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# Picking the Brain: Neuroinflammation in Alzheimer's Disease

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## Statement of Thesis

This thesis should be used as a guide to understand how neuroinflammation in the brain underlies the pathology observed in Alzheimer's disease. I will aim to outline how healthcare practitioners diagnose and treat their patients, providing linkages between how neuroinflammatory processes can be targeted for future therapies. Additionally, I will discuss the psychological effects of this progressive and deadly disease and assess how patients and families cope with this prognosis.

## Introduction

Alzheimer's disease (AD) is a progressive and deadly disease that is marked by cognitive decline, including memory impairments and language disturbances, as well as the development of senile plaques and neurofibrillary tangles (Zarow et al., 2007). Approximately 70 million people worldwide have been diagnosed with Alzheimer's disease; this number is projected to increase to approximately 370 million people by the year 2050 (Schachter, 2000). Along with a diagnosis of Alzheimer's disease, the patient's lives as well as the lives of the patient's family are forever altered. Like so many others, my family felt the grief and anxiety that accompanies a loved-one's diagnosis of Alzheimer's disease.

Throughout the beginning of my childhood, my family would notice that my grandmother, who I lovingly called Nana, started to exhibit memory loss. She struggled to remember my name, as well as the names of our other family members, but this was easily dismissed, as my mother is one of six children, all of whom are married with children, and most of their children have children as well. In 2012, the lives of my family would be altered forever. One day, my Grandpa Bill took a fall that resulted in a severe head injury. As a result, Nana wanted to be by his side while he stayed in the hospital. As my grandmother drove this familiar route to the hospital, she unfortunately drove off the road. Fortunately, she was not severely injured; however, my family felt it best that Nana would permanently retire from driving. Several days later, Grandpa Bill unfortunately passed away with Nana by his side. As my family grieved our loss, we continued to worry about the state of my grandmother. She was now living alone and had no means to drive to see any of her family members. Ultimately, my family decided it would be best for Nana to be moved to an assisted living building at a retirement community, of which she already resided. In her new living arrangements, she was receiving

more medical attention; the nurses noted that she was struggling to eat and began having hallucinations. She also began telling outrageous stories, likely as a result of her cognitive decline.

Finally, she saw a physician who diagnosed her with dementia, likely resulting from Alzheimer's disease. AD is the most frequent cause of dementia. Although the average survival duration is approximately 5-8 years after clinical AD diagnosis, the pre-dementia phase could potentially last decades; however, there is no way to establish the onset of this phase. Within the pre-dementia stage, mild cognitive impairment (MCI) is often a symptom. This impairment can result in frustration and in some cases, severe depression; however, the mild cognitive impairment does not otherwise seem to significantly impact Activities of Daily Life (ADL) at this early stage in the disease (Förstl et al., 1999). Individuals in the pre-dementia stage tend to struggle to identify objects and additionally show decreased word fluency. Spatial disorientation is a common symptom; therefore, patients who even mildly suffer from AD should not drive. After the disease has progressed, individuals may exhibit aggression and violence, commonly due to confusion. Many patients additionally suffer from extreme apathy and exhaustion, furthering aggressive behaviors (Förstl et al., 1999). My grandmother exhibited many of these same symptoms, leading to her dementia diagnosis. We were devastated by her diagnosis, but at least had an understanding as to why she was struggling to eat and had notable memory deficits. Over the course of several years, Nana continued to decline. Luckily, Nana lived nearby, so my family visited her as often as we could, bringing her favorite meals and new clothes at each visit. In the winter of 2019, before heading back to DePauw University for spring semester, my brother and I saw my grandmother for the last time. At our last visit, not only did Nana not recall my name nor my brother's, she clearly did not recognize us at all; she became extremely

nervous when my brother and I entered her room. Unsure of what to do, I called my mom, hoping that Nana would recognize her daughter's voice, easing her anxiety and nervousness. Eventually, my brother and I were able to give Nana a hug and a kiss goodbye, hoping to see her soon. She unfortunately died that Spring, nine days shy of her ninety-second birthday.

Nana faced a devastating uphill battle against a deadly disease for which there is currently no cure. She was an inspiration to her 6 children, 14 grandchildren, and 15 great grandchildren to never give up and to never lose hope; she fought until the very end and never let her disease define her. She continued to enjoy the company of loved ones and always beamed with joy upon hearing the successes of her family, such as receiving job opportunities, getting into college, or winning a soccer game. My grandmother's strength and never-failing hope has inspired me to want to work in healthcare; I hope to treat patients with the same encouragement and hope that my grandmother showed every day. My grandmother's story is likely a familiar tale; patients and loved ones undergo much the same story. Cognitive decline and changes in personality, among many other symptoms, mark a drastic change in the patient's quality of life, leaving patients and families feeling helpless. The inflammatory processes that occurred in her body as a result of AD resulted in the perpetual cycle of inflammation, furthering the progression of this disease. Ultimately, I hope that future advancements will find a cure, allowing for increased quality of life, rather than live with a known death sentence.

Unfortunately, the story remains unchanged; clinicians aim to treat their patients as best as they can, but the few available treatments merely delay the progression of Alzheimer's disease by a few years at best (Weller et al., 2018). Thus, it is ideal that patients aim to mitigate their chances of ever developing the disease to begin with. Our current understanding of the neuroinflammatory processes involved in the onset of Alzheimer's disease will hopefully allow

for further research aimed at a cure, increasing the quality of life of patients diagnosed with Alzheimer's disease.

**Early Understandings of Alzheimer's Disease**

Dementia and AD have been discussed by famous scientists, researchers, and profound intellects for centuries, even before Alzheimer's disease was defined in 1906. Around 3,000 B.C., Prince Ptah-Hotep governed a city in Egypt. He was known as a vizier, which was the highest governing position in ancient Egypt, second to the pharaoh. Prince Ptah-Hotep was an extremely wise and well-respected man; he spoke of fairness, kindness, and the rules of etiquette. Additionally, he described the onset of old age, which he claimed brought senility. Interestingly, senility is an outdated word used to describe people with AD or dementia, so it is possible that Prince Ptah-Hotep was actually describing the symptoms of individuals with AD, rather than the common occurrences of old age. He claims senility is marked by the inability to remember the past, a change in personality, and an inability to properly taste (Fontaine, 1981).

Although these are all common occurrences associated with aging, people with AD have these same symptoms. Interestingly enough, the word 'senility' is an outdated term used to describe people with AD or dementia; thus, it is possible that Prince Ptah-Hotep was actually describing the symptoms of AD. Regardless, his writings and teachings are some of the oldest known teachings regarding the topic of the elderly. Additionally, the Ebers Papyrus, an ancient Egyptian medical analysis by an unknown author, describes the relationship between cardiovascular illnesses and senile decay, which is interesting given that cardiovascular disease is a risk factor for AD (Fontaine, 1981). Thoughts from Prince Ptah-Hotep and the writings from the author of the Ebers Papyrus indicate that much was known about diseases, potentially including AD.

Terminology, such as the word ‘dementia’ has been known to exist since approximately 25 BC when Aulus Celsus used the term for the first time in his Treaty of Medicine. Celsus described an individual who has dementia to exhibit “irrational imaginations…[and] the person speaks irrationally” (Bán, 2019). Dementia is now recognized as a possible outcome of the progression of AD; however, given the generality of the symptoms described by Celsus, it is possible that he was again describing a patient suffering from AD. Regardless, it is evident that wise scholars thousands of years ago were familiar with the common occurrences as one progressed through different stages of life, leading to illnesses that can be identified as dementia or AD.

Hippocrates, who has been deemed the “father of medicine,” has been credited with being the first physician to ever describe epilepsy and pneumonia (Pappas et al., 2008). He aimed to use logic in his everyday life to treat the mysterious symptoms that his patients presented. In fact, he differed from many physicians during his time, such that he did not believe illnesses were God-sent. Many physicians throughout this time believe that doctors were a sort of punishment sent by God, whereas Hippocrates did not believe that God was punishing individuals, but that patients were merely unfortunate to have developed such diseases. Additionally, Hippocrates rejected the idea that the practice of medicine should be passed down between family members; instead he opened the School of Kos where he taught medicine to anyone who wanted to learn his popular medical techniques. Hippocrates changed the practice of medicine, allowing for more people to be effectively treated during this time.

Hippocrates gave both specific and general advice to his patients, depending on the patient’s symptoms. More generally speaking, he explained that “The most famous doctors cure by changing the diet and lifestyle of their patient and, by using other substances. Such capable

doctors have the knowledge and ability to use the therapeutic properties of most natural or man-made products" (Tsiompanous & Marketos, 2013). This advice still is beneficial today; we know that eating habits, activity levels, sleep patterns, and other lifestyle choices are important habits that contribute to an individual's likelihood to develop certain diseases. This advice is especially pertinent to individuals who want to mitigate their chances of developing chronic or terminal illnesses, including AD; those who lead healthier lifestyles have a better chance of offsetting their likelihood of developing AD. Additionally, Hippocrates "believed that there is an association between mental health and intestinal flora imbalance" (Sochocka et al., 2018). Over the past decade, Hippocrates' beliefs have led to research surrounding the importance of a balanced gut microbiome. Now, it is understood that an imbalance in the gut microbiome can cause illnesses, both chronic and acute, including AD (Sochocka et al., 2018). However, Hippocrates believed that four humors governed the body. One of these humors was associated with the temperament of melancholy. For Hippocrates "there was no differentiation between dementia and chronic mental syndromes, as he classified all as 'melancholy'" (Vatanabe et al., 2020); whereas today, we know there are differences between depression, schizophrenia, AD, and other neurological illnesses, all of which Hippocrates would have classified as 'melancholy.'

Thus, it is evident that the concept of dementia was well-known throughout history. Furthermore, it is evident even in popular literary novels that dementia was a known and arguably feared illness. Many have hypothesized that William Shakespeare's King Lear may have suffered from dementia when King Lear states that "I fear I am not in my perfect mind. Methinks I should know you, and know this man. Yet I am doubtful, for I am mainly ignorant. What place this is, and all the skill I have remembers not these garments. Nor I know not where I

did lodge last night" (Shakespeare, 1999). King Lear describes himself as unable to identify familiar faces and even his whereabouts from the day prior. In the plot, King Lear even disowns his favorite daughter; in this way, Shakespeare was likely emphasizing the intense shifts in mood and personality, a common symptom of dementia or AD.

Later, in the 1800's, Philippe Pinel began classifying different psychiatric disorders. Similar to Hippocrates, Pinel made amazing breakthroughs within the medical community, but in an entirely different way. He focused his research on "only those symptoms and distinctive signs which are recognizable by the senses and which are not susceptible to vague reasoning" (Woods & Carlson, 1961) indicating that he focused primarily on psychiatric illnesses. Up until this point in time, patients who suffered from psychiatric disorders were placed in psychiatric institutions, where they were commonly chained up and otherwise treated poorly; these patients were deemed inhuman and were commonly feared by everyday people. Through his years of research, he realized that these patients suffered from "insanity" (Woods & Carlson, 1961), which he believed to be a disease, rather than a crime. He later became the resident physician of two Paris asylums, due to his passions for understanding mental illness.

