Alzheimer’s Disease: Risk Factors, Pathogenesis and Treatments

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Spring Senior Thesis 2014

A critical literature review submitted in partial fulfillment of the requirements of senior research thesis.
Abstract

Alzheimer’s disease is a critical neurodegenerative disorder in the category of dementia. In fact, it is the most widely occurring form of dementia, with health care costs exceeding $170 billion per year. Its main brain-altering symptoms are that of amyloid-beta plaques, composed of unnatural build-ups of the protein amyloid-beta 42, and neurofibrillary tangles, composed of build-ups of misfolded tau protein. As the two main symptoms of Alzheimer’s disease, these aspects are correlated with increased levels of brain inflammation, problems in neural signaling and impaired cognition, among others. In terms of treatments, much evidence exists surrounding the benefits of non-steroidal anti-inflammatory drugs (NSAIDs) that may improve cognitive symptoms of AD through decreases in brain inflammation and interactions with amyloid-beta pathways. Other treatments include acetylcholinesterase inhibitors, which target the crucial cognitive neurotransmitter acetylcholine, direct treatments of amyloid-beta and NFTs, and immunotherapies that focus on developing vaccinations of AD pathology. Due to genetic risk factors, pre-screening for AD will be beneficial for the treatment and prevention of AD symptoms, increasing individuals’ knowledge of their possibility of developing the disorder.
Memory is one of the most important aspects of an individual’s ability to function on a daily basis. Phenomena like implicit memory allow us to carry out tasks more easily, while explicit memory allows us to remember great amounts of information that serve us in our daily interactions. When considering how important memory is, and how many daily processes it affects, the degeneration of memory is a debilitating circumstance that often accompanies the normal aging process of individuals. However, certain changes in one’s body may actually cause this degeneration of memory to accelerate. Disorders like these, called neurodegenerative disorders, increase the rate at which the neurons of the brain die, leading to difficulties in functioning in all manners of life, not just in memory. However, this paper focuses on a specific memory-impairing neurodegenerative disorder: Alzheimer’s disease.

Alzheimer’s disease is the most prevalent type of dementia, and is associated with estimated health care costs of $172 billion per year (Reitz and Mayeux, 2014). Most of this expenditure is dedicated to research, as at the time of this writing there is no cure for the disorder. Several treatments for the disorder remain in use, but their benefits for the afflicted individuals are marginal and not widely sought. Like other forms of dementia, Alzheimer’s disease (AD) is characterized by significant cognitive impairment that affects the individual’s ability to perform daily functions, mainly through memory impairment. Separating AD from other forms of dementia is the presence of a few main biomarkers in the impaired individual: amyloid-beta plaques, neurofibrillary tangles, neuronal loss and reduced synaptic density (Reitz & Mayeux, 2014).

In this critical literature review, we outline the major aspects of Alzheimer’s disease. Initially, we focus on the factors that lead to the development of the disorder, like amyloid-beta and its associated plaques; tau protein and its associated neurofibrillary tangles; and the
neurotransmitters acetylcholine and glutamate. Later, we focus on treatments, such as non-
steroidal anti-inflammatory drugs, acetylcholinesterase inhibitors, neurofibrillary tangle
treatments and amyloid-beta inhibitors. Further, immunotherapies that focus on prevention of the
disorder are also discussed. Finally, we discuss some future directions and the prognosis for
individuals afflicted with Alzheimer’s disorder.

**Risk Factors and Pathogenesis**

**Amyloid-Beta 42 and Plaques.**

Amyloid-beta is a naturally occurring protein in the neurons of the brain. However, the
length of the amyloid-beta 42 that appears in AD is different from that of the naturally occurring
amyloid-beta in the brain. In order to produce the amyloid-beta protein, a precursor, amyloid
precursor protein (APP) is cleaved by gamma-secretase, producing an amyloid-beta protein of
varying lengths (Bali et al, 2012). Normally, this enzyme produces an amyloid-beta protein with
a length of 40 base pairs. However, during the pathogenesis of AD, the APP is improperly
cleaved, resulting in an amyloid-beta protein with a length of 42 base pairs.

