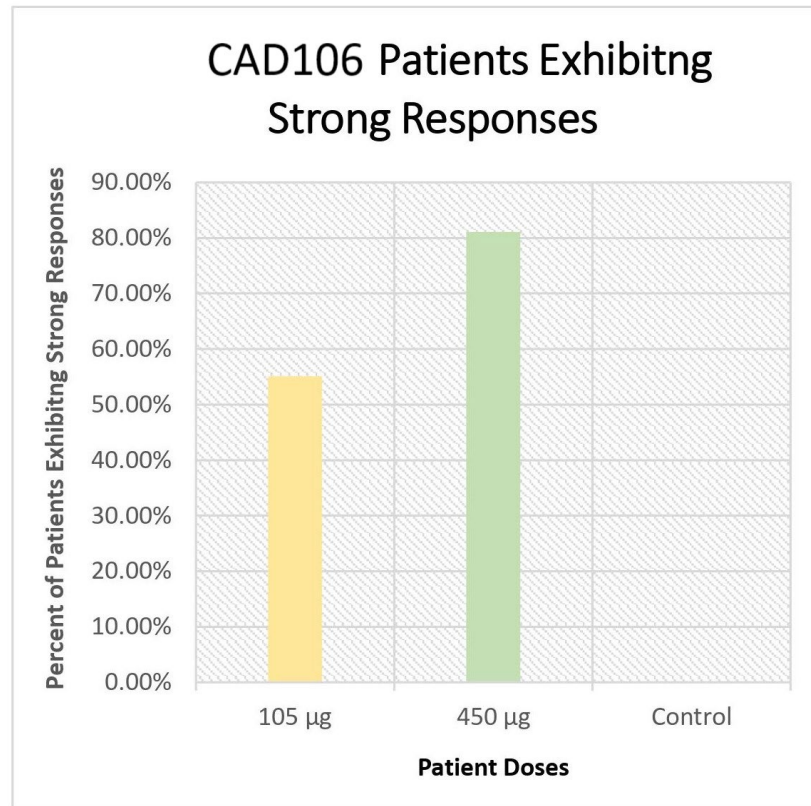


**Figure 10.** Graph displays the progression of cognitive function over time. 1. Normal aging; 2. Dementia; 3. Future treatments which slow the progression of AD; 4. Current treatments which increase cognitive ability but do not affect progression of AD. CA, Cognitive Ability.

### *Future Treatments: CAD106*

CAD106 is a second-generation immunotherapy that is currently being tested for its effectiveness against AD. It is currently in phase III trials and is meant to help patients in the early stages of AD (Hameed et al., 2020). CAD106 is a vaccine that contains antibodies that actively find and act against the A  $\beta$  peptides. Earlier, in a phase II study (Vandenberghe et al., 2017), different doses of CAD106 (105 and 450  $\mu$ g) were given to patients as well as placebos to a control group. The vaccine was able to elicit a serological response in most patients who had taken it. However,

the functionality of the antibodies themselves still needed to be improved. In the group of patients that received a 105 µg dose, 55.1% produced enough antibodies to be considered as having a strong response over the course of 60 weeks. In the group that received the 450 µg dose, 81.1% met the criteria for a strong response in the same time period. In the control group, none of the patients had any response (Fig. 11). Even though the antibodies were produced by the patients somewhat consistently, the antibodies themselves did not act as intended. CAD106 is still under trial and being developed. Besides the results of CAD106, adverse events (AEs) were reported in 24.5% of the patients receiving treatment and in 6.7% of the placebo group. These AEs included amyloid-related imaging abnormalities (ARIAs), all of which were asymptomatic, headache, hypertension, pyrexia, among others.



**Figure 11.** A chart displaying the percentage of patients in the 105 µg and 450 µg dosage groups as well as the control group of the overall active test group who exhibited strong responses to the drug. Data sourced from Vandenberghe et al, (2017).

### *Future Treatments: Lecanemab*

Lecanemab is an upcoming AD drug that has recently been gaining popularity as it has just now, in 2023, been granted accelerated approval by the FDA and approved for medical use in the United States. Lecanemab is a monoclonal antibody that, similarly to CAD106, binds to Aβ peptides and removes excess from the patient’s body. Lecanemab, though, is the antibody itself administered to the patient via IV, unlike CAD106, which triggers the production of such antibodies by the body. Earlier this year, a phase III trial of the drug was performed (Dyck et al., 2023), consisting of a total of 1795 patients over 18 months. The patients varied in age from 50-90 years and were all diagnosed with mild cognitive impairment. The study had 989 patients assigned to receive Lecanemab and 897 to receive a placebo. The patients in the experimental group were administered 10mg of the drug intravenously per kilogram of body fat every two weeks. At the end of the 18 months, all patients were analyzed and scored with the Clinical Dementia Rating-