A movement spread across Europe, leading to the unshackling and freeing of these prisoners, allowing for the patients to undergo various therapies to treat their disorders. Through his research he was able to classify mental disorders into five major groups: dementia, idiocy, melancholia, mania with delirium, and mania without delirium (Vatanabe et al., 2020). Specifically, Pinel referred to dementia as a "complete forgetting of any prior state, prejudice of judgment, repeated acts of extravagance, all in a rapid succession, or in an uninterrupted alternation of insulated ideas" (Vatanabe et al., 2020); these symptoms closely

mirror the symptoms that have been used to describe individuals with dementia or AD today. People with AD tend to exhibit memory loss, difficulty organizing thoughts, and extreme changes in mood, all of which Pinel captured throughout his research.

Pinel's dedication to understanding neurological illnesses allowed later physicians to be better equipped to treat their patients with more care and compassion. Although descriptions of dementia and AD have been discovered from as early as the time of the ancient Egyptians, people who suffered from neurological illnesses, including dementia and AD, were often feared and deemed as outsiders from society. Pinel led the movement allowing all patients to be treated with an open mind, leading to better and more thorough treatment methods, and opening the doors for future physicians, such as Jean-Etienne Dominique, to more thoroughly study the illnesses identified by Pinel.

As Pinel's student, Esquirol learned the importance of compassion and care towards patients suffering from neurological illnesses. Esquirol helped to continue the reforms that Pinel had set into motion; Esquirol introduced the Law on Alienated Persons of 1838 to ultimately help to improve conditions in asylums and allow for better medical treatment. Additionally, Esquirol further elaborated upon the definitions of various diseases, which had been previously defined by Pinel. For dementia in particular, Esquirol reasoned that dementia should be defined as follows: "the incapacitation of the organs of thought because they have lost the energy and force required to perform their functions" (Huertas, 2008). He also described other conditions, which he called monomania, lypemania, mania, and imbecility. In contrast with Pinel's belief that patients could only suffer from one mental illness, Esquirol noted that some patients suffered from all of these types of mental disorders, emphasizing his belief that all patients present different symptoms for various neurological illnesses. In one of his doctrine's, he notes that the

challenge of diagnosing neurological illnesses "has led some physicians to reject any distinction and not to admit in madness any more than a single disease, presented in varied forms. *I do not share this way of seeing things*, and consider the genera ... to be sufficiently different so as not to be confused" (Huertas, 2008). He urged medical practitioners to more fully analyze their patients, to create more individualized treatments.

Along with his progressive ideas, allowing for more thorough analysis of the patients which would provide better patient care, he was able to further subdivide Pinel's established categories of psychiatric illnesses. For dementia in particular, Esquirol was able to differentiate between three different types: acute, chronic, and senile. He specifically related senile dementia to "old age, alterations in memory, especially the recent type, difficulty of attention and its captious progress" (Vatanabe et al., 2020). Although this definition appears to be all-encompassing, Esquiol's identification of senile dementia sounds similar to AD. Overall, Esquirol's elaboration on Pinel's work allowed for better care for patients. Esquirol continued the reforms that were introduced by his predecessor, Pinel; both Pinel and Esquirol opened the doors for further research to be done to better understand the mind of an individual suffering from neurological illnesses.

Another scientist, Emil Kraepelin, seemed to follow in the footsteps of Pinel and Esquirol. In the late 19th and early 20th century, Emil Kraepelin became a popular psychiatrist; like Pinel and Esquirol, Kraepelin had a major impact in the field of medicine. He dedicated most of his time in the lab, and as such, he lost his merits as a clinical physician. This did not deter him though, as he later founded the Department of Psychiatry in Munich. He had many important achievements in the field of psychiatry including the differentiation between 'dementia praecox,' which we now refer to as schizophrenia, and 'manic depression' (Ebert & Bär,

2010). He determined that 'dementia praecox' was a progressive neurodegenerative disease. Even with Pinel's and Esquirol's asylum reforms, individuals suffering from dementia praecox were commonly viewed as unstable and even dangerous, and ultimately did not receive proper medical treatment. In contrast with dementia praecox, Kraepelin believed that manic depression is "an episodic disorder, which does not lead to permanently impaired brain function" (Ebert & Bär, 2010). Ultimately, Kraepelin's work led to a greater understanding of treatments and diagnoses for neurological illness. Unlike Pinel and Esquirol, Kraepelin did not show great compassion for the patients he studied. He believed that compassion posed as an obstacle for objective research. Instead, Kraepelin focused on the patient's words and studied those words incessantly, aiming to find answers, which led him to better understand neurological illnesses. Although Kraepelin did not necessarily have a direct impact on dementia research, his lab became renowned; famous scientist Alois Alzheimer, who actually discovered AD, was actually a student in Kraepelin's lab.

During the initial semesters of Alzheimer's college career, he showed interest in anatomy and learned how to work with microscopes. Interestingly enough, Alzheimer focused all of his interests within the clinical realm of medicine and completely neglected the field of psychiatry altogether (Hippius & Neundörfer, 2003). Alzheimer likely became interested in psychiatry after being approached by a wealthy family, who needed someone to travel with their mentally ill relative. Alzheimer allegedly traveled with this patient for five months, but neither the name or diagnosis of the patient is known. After returning from his five month expedition, he applied for a position at the Community Hospital for Mental and Epileptic Patients in Frankfurt. Through this position, Alzheimer became a renowned clinician, furthering his interests in psychiatry. As his career developed, his popularity grew and he was later invited to join Kraepelin's lab.

In Kraepelin's lab, Alzheimer researched the brain of Auguste D., a woman who was described as a 51-year-old female who had delusions, anxiety, and was disoriented and forgetful. She additionally became extremely paranoid and believed that she expressed fears of "being persecuted and bothered by the neighbors" (Ramirez-Bermudez, 2012). It became apparent that she suffered from some neurological illness, at which point Alzheimer was assigned to her case to investigate. According to Alzheimer, "she showed rapidly increasing memory impairments; she was disoriented carrying objects to and fro in her flat and hid them. Sometimes she felt that someone wanted to kill her and began to scream loudly" (Ramirez-Bermudez, 2012). He also noted that she was completely unable to perform various tasks correctly; when asked to draw the number '8,' she would write her name instead. Additionally, she was unable to recall her last name, and could only correctly provide her first name. After her death, Alzheimer received her spinal cord and brain for study. At a conference in 1906, Alzheimer first presented the neurofibrillary tangles and senile plagues found in Auguste D's brain. These findings made Alzheimer the first to link these pathological markers of disease to Alzheimer's disease, a term coined by Kraepelin.

Although Auguste D. was arguably Alzheimer's most famous patient, Alzheimer also gathered valuable evidence from Josef F. After three years of hospitalization, Alzheimer was able to study Josef F.'s brain and determine that he had also suffered from AD. Interestingly, this patient's brain did not have neurofibrillary tangles, but instead showed a great accumulation of senile plagues only. For a long time, researchers believed that Josef F.'s case was a mere contradictory to the many other AD brains, which presented with both senile plagues and neurofibrillary tangles. However, over time, the cases of Josef F. and Auguste D. were re-

investigated, and it was determined that both Auguste D. and Josef F. suffered from AD, but Auguste D. died at a much more progressive state in her disease than Josef F.

Overall, the findings from Pinel, Esquirol, Kraepelin, and Alzheimer have led to great reforms in regards to the proper treatment for those who suffer from various neurological illnesses. Pinel and Esquirol worked to reform asylums by literally unshackling patients. Additionally, Pinel and Esquirol pushed for these patients to be treated with care and respect in order to receive proper treatment. The initial reforms presented by Pinel and Esquirol opened the doors for future healthcare providers and researchers to gain more understanding of neurological illnesses. Kraepelin followed in the footsteps of Pinel and Esquirol by paying close attention to the symptoms his patients presented. He worked to provide objective findings that later allowed him to differentiate between dementia praecox and manic depression. Kraepelin questioned the works of his predecessors to improve the field of psychiatry; Alzheimer followed in his footsteps by understanding the pathological markers that underlie diseases, specifically AD. Even today, there is so much unknown about AD; there is currently no cure for AD and few treatments that effectively slow the progression of the disease. The works of these previous researchers prove that medicine and science should be questioned until complete answers are found.

**Neuroinflammation in Alzheimer's Disease**

AD is now the most common cause of dementia in the elderly and affects more than 4 million people in the US. AD is a progressive and deadly disease that affects cognitive function, the ability to communicate, and the ability to carry out daily tasks. Most popularly, Alzheimer's pathology is defined by the presence of extracellular plaque deposits of β-amyloid peptide (Aβ) and neurofibrillary tangles made up of protein tau. Aβ has been recognized as a protein that disrupts synaptic function, neural connectivity, and even induces neuron death (Murphy & LeVine, 2010).

Inflammation in the brain is one of the hallmarks of AD; at first, this inflammatory response acts to eliminate cell injury and dead cells and tissues. However, over time, this inflammation becomes chronic, destroying the surrounding tissues, leading to severe tissue deterioration. This inflammatory response is driven by microglia, astrocytes, and neurons. Specifically, regarding inflammation in AD, β-amyloid (Aβ) plaques and neurofibrillary tangles activate inflammatory cells, such as astrocytes and microglia. Responses from cytokines and chemokines tend to be altered due to this inflammation, and altogether further propel this neuroinflammatory response. Inflammation initially occurs as a sort of protective response against stress, injury, or infection. Unfortunately, this continued inflammatory response contributes to the progression of AD. Microglia has been shown to play an important role in AD. Microglia has both protective and neurotoxic effects in the brain. Activated microglia release proinflammatory mediators. Aβ, which is a hallmark of AD, can attract and activate microglia (Rubio-Perez & Morillas-Ruiz, 2012). Activated microglia can release toxic factors, which can lead to neuroinflammation and may trigger the progression of AD. Additionally, astrocytes are attracted to Aβ deposits in AD suggesting that these lesions may in part induce

astrocyte recruitment. Astrocytes play a role in Aβ clearance and degradation; however, they tend to release proinflammatory molecules are thought to accelerate the progression of AD. Neurons also contribute to this neuroinflammation; they produce several chemokines and cytokines, which act to result in proinflammatory cytokine production in microglia. These pro-inflammatory mediators may trigger further neuroinflammation and lead to further neuronal damage in AD pathology (Rubio-Perez & Morillas-Ruiz, 2012).