Isoforms of these improperly cleaved amyloid-beta peptides aggregate into
neurodegenerative plaques that cover brain cells, though the plaques seem to also include
isoforms of the normal amyloid-beta 40, as well (Macias et al, 2014). The behavioral symptoms
of AD suggest that these amyloid plaques are toxic to the neurons of the brain, leading to cellular
apoptosis and subsequent neurodegeneration. However, the presence of the abnormally cleaved
amyloid-beta and its aggregate plaques may simply be a consequence of AD pathology. Research
conducted by Sipos and colleagues (2007) provides evidence to the neurotoxicity of the amyloid-
beta structures. In their study, which was performed on rats, Sipos and colleagues (2007) injected
amyloid peptide (amyloid-beta 1-42) bilaterally into the entorhinal cortex (EC) of the temporal
lobe. In comparison with subjects injected with saline, the rats in this treatment condition showed impaired abilities in object recognition tasks and spatial reference memory tasks in a water maze. The researchers found that the injections of amyloid peptide directly affected the hippocampus and the parahippocampal areas, including the EC, resulting in direct aggregation of plaque-like structures (Sipos et al, 2007). That is to say, the amyloid-beta protein in its lengthened form is unusable by the cells and collects together as protein deposits, forming the plaques that are visible in many brain scans. The aggregates of the amyloid plaques may have activated microglial cells and astrocytes, factors important in the creation of inflammation that may also directly affect the function of neurons.

Further supporting the significance of amyloid-beta in the neurodegeneration of patients with AD is the work of Christensen and colleagues (2008). In a paradigm similar to the Sipos et al (2007) study, Christensen et al (2008) administered injections of amyloid peptide bilaterally to the dorsal hippocampi of rats. Similarly, the researchers found that the treatment rats had impaired social recognition memory compared to those that had been injected with saline. In these social recognition memory tasks, the rats were placed in a cage with a juvenile rat twice, with 48 hours in between sessions. If the rats spent less time exploring the previously unknown rat during the second trial, social recognition memory was assumed (Christensen et al, 2008). However, the researchers also uncovered alternate effects of amyloid-beta. They measured reduced 5-HT${}_{2A}$ (a G-protein coupled receptor, important in excitatory processes (Cook et al, 1994)) protein receptor levels in the hippocampi and frontal cortices of the treated rats (Christensen et al, 2008), as well as reduced levels of Brain Derived Neurotrophic Factor (BDNF). These findings suggest that, in addition to the neurotoxic effects of amyloid-beta in the
form of plaques, the protein also affects other mediating factors that are essential for memory, like 5-HT$_{2A}$ and BDNF.

While the amyloid-beta peptide is naturally occurring in brain cells as amyloid-beta-40, it seems that the increased amounts in the brains of these subjects led to memory deficits, suggesting that there is some threshold for healthy levels of amyloid-beta in the brain. Once that threshold is reached, excess (i.e., unusable) amyloid-beta may aggregate as neurotoxic plaques, leading to memory degeneration. At a cellular level, Macias and colleagues (2014) were able to model amyloidogenesis in human neuroblastoma M17 cells, creating a human-based model of amyloid-beta production in AD pathogenesis. Like in animal studies, the researchers cited the significance of gamma-secretase and beta-secretase, specifically the Beta-site APP-cleaving enzyme-1 (BACE1), in the production of amyloid-beta peptides. This is the major beta-secretase in the brain, and beta-secretase has been implicated as the first cleavage in the pathway of amyloid genesis, as it prepares the protein to be cleaved by gamma-secretase into some amyloid-beta isoform between 38 and 43 base pairs in length (Macias et al, 2014).

Due to the prevalence of familial AD (FAD), many researchers question whether amyloid-beta production in AD is genetically linked. Some AD research reveals evidence of specific mutations of the genes presenilin-1 and presenilin-2, which are thought to directly facilitate the development of the 42-base-pair amyloid-beta protein (Bali et al, 2012). These presenilin genes seem to be part of the aforementioned gamma-secretase complexes that are responsible for the cleavage of amyloid precursor protein (APP) (García-Ayllón et al, 2014). Bali and colleagues (2012) also suggest that while some genes seem to be correlated with AD susceptibility, like the apolipoprotein allele (apoE), they do not directly affect amyloid-beta ratios. Though each type of apolipoprotein allele may be implicated in AD pathology, the
presence of the apoE4 allele seems to one of the most apparent risk factors for AD development. ApoE4 is a single nucleotide polymorphism of the apoE allele that, when present, increases the likelihood of AD development 2-3 times that of a normal individual (Kim, Basak & Holtzman, 2009). A strong association between amyloid-beta and apoE4 suggests that apoE may facilitate the binding of amyloid-beta, increasing the number of plaques in the brain (Kim, Basak & Holtzman, 2009). The results of Bali and colleagues (2012) may suggest that the presence of amyloid-beta may be a result of some other aspect of AD, though it is certain that the two are related.