Sum of Boxes (CDR-SB); the score could range from 0-18, with higher scores indicating greater impairment and scores 0.5-6 indicating early Alzheimer's Disease. Initial preparation for the study found that the mean CDR-SB score at the beginning of the study was 3.2 in both groups. The results of the study found that the adjusted mean change from the baseline was 1.21 in the Lecanemab group and 1.66 in the placebo group, meaning the disease progressed slightly slower with the drug. The experiment also grouped some of the patients (698 of them) into a sub-study to evaluate the change in A $\beta$  levels. This sub-study group, at baseline, had a mean amyloid level of 77.92 centiloids (a standardized measurement of amyloid in PET imaging). Again, the Lecanemab group had success after the 18 months with an adjusted mean change of -55.48 centiloids, while the placebo group had an adjusted mean change of 3.64 centiloids. This meant that the patients in the experimental group reduced in amyloid levels while the placebo patients actually increased in them. It was concluded that Lecanemab reduced markers of A $\beta$  in early-stage AD and moderately resulted in moderately less decline in cognition than placebo. However, as with most trials, there occurred adverse events. The most common AEs that were reported in the Lecanemab group included infusion-related reactions, ARIA with cerebral microhemorrhages, cerebral macrohemorrhages or superficial siderosis, and headaches.

### *Future Treatments: Gamma Oscillation Therapy*

Unlike the previously mentioned AD drugs, this treatment is nothing usual. It is a recent pioneering approach that aims to use brain waves to treat AD pathology. Gamma waves are the fastest type of brainwaves in the human brain and are produced when masses of neurons pulse together in a synchronized fashion and resonate at frequencies approximately between 25 Hz and 100 Hz. Other studies have suggested that rhythms made by patterns of gamma waves, or gamma oscillations, may play a role in memory functions. Along with this, evidence has shown that the reduction of slow gamma activity (25-50 Hz) impaired memory function, and in AD patients and mice modified to exhibit AD pathology, gamma activity was lower than normal. Gamma Oscillation therapy aims to artificially induce these waves back into the brain by exposing patients to stimuli at gamma frequencies (Traikapi & Konstantinou, 2021). For example, a patient could spend some time looking at a light flashing at a gamma frequency or listen to a tone resonating at the same frequency.

In a study conducted by Iaccarino et al. (2016), mice were modified to exhibit AD pathology similar to humans. A non-invasive brain stimulation technique was used in order to flicker a light at 20, 40, and 80 Hz at the mice. There was also a control group that was exposed to no light. After 1 hour of stimulation, a 60% decrease in A $\beta$  levels was observed in the visual cortex compared to the dark controls. Similar procedures were performed on other mice models, which were also engineered to exhibit AD pathologies. In another study by Martorell et al. (2019), AD mice models were presented with auditory stimulation with tones at 8 Hz, 40 Hz, and 80 Hz for 1 hour each day for seven days. The authors reported similar results to the first study, this time in the primary auditory cortex and hippocampus, along with memory improvements.

Obviously, testing this therapy on modified mice is not enough to draw conclusive results about its effectiveness. A study done by Suk et al. (2020) developed a device that would provide both audio and visual stimuli at 40 Hz to different types of patients, including cognitively healthy, AD, and epileptic patients. The study was not focused on measuring the patients' cognitive abilities or improvements in disease pathologies; rather, it was focused on gathering preliminary evidence of the safety and feasibility of the stimulation therapy. Other studies (Chan et al., 2021 and He et al., 2021) aimed to provide insight into the efficacy of Gamma Oscillation Therapy in humans, both of which exposed mild AD patients to 1 hour of audiovisual stimulation each day. The first study had patients use a stimulation device at home for three months, and the second study had patients receive therapy over the course of 4 to 8 weeks. Both studies resulted in the reduction of functional connectivity loss in the brain, and the 3-month study even improved memory performance and showed less brain and hippocampal atrophy or ventricular expansion than the control group. These results showed a possible delay in disease progression.

## Conclusion

Alzheimer's Disease (AD) is one of the most unforgiving diseases known to humans, and there is still much to be learned from it. The brain is a very complex organ that still puzzles many researchers to this day, and a disease that affects it can be just as confusing. However, that is not to say we haven't made progress, and we've made a lot of it. From analyzing major genetic causes of the disease, understanding its signs and symptoms to diagnose it, to creating and continuing to research treatments that can slow and possibly, in the future, cure the disease altogether. Because dementia's early stages are shared with the natural effects of typical aging, it is still hard to diagnose AD earlier on. However, thanks to developments in neuroimaging techniques and technology, like CT and amyloid PET scanning, we can assess and track the disease's progression and its markers in order to find signs of it earlier on. The drugs we have developed, although for now, only temporarily increase cognitive function and only treat the disease's symptoms, have paved the way for future treatments like Lecanemab, CAD106, and Gamma Oscillation Therapy to develop much faster and target the disease itself.

From here, there is a lot more improvement to be made. There are still other debated causes of AD that have yet to be investigated thoroughly. Drugs like Lecanemab and CAD106 seem to suggest that A $\beta$  antibodies may be the future of AD treatment. However, the creation of these antibodies using CAD106 and the general effectiveness of the antibodies themselves in removing amyloid plaques is something that can be improved through more trials and research. Gamma Oscillation Therapy, on the other hand, seems like a miracle. It's highly affordable compared to other drugs and more accessible to patients. The use of light and sound to treat a disease as cruel as AD would sound too good to be true, but maybe it is the key to preventing and slowing early AD.

## Acknowledgements

Huge thanks to all my wonderful advisors for guiding me through this huge project. Thank you, Dr. Raj, for your amazing insight into my topic of research and thanks to Mrs. Kethar for advising my writing. I could not have done this without you both.

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