The identification of Aβ in the autopsied brains of individuals with AD led to the amyloid cascade hypothesis, which essentially asserts that Aβ plaque deposits result in neuronal death, leading to cognitive decline. This hypothesis has since been supported due to the finding that AD inducing mutations in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes, all of which increase Aβ production. The cleavage of APP, via the sequential cleavage by β- and γ-secretase generates Aβ fragments. Although all of the exact functions of APP remain elusive, overexpression of APP is known to maintain neural integrity.

Microglia likely play a role in the inflammatory response in patients with AD; in a healthy brain, microglia are inactive. When microglia sense damaged tissue, this leads to microglial activation. Different phenotypes of microglia have different functions: M1 has a pro-inflammatory function, while M2 has an anti-inflammatory function. In patients with AD, it has been proposed that pro-inflammatory microglia are activated in the presence of Aβ, resulting in phagocytosis of Aβ. After an extended period of time, microglia are no longer able to process Aβ, leading to accumulation of Aβ; this could be due to a malfunctioning TREM2 gene. TREM2 essentially instructs microglia to clear debris or plaque build-up around a neuron. When this gene does not function properly, and the microglia sense damage, they accumulate around the neuron, but do not complete their job by clearing away plaque, potentially causing the Aβ

accumulation in individuals with AD (What Happens to the Brain in Alzheimer's Disease?, 2017). Due to the inability to process Aβ, pro-inflammatory cytokines are released, exacerbating neuroinflammation and contributing to neurodegeneration, and increased activation of microglia. Microglia represent the first line of defense against invading pathogens or other brain tissue injury. These cells aim to clear debris from the damaged area. Microglia may be associated with amyloid plaque; disruption of the APP gene delays microglial activation. In most ways, the role of microglia has been found to be beneficial. Studies have indicated that activated microglia can reduce Aβ accumulation by increasing phagocytosis. Therefore, microglia may be utilized in a future approach for human Aβ immunization. Chemokines, which are expressed and secreted by neurons, act as regulators of microglial migration and recruitment of astrocytes, likely play a role in inflammatory responses in the brain. Various chemokines have shown to be upregulated in AD, generating an upregulated deposition of microglia and astrocytes to damaged areas in the brain, potentially leading to further inflammation, which of course could lead to AD development (Kinney et al., 2018).

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that is commonly upregulated in the brains of individuals with AD. TNF acts to upregulate other pro-inflammatory cytokines such as IL-1 and IL-6 both of which are also commonly upregulated in individuals with AD (Su et al., 2018). Interestingly, one study showed that when TNF knockout mice were injected with bacteria, there was no protective response, and the mice developed a severe and inflammatory reaction, resulting in death. Thus, the study indicates the initial inflammatory response by TNF is protective; however, in individuals with AD, this response becomes cyclical and eventually causes more harm, damaging brain tissue and ultimately

resulting in cognitive decline. TNF also increases the production of Aβ, a hallmark of AD (Su et al., 2018).

Astrocytes additionally play an important role in Aβ clearance, by supporting neurons. In some conditions, however, overactivity of astrocytic β-secretase results in increased generation of Aβ in chronic stress, suggesting that astrocytes play a role in the inflammatory response in AD. Additionally, recent studies have shown that neurons play a role in neuroinflammation. Evidently, neurons generate inflammatory molecules, further contributing to the inflammatory response in AD pathology (Kinney et al., 2018). Additionally, neurons produce and secrete various chemokines and cytokines, both of which are upregulated in individuals with AD.

Cytokines, which are secreted by immune cells as well as neurons, play a role in inflammatory responses. Most cytokines are produced by neurons or glia; given that numbers of glia and neurons are increased in AD brains, cytokines likely play an important role in neuroinflammation responses. Cytokines are referred to as either proinflammatory or anti-inflammatory. Inflammatory cytokines are secreted by microglia and astrocytes and contribute to neuronal death. Inhibitory cytokines can suppress proinflammatory cytokine production, which is critical to the concept of balance among both types of cytokines. Dysregulation of this balance can lead to cytokine production which can induce cytotoxicity, which is prevalent in AD pathology.

Recent studies have indicated that Triggering Receptor Expressed on Myeloid Cells- 2 (TREM2) may additionally play a role in AD pathology. There are three important roles that TREM2 may play. In AD pathology: 1) regulation of phagocytic and autophagic processes; 2) myeloid cell survival and proliferation; and 3) regulation of inflammation. Myeloid cells have the ability to mature into red blood cells or various types of white blood cells (Raymaakers,

2020). Studies have shown that myeloid activation patterns, which at some point rely on TREM2, convert to a neurodegenerative pattern, altering phagocytosis and lipid metabolism.

Lastly, growth factors, which are proteins that support the survival of cells of the central and peripheral system play a role in the development of the brain, regulating the growth of different cells in the brain. Nerve growth factor (NGF) is commonly unregulated in patients with AD, indicating that NGF plays a specific role in AD development. Studies have indicated that NGF accumulates in neurological disease, emphasizing the idea that NGF might play a role in inflammatory responses in the brain of individuals with AD (Kinney et al., 2018).

Just as the amyloid cascade hypothesis accounts the accumulation of Aβ plaque deposits, the tau hypothesis accounts for the hyperphosphorylation of tau. Like amyloid plaques, neurofibrillary tangles are a hallmark of AD. Tau is a microtubule-associated protein (MAP) which helps to stabilize neuronal microtubules (Mandelkow & Mandelkow, 1998). Microtubules in a neuron are generally found in the axon and help to provide structure to the cytoskeleton of the cell as well as assist in transporting substances to different parts of the cell. Tau can be phosphorylated at many sites, some of which are responsible for microtubule-binding (Mandelkow & Mandelkow, 1998). Normally, tau is soluble and unfolded, but when tau is mutated, tau can become hyperphosphorylated, which ultimately leads to death by apoptosis. Additionally, hyperphosphorylated tau shows improper microtubule binding, leading to a breakdown of the cytoskeleton of the cell as well as an inability to transport substances to different parts of the cell. Tau aggregates, called 'paired helical filaments' (PHF) form as a result, which then turn into insoluble neurofibrillary tangles. These tangles accumulate over time, blocking synaptic communication between neurons (What Happens to the Brain in Alzheimer's Disease?, 2017). The inability of neurons to communicate to one another as well as

the inability for microtubules to transport essential nutrients causes the neuron to be unable to create and process various proteins, ultimately leading to cell death. Tau tends to accumulate starting in the entorhinal cortex, an area involving smell, indicating one reason why many individuals with AD tend to lose their sense of smell first. Tau aggregates then tend to accumulate in the temporal and frontal parts of the brain, resulting in affected speech and executive functions (Yang et al., 2005). Additionally, research has shown that the inflammatory processes involved in the AD brain can induce tau hyperphosphorylation via the MAPK pathway. This pathway is responsible for directing responses from different stimuli, including proinflammatory cytokines. Thus, the inflammatory response that induces hyperphosphorylation of tau then causes an upregulation of proinflammatory cytokines, encouraging a proinflammatory cycle (Zilka et al., 2012).

Researcher Yang emphasizes the concept that it appears that once neuroinflammation begins, this cycle of neuroinflammation continues, causing AD to progress as a result of the accumulation of amyloid β-amyloid and neurofibrillary tangles. Yang points out that "immune cells are activated and produce a variety of inflammatory mediators such as cytokines and chemokines" (Yang, 2019). Chemokines and cytokines are known to play a role in the progression of AD through various inflammatory processes. Past studies have even indicated that "elevated cytokine levels are significantly correlated with microglial activation and have effects on Aβ generation, neurodegeneration, and cognition" (Yang, 2019), which is one reason why individuals who suffer from AD show memory and other cognitive declines. Additionally, it is evident that microglia, astrocytes, and neurons seem to begin and even perpetuate this neuroinflammatory cycle, causing AD to progress, and cognitive function to decline. It is important to understand that the production of one type of molecule does not explain the

neuroinflammatory processes that occur in the brains of AD individuals; this neuroinflammation is a perpetual cycle induced by a combination of many factors, which initially cause the accumulation of Aβ plaques and neurofibrillary tangles. Both of these entities essentially contribute to the overall neuroinflammation in AD individuals.

**Modern Forms of Treatment**

Unfortunately, there is currently no cure for AD; however, researchers and healthcare providers work hard to find the best approaches to delay the progression or onset of AD. Currently, there is no treatment option that can help to delay the progression of the disease, once the disease has progressed to a certain extent. Few medications are currently marketed to individuals diagnosed with AD. Thus, as of now, it is vital that healthcare practitioners advise their patients to make healthy lifestyle choices in efforts to prevent the onset of the disease.

Because many believe that a proinflammatory response in the brain is one mechanism through which an individual can suffer from resulting AD, some treatment options directly attack these proinflammatory processes in the brain. One such treatment option is the use of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are a group of drugs that aim to decrease inflammation and reduce fevers by blocking cyclooxygenase (COX), an enzyme that produces prostaglandins, lipids that are made at sites of tissue damage or infection. By limiting the amount of prostaglandins, individuals should see pain relief and reductions in fevers. Although NSAIDs are most commonly used to treat pain or fevers, interestingly, studies have shown that individuals can reduce their likelihood of developing AD as a result of taking NSAIDs (Ozben & Ozben, 2019). Some patient studies have indicated that NSAIDs can reduce the incidence of AD by 30-80%; this wide range indicates the more research needs to be conducted to understand the usefulness of NSAIDs in AD prevention.

Researchers have also utilized animals to understand the role NSAIDs potentially play in AD prevention. One animal study used a Tg2576 line of APP-transgenic mice; this particular mouse model causes the mice to show characteristic symptoms of AD as well as the inflammatory processes known to induce AD. Through the course of this study, mice were given

a substantial dose of ibuprofen (62.5 mg $kg^{-1}$ $day^{-1}$), a common NSAID used as a painkiller. Over the course of a six-month trial, the mice showed a significant reduction in "amyloid plaque pathology and Aβ levels, reduced microglial activation and reactive astrocyte numbers, and reduced levels of the pro-inflammatory cytokine IL-1β" (Weggen et al., 2007). Subsequent studies utilizing this particular mouse model have shown similar results.

NSAIDs are believed to interfere with pro-inflammatory cytokines such as IL-1 and TNF-α, both of which are upregulated in individuals with AD. Both of these cytokines upregulate COX. An enhanced expression can upregulate neurons, astrocytes, and microglia, which over time can lead to increased neuronal loss. Interestingly, blocking COX can also induce neuronal loss. Although the use of NSAIDs could potentially prevent the onset of AD, the mechanism by which this occurs is not fully understood. Additionally, COX is not believed to be upregulated in individuals with AD and "neuronal COX expression has been found to be unchanged in the Tg2576 mouse model of AD" (Weggen et al., 2007). The usefulness of NSAIDs in treating and preventing AD has been disputed, and healthcare practitioners are currently not advised to prescribe NSAIDs for the sole purpose of treating or preventing AD.