In sum, although amyloid-beta is naturally occurring as amyloid-beta-40 in brain neurons, presence of the abnormally cleaved amyloid-beta-42 is correlated with AD pathology and dementia symptoms. The subsequent plaques that are comprised of amyloid-beta-42 may be directly toxic to neurons, but they may also activate microglial cells and astrocytes that create damaging inflammation to the brain neurons. Amyloid-beta-42 may also negatively affect some mediating neural signals, like receptors of neurotransmitters acetylcholine and serotonin. Enzymes, like beta- and gamma-secretase, that control the cleaving of amyloid precursor protein into different amyloid-beta lengths, may modulate levels of this brain damaging peptide. Subsequently, genetic risk factors, like the presence of amyloid-facilitating apoE4 and mutations in presenilin genes that modify gamma-secretase complexes, may increase an individual’s likelihood of expressing amyloid-beta pathology. As will be discussed later, amyloid-beta is an integral part in other facets of AD, as well.

**Tau and Neurofibrillary Tangles (NFTs).**

Another significant biomarker of Alzheimer’s disease is the aforementioned neurofibrillary tangles (NFTs), structures that can build up on the surface of the brain, much like
the amyloid-beta plaques. These tangles are intracellular and consist of filaments of misfolded/improperly phosphorylated tau protein (Braak & Del Tredici, 2010). In normal form, the tau protein helps the cell, as it stabilizes its structure; however, in its abnormally phosphorylated form, the tau cannot be broken down and used by the cell, leading it to bind together and cause build-ups (Braak & Del Tredici, 2010).

Previous research has implicated the protein tau in the production of these NFTs. For example, Bancher and colleagues (1989) stained autopsy tissue of the brains of both AD patients and of normal adults. The researchers found that staining for phosphorylated tau resulted in higher levels of staining in early, immature tangles (Bancher et al, 1989). However, the staining of these tissues with antibodies also resulted in reactivity of neurons that did not exhibit NFTs, suggesting some problem exists in the protein phosphorylation mechanisms of these neurons. Bancher et al (1989) claim that this fault in the phosphorylation system leads to the production of abnormally phosphorylated tau protein, an early biomarker of the production of NFTs in AD.

Though we now know that elevated levels of phosphorylated tau may be a precursor to the presence of NFTs, the question of their genesis is still evident. Gotz and colleagues (2004) suggest that NFT generation does indeed involve tau and that it may actually be induced by the aforementioned amyloid cascade hypothesis. Gotz and colleagues (2004) hypothesize that connections exist between the development of amyloid plaques and NFTs due to the fact that individuals with mutations of the APP gene seem to develop both biomarkers. In addition, the researchers found through injections of fibrillar amyloid-beta into rhesus monkey subjects resulted in neuronal loss, tau phosphorylation and microglial activation (inflammation) (Gotz et al, 2004). As the rhesus monkeys are higher order primates, like us, these findings contribute more to the knowledge of how AD mechanisms function in human brains. Similar findings were
not found in the brains of rats or in the brains of younger aged rhesus monkeys (Gotz et al, 2004), suggesting that there is something unique about both the brains of higher order primates, in older age, that are susceptible to the development of AD pathology. In human tissue culture, Gotz and colleagues (2004) found that the presence of amyloid-beta 42 actually induced the formulation of tau filaments, suggesting that NFT formation may be downstream in the amyloid cascade.