Although this finding has been disputed, "the incidence of AD was found lower in patients with rheumatoid arthritis with long-term NSAIDs medication" (Ozben & Ozben, 2019). Thus, NSAIDs prove to be a promising therapeutic option or a potential preventative treatment for individuals who are at a higher risk of developing AD. Another study tried to analyze the usefulness of the NSAIDS naproxen and celecoxib in preventing AD; unfortunately, this study showed that the use of these particular NSAIDs did not seem to prevent the onset of AD. In fact, this particular study had to be halted, due to the increased incidence of cardiac disease in patients specifically treated with naproxen (Ozben & Ozben, 2019). Although NSAIDs show potential in

treating or preventing the onset of AD, results have been disputed. Additionally, with the associated side effects and risks associated with long-term NSAID use, there is no official directive for healthcare providers to prescribe NSAIDs with the sole purpose of preventing AD.

Although NSAIDs have the ability to reduce the inflammatory processes and clear Aβ plaques in the brain, they are currently not a suggested therapy due to the various side effects of long-term usage. Currently there is a great need for AD drug research, because there are few effective therapies available. The two classes of drugs used to treat AD are called cholinesterase inhibitors as well as an N-methyl D-aspartate (NMDA) antagonist. These drugs are effective in reducing the symptoms of AD, which can provide relief to patients and families.

There are three different drugs classified as cholinesterase inhibitors that are approved treatment options for individuals with AD, which include donepezil, galantamine, and rivastigmine. Currently, donepezil is used to treat all stages of the disease, galantamine is used to treat mild to moderate forms of AD, and rivastigmine is also used to treat mild to moderate forms of AD (Alzheimer's Association, 2021). All three drugs come with various side effects, including nausea, vomiting, and loss of appetite, but overall these medications are tolerated well. Cholinesterase inhibitors are used to treat cognitive symptoms, such as memory loss, confusion, and problems with thinking and reasoning (Alzheimer's Association, 2021). Cholinesterase inhibitors are "a group of drugs that block the normal breakdown of acetylcholine (ACh) into acetate and choline and thereby increase both the levels and duration of actions of acetylcholine found in the central and peripheral nervous system" (Singh & Sadiq, 2020). Acetylcholine plays a major role in memory and overall cognition, thus the increased acetylcholine as a result of consuming a cholinesterase inhibitor could effectively treat cognitive symptoms. Cholinesterase inhibitors also have the added benefit of improving muscle activation,

contraction, and strength due to the increased acetylcholine at neuromuscular junctions (Singh & Sadiq, 2020). Additionally, cholinesterase inhibitors are effective at delaying the progression of the disease, which can provide overall relief to patients and families.

Additionally, a medication called memantine, an NMDA receptor, is also a verified treatment option for individuals with AD. This medication acts to "Block the toxic effects associated with excess glutamate and regulates glutamate activation" (How is Alzheimer's Disease Treated?, 2018). More specifically, "The principal mechanism of action of memantine is believed to be the blockade of current flow through channels of N-methyl-d-aspartate (NMDA) receptors--a glutamate receptor subfamily broadly involved in brain function" (Johnson & Kotermanski, 2006). This medication is approved to treat moderate to severe forms of AD and has even been shown to have neuroprotective effects; memantine has been shown to improve mental function and the ability to perform daily activities for some people, allowing individuals with AD to retain their independence, something that is consistently lost through the progression of the disease.

Ultimately, these approved treatments are great options for individuals suffering from AD. They can relieve symptoms and ideally allow an individual to retain their independence for a longer period of time. Losing an individual's independence and having to rely on others for activities of daily life can generate frustration and a loss of hope in many patients. Thus, the use of these medications could make a huge impact on an individual's overall well-being. Cholinesterase inhibitors and NMDA receptors, both of which are currently marketed as AD medications, have specific methods of action, by reducing the breakdown of acetylcholine and regulating glutamate activity, respectively. Although there are few treatments available to patients, these treatments are effective. Ideally, future research will find therapies that are

neuroprotective and can alter the course of the disease, relieving patients and families of the fear that accompanies an AD diagnosis.

**Failures of Treatments**

Given that AD is characterized by Aβ plaques and tau proteins, researchers initially hypothesized that removal of the buildup of these proteins could cure AD. Unfortunately, after several failed drug trials in which patients did not have improved memory, agitation, or anxiety, researchers looked to different mechanisms that played a role in the development of AD. Interestingly enough, survivors of the 1918 flu pandemic were at a higher risk of developing AD (Myrskylä et al., 2013). Thus, researchers began to wonder if antimicrobials, which help the immune system fight disease, play a role in AD development and progression. Eventually, researchers were able to determine that microglia and astrocytes, which play a role in brain function, play a unique role in the immune system as well and may promote AD development. Astrocytes and microglia initially cause neuroinflammation in the brain when aiming to fight off disease or invading pathogens; however, this continued neuroinflammation is harmful and can lead to AD. Although the exact process remains unclear, research has concluded that environmental pollutants and genetics play a large role in the risk associated with AD. For example, gum disease, herpes virus, and gene APOE4 implicate a greater risk of developing AD as a result of initiating the inflammatory processes in the brain. In the coming years, anti-inflammatory drugs will be continuously developed in efforts to at least halt the progression of AD (Weintraub, 2019).

It is important to understand various contributors to the pathology of AD, to allow researchers to find effective targets for therapies. Researchers have developed few effective therapies that help to combat the symptoms of AD. Currently, the medications marketed for AD allow patients to retain their independence for a longer amount of time, but there are few drugs available to treat AD; thus, future research is necessary to find new drugs, allowing individuals

to find a treatment option that is best for them. Additionally, most of the drugs on the market delay the onset or progression of symptoms, but fail to change the outcome in a patient's life. Ultimately, the disease will kill the patient. The strides in AD research have made major breakthroughs allowing for better understanding of the complex mechanisms involved in the onset of the disease; however, still, no drug has the power to reverse the path of the disease. Researchers and healthcare providers are racing for a cure, hoping to heal their patients, better the lives of families, and ease the economic burden imposed by AD.

Along with the motivation to allow for increased quality of life in patients with AD, the large economic burden imposed by AD is a great incentive for researchers to find a cure. According to the President and CEO of the Alzheimer's Association, Harry Johns, "Caring for people with Alzheimer's will cost all payers - Medicare, Medicaid, individuals, private insurance and HMOs -- $20 trillion over the next 40 years, enough to pay off the national debt and still send a $10,000 check to every man, woman and child in America" (Johns, 2013). This is a staggering statistic implying that the impending cost acquired through the care of AD patients not only affects patients and families, but also places a burden on the economy; major breakthroughs need to be made immediately in the realm of AD research. Additionally, the World Dementia Envoy, Dennis Gillings, explains that 'Dementia is a ticking bomb costing the global economy £350 billion and yet progress with research is achingly slow (Burke, 2014). Gillings and Johns would likely agree that there is a great need for AD research, especially to dampen the economic burden placed on families, patients, and all other payers.

Aside from the economic burden of AD, families are strongly affected by an AD diagnosis. On the Alzheimer Society website, family members share their stories of loved ones

affected by the deadly disease under the hashtag #StillHere. Rachel Smith, a 26-year-old, explains that her father was recently diagnosed. She writes that "I hope that one day Dad will be able to walk me down the aisle and hold my future children in his arms, but I fear that he may not be able to when the time comes" (#StillHere - five personal stories, 2021). Rachel goes on to explain that her father's diagnosis has been devastating to deal with as a 26-year-old. She describes the dramatic role reversal, requiring her to take care of her father, rather than her father taking care of her. Another woman, Samantha, describes her mother's recent AD diagnosis. Like Rachel, Samantha is a young 26-year-old; she struggles to find time to finish school and find a career while acting as the primary caregiver to her mother. Samantha explains that the most devastating aspect of the disease is the concept that her mother may one day forget her. Samantha writes "I still have my mom physically, but I'm losing more and more of her. My mom has accepted having dementia and knows that something is wrong, that her brain isn't working 'right', but she doesn't like to use the word 'Alzheimer's'. She's depressed and cries a lot, saying she hates this disease and that she wishes it never happened to her. On the worst day it's only our toy poodle, Lucy, who can bring a smile to her face" (Meet Samantha and Shawn, 2020). It is clear that this disease takes a toll on families. The devastating news of an AD diagnosis causes family members to feel like they have already lost a family member, given the inevitable outcome of the disease.

Patients who are diagnosed with AD additionally suffer not only from the symptoms of the disease, but also from the grief of knowing and understanding the progression of the disease. The Alzheimer's Association website posted "Alzheimer's: A Real Love Story…" which describes a beautiful story between married couple Mark and Julia Balson. Married for 47 years, Mike and Julia enjoyed an adventurous life together, full of traveling, time spent with their

kids as well as each other. Eventually, Mike received the devastating news of an AD diagnosis, completely turning his world upside down. In his youth, Mike was the picture of health; he had even played professional soccer in the U.K. for more than a decade. Thus, the couple never predicted an AD diagnosis. Both Julia and Mike discuss that symptoms had been apparent for months, but the couple often excused Mike's forgetfulness as purely mental fogginess. Eventually, Mike sought help from a healthcare practitioner who was able to provide Mike with a diagnosis. Although the family found peace in knowing and understanding Mike's symptoms, they struggled to deal with the prognosis of AD. They acknowledge that both of them have "off" days, but that ultimately this hardship has made their relationship stronger; however, their relationship does not look the same. Mike describes one of the most upsetting aspects of the disease is that he is unable to take care of his wife like he used to. The role reversal has shifted the dynamic of their relationship, and although Mike struggles with the inability to provide and properly care for his wife as he sees fit, he acknowledges that his wife is the only person he would ever want taking care of him. He believes the strength of their relationship will allow them to face this disease head-on, together.

Clearly, the devastation that families and patients feel as a result of an AD diagnosis is insurmountable; patients fear of forgetting their loved ones, and family members fear of being forgotten. Although great strides have been made in the realm of AD research, the need for a cure is apparent now more than ever. Because the baby boomer generation is turning 65, and because aging is the biggest risk fact in the disease, more and more people will inevitably be diagnosed with AD than ever before. Additionally, the economic burden of AD is extreme; thus, there is a great need for curative AD research. Currently, there are several clinical trials underway. In the past, research has targeted a range of different mechanisms involved in the

onset of AD, including monoclonal antibodies, Gamma secretase inhibitors, and neurochemical enhancers (Mehta et al., 2017). Unfortunately, these trials were unsuccessful, causing researchers to look at different AD causing pathways. It is imperative to understand and analyze different failed treatments in order to move forward with AD research.

Although many of the mechanisms that induce AD are widely understood, which in turn allowed for the generation of the amyloid cascade hypothesis as well as the tau phosphorylation hypothesis, there is still no cure for this progressive and deadly disease. Many pharmaceutical companies, hospitals, and private organizations have been on a wild goose chase, searching for a cure for AD. Unfortunately, approximately 99% of of AD drugs fail, according to a study conducted by the Cleveland Clinic Lou Ruvo Center for Brain Health (Drugs Discovery Trends Editor, 2019). This consistent failure in treatments likely pertains to the fact that, although many of the mechanisms contributing to AD are well understood, the efficacy of one drug likely will not have a major impact on the progression of the disease, because of the complexity of the various mechanisms that contribute to AD onset. Over the course of decades, companies have continued to try to find a cure or better forms of AD treatment, with little to no luck. For example, between 2002 and 2012, 244 compounds were studied in 413 clinical trials; however, only one drug was approved. Because of the complexity of the disease, it is extremely challenging and likely discouraging for the researchers who long to find a cure or different treatment. Along with the challenges researchers face as they strive to find a cure, unfortunately, AD research is widely underfunded in comparison to the challenges imposed by the disease (Drugs Discovery Trends Editor, 2019). Thus, more funding is essential for future research.

Along with increased AD research funding, it is important that researchers understood previously tested and failed treatments in order to further understand the complex mechanisms involved in the disease. Recently, Eli Lilly Pharmaceuticals developed a drug called solanezumab. This drug was created to target and remove or prevent the accumulation of amyloid, which in turn, they hoped would prevent AD progression (Belluck, 2016). Phase 1 and 2 clinical trials of solanezumab showed great results; the drug was tolerated well in healthy volunteers and in patients with mild to moderate AD (Almeida, 2019). Thus, researchers were confident in the drug's ability until Phase 3 of clinical trials. During this clinical trial, the researchers were hoping to see that the drug helped to slow cognitive decline in patients suffering from mild to moderate AD. They were able to determine that individuals suffering from AD showed less worsening in cognition versus the placebo group; however, these results were not statistically significant. Additionally, the effects of solanezumab showed "no evidence of slowing of cognitive or functional decline...in those subjects who had moderate AD at study commencement" (Siemers et al., 2016). Ultimately, the researchers were unable to provide an absolute conclusion in regards to the efficacy of solanezumab in patients with mild to moderate AD, which called for termination of the clinical trials. However, the drug is currently being tested in clinical trials for individuals who are at risk of developing AD (Belluck, 2016). The President and Chief Executive of Eli Lilly, Dave Ricks, admits that the failure of solanezumab was heartbreaking, because the results indicated that the drug would not be effective in altering the progression of the disease. However, the study was able to provide insight in regards to the complexity of the disease. Dr. Lon Schneider, director of the California Alzheimer's Disease Center at the University of Southern California recognizes that "as the brain is failing or dying, it is dying on all levels" (Belluck, 2016) implying that the efficacy of one drug potentially depends

on the drug's ability to alter multiple different mechanisms in the brain. Future clinical trials for solanezumab will ideally show that the drug is able to clear or prevent amyloid accumulation in individuals that have not received an official AD diagnosis, preventing the onset of the disease.

In addition to Eli Lilly's recent trials for solanezumab, Roche Diagnostics produced a drug called gantenerumab. Like solanezumab, gantenerumab was created to "connect to aggregated forms of beta-amyloid and remove beta-amyloid plaques, a pathological hallmark of AD that is believed to cause brain cell death" (Roche's gantenerumab fails to meet primary endpoint in Alzheimer's Disease trial, 2020). Researchers predicted that the removal of Aβ plaques would prevent the progression of the disease as well as restore various cognitive deficits that result from AD. Unfortunately, the study failed to meet its primary endpoint, indicating that the drug was unable to slow the rate of cognitive decline in individuals with autosomal dominant AD. The drug is now being tested in other clinical trials, with hopes that gantenerumab will have the ability to protect individuals with a form of AD that is not directly caused by a gene. Ideally, this drug will be able to reverse the inevitable deadly progression of AD, allowing for relief amongst patients and families.

Thus far, researchers and pharmaceutical companies have been unable to develop an effective drug that combats the accumulation of Aβ plaque in AD brains. Other drugs have been developed to treat different mechanisms in the AD brain. For example, a drug called idalopiridine was developed jointly by Lundbeck and Otsuka Pharmaceuticals (Kegel, 2018). This drug was developed as "a neurochemical enhancer that antagonizes 5-HT6 receptors. Inhibiting 5HT6 enhances acetylcholine release in the brain and is therefore pro-cholinergic" (Mehta et al., 2017). Therefore, the drug was created to relieve symptoms of AD,

rather than change the direction of the disease's course (Kegel, 2018). Phase 2 trials were able to show that the drug was effective in improving cognition; however, phase 3 trials did not show these same results. Although this difference in results may seem contradictory, there was one major difference between phase 2 and phase 3 trials: the dosage. In phase 2 trials, the participants received a 90 mg dose of idalopiridine, three times daily. The U.S. Food and Drug Administration suggested in the phase 3 trial, that the dosage should be lowered and additionally that participants should only receive the medication once daily. The U.S. Food and Drug Administration determined that the "side effects of the treatment were relatively common in the Phase 2 study. In addition, other research showed that idalopiridine bound to more than 80 percent of its target receptors at much lower doses, suggesting the high dose was unnecessary" (Kegel, 2018). Although it was determined that a high dosage of idalopiridine was unnecessary, the phase 3 trials provided different results than the phase 2 trials; the phase 3 trials showed no improvement in cognition. It has not been determined why these differences in results were produced; however, given the lowering of the dosage as well as the lessening of the distribution of the drug to participants from three times daily to once daily, these differences could have impacted the efficacy of the drug for unknown reasons. Although the phase 3 trials provided disappointing results, the data was shared with the Critical Path of Alzheimer's Disease (CPAD) consortium database, allowing for CPAD to "develop a model of disease progression across the entire spectrum of Alzheimer's from its earliest to late stages" (Pataia, 2020). Thus, although the drug ultimately failed to improve cognition in patients with mild to moderate AD, the data collected will further contribute to AD research and allow for a more thorough understanding of the disease progression. Dr. Dave A. Bennett of Rush University Hospital believes that with the data collected from the idalopiridine trials, "It is just a matter of time before that knowledge is

translated into effective strategies for the treatment and prevention of Alzheimer disease dementia" (Kegel, 2018).

These failed treatments that have been discussed thus far have been unable to improve cognition in patients and have additionally failed to reverse the progression of the disease. Other drugs have been developed to target different mechanisms of the disease, and in 2009, a drug called avagecestat was developed "for the selective inhibition of β-amyloid synthesis" by inhibiting γ-secretase (Avagacestat ineffective for Alzheimer's disease, n.d.). Phase 1 trials indicated that the drug was effective in decreasing the amount of Aβ plaque build-up in the brain in AD participants, furthering researchers' belief in the drug's promising results. The drug proceeded to phase 2 trials, where, unfortunately, the "Researchers observed increases in nonmelonoma skin cancer" (Avagacestat ineffective for Alzheimer's disease, n.d.), indicating that the drug is unsafe and should not be administered to patients suffering from mild to moderate forms of AD. Gastrointestinal side effects also occurred, including diarrhea, nausea, and vomiting (Avagacestat, 2021). Along with the low tolerance of avagecestat among participants, the drug showed no significant effectiveness in comparison to placebo groups; patients in the treated and placebo group showed disease progression at similar rates, as was indicated by assessment of participants' brain imaging and fluid biomarkers, as well as cognition (Avagacestat, 2021). These were devastating findings given that participants suffered tremendously as a result of receiving and taking avagecestat. Additionally, one study indicated that, rather than lowering the amount of Aβ plaque in the AD brain, the consumption of the drug increased Aβ production at low doses, and therefore contributed to increased cognitive decline (Toyn, 2015). Researcher Jeremy Toyn argues that "The known limitations make new AD trials with [gamma secretase inhibitors] very unlikely, so future γ-secretase-targeted compounds would have to display a

radically different mechanism" (Toyn, 2015). Thus, the future of the effectiveness of gamma secretase inhibitors as a treatment option for individuals for AD will likely be ineffective, unless, as Toyn states, a gamma secretase inhibitor is able to target and affect different mechanisms in the brains of AD patients.

Although these different drug trial failures may cause the search for a cure to seem hopeless, even these failed drug trials have provided insurmountable evidence in regards to the different mechanisms involved in AD. For example, the data collected from the clinical trials for the neurochemical enhancer, idalopiridine, provided information regarding the progression of mild to moderate forms of AD, allowing for an exact model of various mechanisms to be produced. This information will allow for future and more accurate research to be conducted for AD. Evidently, it has become clear that the drugs that have been used in various trials only aim to relieve one mechanism involved in AD, when in reality, many mechanisms are involved in AD progression. Ultimately, I predict that the efficacy of an AD drug will depend on the drug's ability to alter multiple different mechanisms as well as relieve the symptoms that result from those various mechanisms. Additionally, research has shown that certain drugs will likely never be a feasible AD treatment, which is still a step in the right direction. For example, unfortunately, the gamma secretase inhibitor, avagecestat, likely caused a further progression of cognitive decline as well as caused nonmelanoma skin cancer in many participants. Researchers now realize that gamma secretase inhibitors are likely not a feasible treatment option for individuals suffering from mild to moderate forms of AD. Lastly, solanezumab, a drug created to remove or prevent the accumulation of Aβ plaques, had promising data in Phase 1 and Phase 2 trials, but the drug was ultimately unable to slow the progression as well as reverse the course of the disease. Researchers are taking steps in the right direction and learning more and more each

day about the complexity behind the mechanisms involved in AD. These failed drug trials presented beneficial data that will allow researchers to target different, and hopefully, multiple mechanisms involved in AD progression. Without these failed treatment options, researchers would not have as much insight to the progression of disease; the results from these drug trials, although devastating to patients and families, provide insight and allow for better research to be conducted. Hopefully, an effective drug will be introduced soon, easing the burden of patients and their families.

Additionally, researchers have tried to understand why exactly these drugs are not producing their desired results by easing symptoms and changing the direction of the disease. According to Mehta et al., current research has been focused on reversing the course of the disease, whereas researchers need to instead focus on symptom relief. Further, Mehta et al. argues that "When long-term trials were done to try to detect disease modifying drug effects, the risk of losing subjects increased and there were other compromises to the integrity of the trial" (Mehta et al., 2017). Because AD is a progressive and deadly disease, over the course of a long-term trial, participants may die or otherwise be unable to participate as a result of failing health. Thus, for more accurate data acquisition, more resources, including a higher number of participants as well as research sites, is required. These cost a lot of time and money, making these needs challenging to attain. Additionally, Mehta et al. argues that the Alzheimer's disease Assessment Scale – Cognitive (ADAS-Cog) is not an accurate measure of cognition among participants within clinical trial studies, because this scale is not standardized. A more accurate measurement tool is required to determine a better representation of the results of these clinical trials. Mehta et al. argues that "Although the ADAS-Cog is the gold standard in clinical dementia trials, the administration procedures, work sheets, and scoring procedures of the

ADAS-Cog were not clearly defined in the original article about the test" (Mehta et al., 2017) making this measurement inaccurate across different clinical trials. Lastly, Mehta et al. argues that these treatment options may be given to individuals for whom it may be too late, which could indicate why so many different treatment options have failed in the past. Therefore, treatments that can altogether prevent the development of AD would likely be key to AD therapy. Additionally, it may also be beneficial to try to find treatments that can relieve symptoms, rather than reverse the disease, which could provide comfort to patients and families.