With the knowledge that AD is associated with the presence of these NFTs, much research revolves around the mechanisms through which the NFTs affect cognitive functioning. Some evidence exists that the presence of the NFTs affects the ability of the neurons to make proper communication with the neurons that surround them. For example, Callahan and Coleman (1995) conducted Golgi postmortem studies using brains of both non-demented elderly individuals and individuals with AD. The researchers’ findings dealt with growth-associated protein 43 (GAP-43), which appears to be important in neuronal plasticity, as it facilitates the path finding and connection building between neurons (Li et al, 2013).

Measuring the message levels of GAP-43, Callahan and Coleman (1995) found negative correlations between the amount of neurons that were affected with NFTs and their message levels. For example, a brain that only exhibited up to four NFT-afflicted neurons showed much greater levels of GAP-43 messaging than did brains that exhibited 11 or more NFT-afflicted neurons (Callahan & Coleman, 1995). These findings suggest that the NFTs exert effects on the synaptic communication of neurons. Though it is not certain, the NFTs may somehow directly inhibit the action of GAP-43 and other receptors and proteins. Also, the presence of the NFTs may somehow stress the tangle-bearing neurons to the point that it degrades their ability to function.
As is the case with amyloid-beta-42 pathology, there exists evidence that there is a genetic component regarding the susceptibility to NFT formation. Research has tied the genetic possession of copies of apolipoprotein E (ApoE) with the incidence of Alzheimer’s pathology. Specifically, the greatest risk factors seem to be tied to ApoE4. Using neural imaging of autopsy cases including both AD patients and normal individuals, Nagy and colleagues (1995) found that amounts of NFTs present in the brains were positively correlated with the number of copies of ApoE4 in the individual’s genome. In fact, in individuals who had two copies of the allele showed almost three times as many NFTs as individuals who presented zero copies of the allele (Nagy et al, 1995). Research regarding the ApoE4 gene lends credibility to a genetic basis for AD pathology, suggesting that individuals with ancestors who possess the disorder are more likely to receive the gene and in turn exhibit AD symptoms.

In sum, some AD symptomatology may be attributed to the presence of neurofibrillary tangles in the brain, intracellular filaments that are created by build-up of misfolded tau protein in neurons. The production of these filaments may be modulated by some problem in the process of tau phosphorylation, and there exists evidence that the presence of NFTs may be correlated with amyloid-beta pathology. NFTs may interfere with neural signaling and neural regeneration through mediums like growth-associated protein 43. Finally, there appears to be a correlation between the aforementioned apolipoprotein allele and the production of NFTs, as individuals who possessed this allele were more likely to display NFT pathological symptoms. As one of the two main symptoms of AD, understanding NFTs is critical to understanding the nature of the disease.
**Importance of Neurotransmitters.**

Neurotransmitters are the basic mechanism of information transmission in the brain, as they are transferred across the synapses between neurons to activate adjacent neurons. In regards to the function of memory, several neurotransmitters are fundamental. These include dopamine, serotonin, acetylcholine, glutamate, norepinephrine and GABA. For the purposes of this review, we will focus on acetylcholine and glutamate. Acetylcholine (ACh) specifically, based in the basal forebrain, has been shown to be involved in activation in the cerebral cortex and the hippocampus (Khan et al, 2014). ACh has been connected with cognitive activity in general, and reductions in ACh activity as individuals age often results in memory impairments, supposedly due to reduced activity of choline acetyltransferase (Khan et al, 2014).

Using transgenic mouse models, Watanabe and colleagues (2009) found connections between amyloid-beta pathology and decreases in acetylcholine activation. The researchers found that brains of transgenic 9- to 11-month-old mice showed significantly less ACh release than control mice of the same age (Watanabe et al, 2009). In this case, the transgenic mice also overexpressed a mutant form of the amyloid precursor protein. The older mice, which also showed significantly higher levels of amyloid-beta in the brain, also had difficulties in a radial maze task, suggesting a correlation between ACh release and memory functioning. Though higher levels of amyloid-beta were correlated with decreased release of ACh, these brains did not show significant amounts of plaques in the hippocampal areas, suggesting that the effect amyloid-beta may exert on neurotransmitter functioning involves some aspect of the amyloid building blocks, rather than the amyloid plaques themselves (Watanabe et al, 2009). That is to say, the individual amyloid peptides are capable of damaging neuronal communication before accumulating into plaques.
Many studies have also implicated the neurotransmitter glutamate in the importance of memory in Alzheimer’s disease. As the primary excitatory neurotransmitter in the brain, evidence exists that glutamate’s excitotoxic effects may be a cause of neurodegeneration in AD (Greenamyre et al, 1988). Much of the research regarding these effects focuses on the role of glutamatergic N-methyl-D-aspartate (NMDA) receptors, which are mediated by glutamate specifically. Glutamate activates these receptors, controlling gated calcium-ion channels at the synaptic terminal. Evidence exists that both amyloid-beta and tau protein concentrations can cause over-activation of NMDA receptors, allowing excess Ca^{2+} ions to enter neurons, leading to cell death (Xu et al, 2012). These NMDA receptors are numerous in the cerebral cortex and in the hippocampus, areas important for cognitive functions and memory. The apoptosis of these cells may contribute to the neuronal loss that is a symptom of AD.