**Preventative Medicine**

Currently, there is no cure for AD; thus, it is important to understand the risk factors involved with the development of AD to aim to prevent its onset. Due to medical advancements, life expectancy has increased, causing age to be the greatest known risk factor associated with AD (Cass, 2017). Ultimately, due to the aging population and the lack of a cure, it is important to try prevent AD onset, especially in at-risk individuals.

The benefits of exercise have been long understood; different forms of exercise can build endurance, strengthen muscles, improve mood, and can even combat certain medical conditions such as depression, anxiety, and arthritis (Mayo Clinic, 2019). Additionally, exercise has been shown to improve cognition, which is heavily impaired in patients with AD. Thus, exercise may be a beneficial method for delaying the onset of AD. The Canadian Study of Health and Aging showed that when controlling for age, sex, and education, individuals who consistently exercise were less likely to show cognitive decline in comparison to sedentary individuals (Stranahan, 2012). It is currently understood that the inflammatory response in AD brains further promotes AD development by promoting microglia to areas of inflammation, furthering this inflammatory response, resulting in cognitive decline. Researchers have discovered that different phenotypes of microglia play different roles by either promoting inflammatory or anti-inflammatory responses. M1 phenotype tends to drive a pro-inflammatory response in contrast with M2 phenotype. The environment in the AD brain tends to promote an inflammatory response, therefore encouraging the production of M1 phenotype. Interestingly, exercise has been shown to promote the conversion from M1 to M2, therefore driving an anti-inflammatory response in AD brains, specifically in the hippocampus. The hippocampus faces great damage due to pro-inflammatory microglia; thus, the conversion from M1 to M2 microglia has ultimately been

shown to improve cognitive function. Additionally, recent research has shown that "the infusion of plasma containing exercise-induced factors obtained from mice that performed voluntary physical exercise during 28 days to sedentary mice resulted in a downregulation of hippocampal neuroinflammatory processes" (Valenzuela et al., 2020), furthering the implication of the beneficial role of exercise in preventing AD.

Additionally, animal research has played an important role in identifying the importance of exercise in preventing the onset of AD, and more specifically, of mitigating the pro-inflammatory response driven by microglia, among other cellular components in the brain. One study utilized the Tg2576 AD mouse model, which results in the overexpression of APP and the resulting accumulation of AB deposits and amyloid plaques. These mice were placed into control/sedentary groups versus experimental/exercise groups. The control group performed no exercise, while the experimental group ran consistently on a mouse wheel for approximately 16-18 months. The control group showed increased levels of interleukin-1β and TNF-α, both of which play a role in the pro-inflammatory response in the brains of individuals with AD. Consistent running in mice also showed increased hippocampal dependent learning, furthering the importance of exercise in efforts to prevent AD.

Interestingly, the results of this specific study were mixed; exercise did not show reductions in AB deposits or APP levels, but still showed improvements in cognition within a radial arm task as well as a water maze task. Researchers have thus theorized that the improvement in cognition is a result of the modulated expression of chemokines, rather than the decreased levels of AB deposits and APP. These findings have pointed researchers in new directions for treatments, suggesting that modulation of inflammatory chemokines may be a potential therapeutic target (Stranahan et al., 2012).

The mechanism in which exercise prevents the onset of AD is not well understood. Recent research utilizing human patients with AD wanted to determine whether exercise could increase the quality of life in individuals suffering from AD. Forty patients aged between 65 and 75 years old participated in this study. Similar to the study utilizing the Tg2576 AD mouse model, participants were split into an experimental group in which participants performed aerobic exercise three times a week over a span of sixteen weeks. The control group did not undergo any form of exercise through the duration of the experiment. Both groups were subjected to testing both before and after the 16-week treatment period; testing included blood samples used to assess interleukin-6 (IL-6) and TNF-α, both of which are pro-inflammatory cytokines commonly found in AD brains, psychological well-being tests, and an assessment of each patient's quality of life. After 16 weeks, participants in the experimental group showed reductions in IL-6 as well as TNF-α, indicating that exercise may reduce inflammation involved in AD development. Additionally, participants in the experimental group showed decreased pain levels, decreased levels of depression, and an increase in overall mental health, indicating an overall better quality of life. Individuals in the control group did not show significant reductions in IL-6 or TNF-α and additionally did not show an overall better quality of life (Abd El-Kader et al., 2016). Ultimately, this research shows the beneficial role of exercise in individuals with AD; that exercise can prevent the inflammatory cycle in patients with AD and can even increase the patient's overall quality of life.

Because the research thus far has shown that exercise can actively reverse the inflammatory response in the brain, exercise can be used to prevent this inflammatory cycle, actively preventing AD onset. Further research is necessary to understand the appropriate

amount of exercise necessary to prevent AD onset; however, thus far, the research has implicated the necessity of exercise, which can be a useful tool in combating AD onset.

Like exercise, social interaction has shown to have protective effects against AD development. Unfortunately, as people age, people are bound to become more socially isolated, due to the death of friends and family. A lack of social interactions has a detrimental effect on an individual's mental health and behavior (Hsiao et al., 2018). Animal research has repeatedly shown that a lack of social interaction exacerbates cognitive decline, including memory deficits, in animal models of AD. Thus, aiming to maintain social interactions is beneficial in mitigating the development of AD.

One study utilizing 126 Long-Evans hooded rats, which were split up into either control or socially isolated (SI) groups (Frisone et al., 2002). SI groups were placed in isolation for six hours per day over a twenty-one day period. Not only was this short-time period enough to raise stress levels in SI rats, but SI rats also had longer latencies when trying to locate a platform in the Morris Water Maze, a common task used to assess spatial memory. Ultimately, the findings from this study indicate that temporary isolation (6 hours per day over 21 days) is enough to impair spatial memory, further indicating the detrimental effects of social isolation.

Additionally, another study showed that SI can induce an inflammatory response in the brain, while simultaneously reducing anti-inflammatory agents. Forty rats were divided into four different groups: control socialized group, AD socialized group, control isolated group, and AD isolated group (Ali et al., 2017). After four weeks, the rats were sacrificed and brains were assessed for AB content and brain inflammatory factors, namely IL-1β and TNF-α. The isolated control group showed significantly more AB content in comparison to the socialized control group. The AD isolated group showed significantly more AB content in comparison to the AD

socialized group. Thus, the results indicate that social isolation plays a strong role in furthering the progression of AD. In addition, the isolated control group showed increased levels of IL-1β and TNF-α in comparison to the socialized control group; the AD isolated group showed increased levels of IL-1β and TNF-α in comparison to the AD socialized group. Ultimately, the results show that social isolation increases the inflammatory response in the brain, furthering the progression of AD (Ali et al., 2017). Ultimately, these findings indicate that social isolation has detrimental effects on the brain and perpetuating the inflammatory cycle in the brain of AD patients. Additionally, these findings point to the idea that socialization has protective effects in preventing AD onset.

Thus far, studies have implicated that a lack of social interactions results in an increased risk of developing AD. Additionally, reports have indicated that maintaining consistent social interactions is beneficial in preventing the onset of AD. Research still needs to be conducted to thoroughly understand the mechanism by which socialization is beneficial to delaying the onset of AD, but it is currently understood that socialization does indeed play a protective role. One study utilized a large group of women without dementia. The women's social networks were measured using a Lubben Social Network Scale (LSBS); women with larger social networks were less likely to develop dementia over a four year follow up period in comparison to women with smaller social networks. Unfortunately, establishing a solid link between social network and cognitive function is relatively complex; however, given that a lack of social interactions results in an increased and perpetuating inflammatory response in the brain of AD patients, it is not unrealistic to hypothesize the maintaining social networks or increasing socialization may have anti-inflammatory effects, and therefore, plays a protective role in preventing AD.

Ultimately, it is understood that socialization does play a protective role, it is simply difficult to link socialization with a anti-inflammatory response in the brain. Data has thus far shown that a lack of social interactions leads to an increase in inflammatory factors, namely IL-1β and TNF-α. Thus, if a lack of social interaction leads to an increased inflammatory response, and it is additionally understood that social interactions play a protective role in preventing AD onset, social interactions may very well actively prevent or reduce the inflammatory cycle that is present in AD brains.

The food we consume plays an integral role in maintaining our health and well-being. Certain diets can interestingly be used to prevent the onset of certain diseases and can even be a treatment option in various diseases. For example, the ketogenic diet, which is a high-fat, low-carbohydrate diet, was developed as a treatment method for individuals suffering from epilepsy. Additionally, gut health has recently become a popular topic in diet culture, likely due to the concept that a healthy gut results in healthy weight loss. Gut health is an important health topic because the foods we consume allow us to maintain healthy lifestyles, preventing the onset or progression of disease. One diet has recently become a popular diet that has potential benefits in preventing the onset of AD: the Mediterranean diet.

The Mediterranean diet is a way of eating consistent with the foods consumed in the islands surrounding the Mediterranean Sea. This diet was initially developed to combat coronary heart disease, because researchers noticed that people living in these areas and consuming the traditional cuisine in these particular islands were at a lower risk for developing coronary heart disease. This diet consists of vegetables, fruits, whole grains, beans, nuts and seeds, and olive oil. Additionally, individuals properly following the Mediterranean diet rarely consume red meat and occasionally drink small amounts of red wine. Those who choose to properly follow the

Mediterranean diet should prepare their meals with plant-based foods as the main focus; for example, fruits and vegetables should be consumed in high amounts, in contrast with meat, which is more commonly the focus during meals. Unlike other diet fads, the Mediterranean diet is one of the only diets that is endorsed by the Dietary Guidelines for America as well as the World Health Organization (WHO) (Mayo Clinic, 2019). Thus, those aiming to live a healthier lifestyle and decrease their risk of developing coronary heart disease may want to consider the Mediterranean diet.

Along with this healthy diet's ability to prevent the onset of coronary heart disease, this diet has also been proved to ease inflammation in AD. Research concerning this diet has mainly been conducted on the foods that make up the Mediterranean diet; for example, researchers now understand that unsaturated fats inhibit oxidative stress and reduce inflammation while saturated fats promote inflammation, mainly in the hypothalamus. Thus far, research has been mainly focused on the beneficial aspects of single nutrients within the Mediterranean diet; however, researchers are beginning to understand the overall benefits of consuming a Mediterranean diet consistently, rather than the simple benefits of each individual food. The overall benefits of consistently consuming a Mediterranean diet has shown to reduce cognitive decline and inflammation, therefore ultimately reducing the risk of AD. Interestingly, MD promotes overall brain integrity; individuals who closely adhere to this diet throughout their lifespan tend to exhibit "greater brain volumes, slower rate of hippocampal atrophy, improved structural connectivity, as well as less Aβ accumulation" (McGrattan et al., 2019), therefore lessening the risk of developing AD.

The entire influence of a dietary pattern on neuroinflammation is not entirely understood; however, the antioxidants present in fruits and vegetables likely suppress the neuroinflammatory

processes by inhibiting free radicals, which are produced by activated microglial cells. An overwhelming amount of free radicals results in oxidative stress, which causes aging and a range of diseases. Flavonoids are found in plants and are consumed in great quantities in individuals who properly follow the Mediterranean diet. Flavonoids play a protective role in preventing AD by fighting toxins, such as free radicals, and therefore prevent neuroinflammation. Additionally, flavonoids likely inhibit pro-inflammatory cell signaling pathways. Consumption of fats, mainly in the form of olive oil and fish, reduces the expression of pro-inflammatory cytokines (McGrattan et al., 2019).

Ultimately, the single nutrients in a Mediterranean diet all possess anti-inflammatory properties; however, the overall consistent consumption of a Mediterranean diet may show greater anti-inflammatory properties in the brain, in comparison to continued consumption of a single nutrient within this diet. The anti-inflammatory properties within the Mediterranean diet, which lessen the risk of AD development, lend to the significance of leading a healthy lifestyle. This diet, along with consistent exercise and adequate socialization, actively allow for an arguably happier, healthier lifestyle, which ultimately will lead to a lessened risk of AD development. These simple lifestyle choices can make a huge and lasting impact on an individual's physical and mental well-being and should be heavily considered, if individuals want to lead a healthy lifestyle and mitigate the risk of AD.

As important as it is to follow a healthy diet, such as the Mediterranean diet, to delay or prevent the onset of AD, it is similarly important to maintain a healthy weight. Obesity has become a prevalent issue, especially across the U.S. Unfortunately, obesity has been linked to a range of chronic illnesses, such as type 2 diabetes, cardiovascular disease, and cancer (Pegueroles et al., 2018). Additionally, obesity has been linked to dementia and AD.

Interestingly, mid-life obesity has more specifically been directly linked to AD, whereas late-life obesity studies have been largely inconclusive, but some studies have determined that late-life obesity may be protective against AD (Pegueroles et al., 2018). More research needs to be conducted to understand the linkage between AD and obesity; however, it remains clear that maintaining a healthy weight could play a protective role against AD onset.

Interestingly, obesity promotes many the same pro-inflammatory processes that are present in the brain in individuals with AD. As a result of obesity, adipocytes, or fat cells, enlarge and spill their contents into their immediate vicinity, which triggers a pro-inflammatory response. Cytokines and chemokines are drawn to this site of inflammation, further augmenting this pro-inflammatory cycle. Similarly, just as exercise promotes the conversion from pro-inflammatory M1 to anti-inflammatory M2, the rapidly increasing number of macrophages, cytokines, and chemokines at the site of inflammation promote pro-inflammatory M1 microglia, furthering this pro-inflammatory cycle. Additionally, TNF-α, a pro-inflammatory cytokine, is actually correlated with body mass index (BMI); research has shown that there is an increase of TNF-α obese individuals in comparison to healthy controls (Letra et al., 2014). Unfortunately, the inflammation resulting from obesity is chronic, meaning that this pro-inflammatory cycle continues until weight loss occurs.

Additionally, obesity has been shown to cause cognitive impairments. It has been hypothesized that these cognitive impairments arise due to the continued inflammation that occurs as a result of obesity. These cognitive impairments affect memory, attention, increased impulsivity, poor organization, and poor planning abilities (Spyridaki et al., 2016), all of which are impaired in AD.

Research surrounding the importance of sleep began between the 1960s and 1970s. The use of electroencephalogram (EEG) allowed researchers to discern distinct patterns of sleep, leading to the classification of stages of sleep, ultimately allowing for the healthcare practitioners to diagnose and treat specific sleep disorders (Worley, 2018). Even more recently, researchers have focused on the deficits that occur as a result of sleep deprivation. It has been uncovered that sleep disruptions have a direct link to hypertension, impaired immune functioning, mood disorders, and of course, AD. Despite the prevalent research regarding the importance of sleep to prevent the onset of harmful diseases, inadequate sleep continues to threaten the health of everyday people. David F. Dinges, PhD, Professor and Chief of the Division of Sleep and Chronobiology in the Department of Psychiatry at the University of Pennsylvania Perelman School of Medicine, points out that "People have come to value time so much that sleep is often regarded as an annoying interference, a wasteful state that you enter into when you do not have enough willpower to work harder and longer" (Worley, 2018). Sleep contributes to our well-being; thus, it is important to prioritize sleep, rather that dismiss sleep as a nuisance.

Most people understand that sleep is beneficial and that everyone should aim for at least six hours of sleep per night; however, many people struggle to initiate sleep and to then remain asleep. Unfortunately, "nearly half of adults older than 60 years of age have difficulty initiating and maintaining normal sleep patterns" (Irwin & Vitiello, 2019), which places these individuals at a greater risk of developing AD among other chronic illnesses. Interestingly, many researchers assumed that sleep disturbances resulted from AD; however, it appears that sleep disturbances actually may contribute to AD onset. Additionally, without sleep, the hippocampus is unable to form new memories; these same processes are impaired in individuals with AD. Essentially, our sleep is governed by circadian rhythms; these activities are commonly impaired

in individuals with AD. Additionally, when these activities are impaired, individuals have an increased risk of mild cognitive impairment (MCI), which can lead to AD. Overall, weaker circadian rhythm activities are associated with poor cognitive function (Uddin et al., 2020).

It is currently understood that sleep deprivation also leads to pro-inflammatory processes, which are involved in the onset and progression of AD. Several sleep analyses have demonstrated that even just one night of partial sleep leads to an increase in inflammatory processes, leading to the continued production of inflammatory cytokines. Interestingly enough, too much sleep has also been shown to increase inflammatory processes and has been shown to specifically increase IL-6, an inflammatory cytokine (Irwin & Vitiello 2019). Thus, it is understood that sleep disturbances are directly linked to increased inflammatory and ultimately the development of chronic diseases, and can therefore be classified as a risk factor for AD onset. More specifically, it has been shown that chronic sleep deprivation activates microglia mainly in the hippocampus, causing the increased production of pro-inflammatory cytokines. In chronically sleep deprived individuals, interleukin-1β, tumor necrosis factor-α, and nitric oxide were increased and positively correlated amyloid deposition in the brain (Lucey, 2020).

Ultimately, more research is needed to more thoroughly understand the associated risk of sleep deprivation and AD onset. Because sleep deprivation can lead to pro-inflammatory processes, and even hinder memory formation, specifically in the hippocampus, it is clear that sleep deprivation is directly linked with AD onset. It is not well understood whether adequate sleep reduces these inflammatory processes, because unfortunately, individuals with AD tend to have sleep disturbances, perpetuating the cycle of inflammation involved in AD. Maintaining a consistent, good sleep schedule, aiming to acquire at least six hours of sleep, could potentially delay the circadian rhythm deficits that so commonly occur as a result of aging.

The glial-lymphatic system, more commonly known as the glymphatic system, is a newly recognized mechanism in the brain that contributes to the removal of neurotoxins, similarly to the idea that the lymphatic system works to breakdown or remove toxins from the body. More specifically, the glymphatic system allows for the rapid exchange of CSF and interstitial fluid (Jessen et al., 2015). Unlike the lymphatic system, which shows increased function when awake, the glymphatic system seems to be hard at work specifically while an individual sleeps (Jessen et al., 2015). Because the glymphatic system allows for the removal of neurotoxins, the glymphatic system has recently become the focus for researchers interested in neurodegenerative diseases, including AD. Interestingly, Iliff et al. discovered that the glymphatic pathway is responsible for clearing beta amyloid plaques, a marker of AD (Jessen et al., 2015). Additionally, a single night of sleep deprivation resulted in a significant increase in amyloid-B burden (Mestre et al., 2020) further indicating the significant role that the glymphatic system plays in controlling and preventing the accumulation of AB plaque deposits. Individuals who sleep less and less tend to show less glymphatic system functioning, given that the glymphatic system works at an optimal level while an individual sleeps. Given that sleep deprivation has recently been classified as a contributor to AD onset and the glymphatic system optimally functions to clear AB plaques while an individual sleeps, it is imperative to find or create a diagnostic tool that can be used to assess glymphatic function in individuals who may be at risk of developing AD.

Overall, it is important to maintain a healthy lifestyle in order to prevent the onset of a range of chronic illnesses, including AD. A disturbance in any of the aforementioned aspects of a daily lifestyle can lead to increased inflammation, and place individuals at a further risk of developing AD. Small lifestyle changes, such as eating a healthy diet, maintaining a healthy social life, and getting adequate sleep could have a huge impact on an individual's well-being

and could be the difference between acquiring AD, a progressive and deadly disease. Ultimately, individuals should aim to eat healthy, socialize, and get adequate sleep to prevent the onset of chronic illnesses, such as AD.

**Future Research/Plans for Treatment**

Although an official diagnosis of AD can mainly be confirmed from an autopsy upon the discovery of Aβ plaque accumulation, there are ways to determine whether an individual may be suffering from AD prior to an official diagnosis from an autopsy. Thus, it is vital that researchers determine different ways to predict the onset of AD to start proactive treatment or offer options for patients to improve their lifestyle, such as exercising or eating a balanced diet.

Some warning signs are more obscure, in contrast with the common loss of memory that is associated with AD. Interestingly, researchers have discovered that simply looking at writing patterns can predict the onset of AD, even before symptoms have appeared (Kolata, 2021). In a study conducted by IBM, the researchers looked at 80 males and females in their 80's; half of the participants suffered from AD, while the other half did not. Prior to half of the participants' development of AD, the researchers asked all participants to take an abundance of cognitive tests as well as look at and subsequently analyze a picture of a boy reaching towards a cookie jar. Through the participants' writing, the researchers looked for subtle errors. More specifically, the researchers looked for repetitive word usage, errors in capitalization, and language that has "a simple grammatical structure, and…missing subjects and words like 'the,' 'is' and 'are' (Kolata, 2021). The researchers predicted that the individuals who made small errors and used simpler words were at a higher risk of developing AD; interestingly, the program predicted which individuals would later be diagnosed with AD with 75% accuracy, indicating that apparent AD symptoms appear well before an official diagnosis.

It is well-known that abnormalities with language occur as a result of AD; thus, this research indicates that this change in language can be shown through an individual's writing skills as well. This study is extremely valuable; AD is a progressive and degenerative disease;

thus, finding a method for earlier diagnosis can provide a huge impact in a patient's prognosis. Through early detection of AD, healthcare providers are better able to advise their patients to make important lifestyle changes that can allow them to at least delay the progression of AD.

The need for future AD research is evident; AD places an economic as well as emotional burden on patients and families. When faced with the devastating news of an AD diagnosis, family members feel they have already lost a loved one, due to the inevitable outcome of the disease. Additionally, AD is a progressive and deadly disease and current therapies are unable to reverse the path of the disease. Additionally, given the fact that the baby boomer population is aging, more and more people will likely face an AD diagnosis, given that the greatest risk factor of AD is aging. Ultimately, future research is necessary to aid in finding a cure for AD. Approximately 90% of AD clinical trials fail; however all of these trials were able to provide data in regards to the various mechanisms involved in the progression of the disease. More clinical trials are currently underway, but according to the National Institute of Aging, "Currently, at least 270,000 volunteers are needed to participate in about 200 active clinical trials and studies that are testing ways to understand, diagnose, treat, and prevent Alzheimer's disease" (Alzheimer's disease fact sheet, 2019). Additionally, all different types of volunteers are needed; "studies need participants of different ages, sexes, races, and ethnicities to ensure that results are meaningful for many people" (Alzheimer's disease fact sheet, 2019). Participating in various trials is one way to fight against the disease; research cannot be conducted without adequate volunteers and other resources. It is necessary to have a large number of participants in various AD studies, because many people with AD tend to suffer from other medical conditions, making it difficult to comply with the clinical trial protocols and older

participants are more likely to die (Alzheimer's disease clinical fact sheet, n.d). Thus, adequate participation is required in many AD studies and could allow for a more thorough understanding of the disease and its progression as well as provide insight to different mechanisms that should be targeted through the use of various therapies.

Various therapies are undergoing clinical trials right now. Currently, "One class of medications that is currently being developed are inhibitors of the beta-site amyloid precursor protein cleaving enzyme (BACE inhibitors). These compounds inhibit the enzyme β-secretase, which is responsible for producing the β-amyloid protein that is responsible for the plaque formation in AD" (Jadoopat, 2019). These compounds were initially introduced, because evidence showed that "a rare human mutation at the BACE1 cleavage site of APP rseults in a 40% decrease in Aβ production" (Das & Yan, 2019), suggesting that this mutation is protective against AD onset. Additionally, APP is processed in one of two pathways. Through the amyloidogenic pathway, APP is cleaved by BACE1, resulting in the production of precursors of Aβ; inflammation causes an increase in BACE activity, ultimately resulting in increased Aβ plaques (Evin, 2016). According to Das and Yan, recent trials for BACE1 inhibition have been able to lessen Aβ production and improve cognitive deficits (Das & Yan, 2019). Additionally, phase 1 trials showed that up to 95% of β-amyloid protein was reduced within the cerebrospinal fluid (Jadoopat, 2019). These results are promising and suggest that current clinical trials may soon be able to produce a BACE1 inhibitor, which will be well tolerated, safe, and effective at reducing Aβ accumulation.

Biogen recently created a drug called aducanumab, which has been created to target β-amyloid by binding to the aggregated Aβ plaques. Aducanumab is then thought to be able to reduce the number of Aβ plaques in the brain, therefore slowing disease progression (Flavell,

2020). Although aducanumab is unable to reverse the path of the disease, slowing the progression can ease the devastation that patients and families often face as a result of an AD diagnosis. Additionally, as a result of the slower progression of the disease, families will likely not have to rush to find proper care for the individual suffering from AD. Aducanumab will allow families to sit down with their loved one to discuss options more thoroughly, allowing the patient to have more autonomy, which can help to preserve family relations.

After my grandmother was diagnosed with AD, her disease progressed quickly. Within a few weeks of her diagnosis, her children had to remove her driving privileges by taking her car keys. Additionally, my grandmother was moved to a memory care unit within the retirement facility at which she already resided. To my grandmother, she felt completely blindsided. She became especially angry with my family and claimed she was capable of driving and did not want to move to a separate unit. My nana likely felt betrayed and hurt that her own family did not allow her to make any of these decisions for herself. In all reality, my family was looking out for her best interests; we wanted her to be safe and cared for, but to my grandmother, she likely felt frustrated that these decisions had been made and communicated with the retirement facility staff, even though she did not agree with these decisions.

Fortunately, aducanumab will allow for a slowing of the progression of the disease, which will not only ease cognitive symptoms associated with the disease, but also allow families to have important discussions, such as removing a patient's driving abilities or moving their home to an area where they can receive proper care. Additionally, Biogen's current tests with aducanumab show that participants "saw an increased ability to manage finances, do chores around the house, go shopping, and leave the home independently" (Aducanumab: Benefits,

Side-Effects & status of clinical trials, 2020). Thus, this drug does much more than alleviate symptoms associated with AD; it allows patients to retain their independence.

Along with the importance of decreasing the amount of Aβ plaques in an AD brain to relieve various cognitive symptoms associated within the disease, there is evidence that "suggests that brain tissues in AD patients are exposed to oxidative stress during the development of the disease. Oxidative stress or damage such as protein oxidation, lipid oxidation, DNA oxidation, and glycoxidation is closely associated with the development of Alzheimer's disease" (Feng & Wang, 2012). Additionally, oxidative stress has been shown to act as secondary messengers in inflammation, indicating that reducing oxidative stress could reduce inflammation and therefore relieve and ideally improve AD symptoms (Stuchbury & Münch 2005). A variety of drugs, called multitarget-directed ligands (MTDLs) have been reintroduced to the realm of AD research. These drugs have the ability to act "at the various neuropathological levels of AD" (Simunkova et al., 2019), which could be beneficial given that AD is the result of various mechanisms in the brain. Ideally, attacking different neuropathological levels will allow for effective symptom relief and could even induce a reversal of the course of disease.

Current therapies for AD include AChE inhibitors such as galantamine, donezapil and rivastigmine, which mainly treat the symptoms of AD. Because there currently are few therapies marketed for AD patients and because the incidence of AD will likely increase over time, new and effective therapies are necessary. First and foremost, researchers should aim to encourage more people to participate in various clinical studies. These clinical trials require a lot of effort from both the researchers and the participants, but the overall outcome of contributing to AD

research and ideally finding a cure can ideally encourage people to participate. A lack of participants could result in an insufficient amount of evidence to produce definitive results.

Additionally, because age is the main risk factor associated with AD, it is more likely that participants will die over the course of a clinical trial. Thus, an even greater amount of participants is required for AD research in comparison to other clinical trials that study the effects of various therapies in disease that are not limited to the geriatric population. Additionally, there are several different paths that healthcare professionals and researchers could analyze to develop future therapies, making it challenging for researchers to determine which path or level of the disease should be targeted. It would be most ideal for a drug to attack at different neuropathological levels for effective symptom relief and even a reversal of the course of disease, such as through studies involving MTDLs. Currently, it appears that the most likely drug to enter the market will be Biogen's aducanumab. Results from phase 2 trials indicated that "all doses of aducanumab (given as monthly infusions into the bloodstream) significantly reduced amyloid plaques in the brain in a time- and dose-dependent manner" (Flavell, 2020). The use of this particular drug has shown encouraging results, promising to retain a patient's independence. Ultimately, any drug that has the ability to alleviate AD symptoms, improve cognitive function, and most ideally, reverse the path of disease provides hope to AD patients and families.

## Conclusion

Life is unpredictable; we will never know what the future holds, in regards to our health. The conundrum of our health, including the etiology and pathology of AD have been long studied and analyzed by philosophers and other great intellects. Even today, medical professionals and researchers do not have a complete and full understanding of AD, suggesting that the complexity of the disease has posed a challenge to researchers and scientists likely for centuries, even before the term 'Alzheimer's disease' had been coined. In more recent years, many researchers have dedicated their lives to finding a cure or other treatment options to help people suffering from AD. The few marketed treatment options as well as the high incidence of AD in the geriatric population emphasize the idea that AD research is important and necessary.

Although much is still unknown about the pathology and etiology of AD, new discoveries are being made each day. For example, it is now common knowledge that Aβ plaques and senile tangles result from, as well as contribute to, the neuroinflammation involved in AD, suggesting that the progression of AD occurs as a result of various cyclical proinflammatory pathways. These proinflammatory pathways can be induced by a variation of genetic factors and unhealthy lifestyle choices. Thus, individuals should aim to make healthy lifestyle choices, thereby lessening the chance of developing chronic or even terminal illnesses, including AD. For example, individuals who follow a Mediterranean diet, sleep an adequate amount each night, exercise daily, and socialize have a lesser likelihood of ever developing AD in comparison to individuals who follow a different, more unhealthy lifestyle. However, leading a healthy lifestyle does not entirely protect someone from developing chronic illnesses, such as AD. My grandmother, for example, was an extremely healthy individual. She always maintained a healthy weight, ate mostly nutritious, whole foods, and was fairly active throughout her life.

Unfortunately, sometimes AD and other illnesses seem to just appear, as a sort of cruel game of chance. This is another example of why more research is needed to fully understand and treat AD.

It is important that patients and families retain the faith that a cure or beneficial treatments will be produced; given the high incidence of AD in the geriatric population, the discovery of new drugs and alternative treatment methods have been long studied. Although there have many numerous treatment failures over the course of several decades, these failures have furthered researchers' desire to continue their search. Many researchers have explained that these failed treatments have in a way, humbled them, allowing them to better appreciate the complexity of the disease. Failed treatment have also allowed researchers to discovery the mechanisms involved within these proinflammatory pathways. For example, researchers understand that the use of multiple drugs may be the more effective method used to find a cure for AD. Because the pathways involved in AD are so complex, no one drug thus far has been able to cease or reverse the progression of the disease, suggesting that multiple proinflammatory pathways should be targeted.

Researchers have become more optimistic recently, especially considering Biogen's current development of aducanumab. This drug promises to slow the progression of AD, allowing individuals to maintain autonomy and independence. This drug marks a major breakthrough, given that roughly 99% of drug trials fail (Drugs Discovery Trends Editor, 2019) by either low toleration of the medication or a lack of effectiveness. Thus, a beneficial AD drug must be effective and tolerated well; it is challenging to create this type of AD drug, because of the multiple pathways involved in inducing the inflammatory processes of the brain. It is remarkable that Biogen and other companies are on the cusp of a breakthrough, discovering and

producing beneficial treatments, which could change the lives of patients and families for the better.

While my grandmother lived with AD, my family never gave up hope that a cure would someday be found. Although my grandmother has now passed on, we still hope and pray for new, reliable treatment options and ideally a cure. We understand how it feels to slowly lose a loved-one due to AD. I have written this thesis to share a part of my life, my grandmother's AD diagnosis, as well as generate a guide for individuals who are struggling or know someone else who may be struggling with an AD diagnosis. With the care, compassion, and understanding of this devastating disease from a medical, familial, and introspective point of view, I believe that a cure will one day be found, ending the panic and dread that accompanies an AD diagnosis.

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