The research of Proctor, Coulson and Dodd (2011) focuses on the interaction between glutamate and a post-synaptic protein called PSD-MAGUK. As an excitatory neurotransmitter, glutamate is partially responsible for the neuroplasticity that enables long-term potentiation, or LTP. These PSD-MAGUK proteins work to regulate some glutamate receptors, like the aforementioned NMDA receptor, stimulating the LTP of the neurons (Proctor, Coulson & Dodd, 2011). In AD, higher levels of amyloid-beta protein may decrease the amount of PSD-MAGUK in post-synaptic regions, impairing the neuronal glutamate receptor regulation; in turn, this would decrease the ability of the neurons to perform LTP and impair memory (Proctor, Coulson & Dodd, 2011). In fact, through connections with the NMDA receptor, these post-synaptic proteins may also have an effect on the gated Ca^{2+} ion channels, leading to more glutamate-induced apoptosis and resulting in neuronal loss.
In sum, acetylcholine and glutamate are specific neurotransmitters that have been connected with AD pathology. Acetylcholine specifically is connected with overall cognitive activity and decreased ACh activity in the elderly is correlated with memory impairments. Also, higher levels of amyloid-beta have been correlated with decreased ACh release. Glutamate, an excitatory neurotransmitter, may be a cause of neurodegeneration in AD. Amyloid-beta and the tau proteins that comprise NFTs may cause over-activation of glutamate-mediated NMDA receptors, resulting in neuronal loss in AD. Also, amyloid-beta may increase levels of post-synaptic proteins that lead to up-regulation of glutamate and greater levels of neuronal loss.

Overall, AD is a complex disorder that consists of many complex risk factors and symptomatic aspects. Primarily, amyloid-beta and NFTs seem to be the most important targets for AD treatment, as their symptom inducing effects are not limited solely to their direct effects on the brain. Amyloid-beta plaques have been correlated with direct neurodegeneration, but it seems that they have associated effects, such as the increase of glutamate excitotoxicity, decreased ACh activity, increased NFT development, and microglial inflammation. Similarly, NFTs may directly cause neuronal loss while at the same time being responsible for secondary effects, like increased brain inflammation. AD would appear to have a significant genetic component, as well, as the presence of apolipoprotein E4 allele has been correlated with increased amyloid-beta pathology and increased AD symptoms. This allele may help reveal an effective prevention strategy for AD, as those who express it are much more likely to possess the disorder. Several treatments have been shown to be advantageous in the quelling of AD symptomatology.
Treatments

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

There is significant evidence that the neurofibrillary tangle (NFT) accumulation that seems to be a factor in Alzheimer’s disease symptoms and pathology is accompanied by inflammation of the brain in these same areas (Cudaback et al, 2014). Using this idea as a base, many researchers have studied the benefits of NSAID use on Alzheimer’s pathology. Simple NSAIDs, like ibuprofen, are widely used and easy to acquire, and due to the small size of their molecules, are able to pass through the blood-brain barrier (BBB), which blocks many larger molecules that are intended to treat brain disorders, like protein and peptide drugs (Zhang et al, 2014).

NSAIDs function by inhibiting a specific type of enzyme, the cyclooxygenase (COX) enzyme (Cudaback et al, 2014). One specific function of this type of enzyme is regulating the synthesis of molecules called prostanoids. One specific type of prostanoid, prostaglandin E2, is thought to be involved in the propagation of inflammation (Cudaback et al, 2014). In AD, there seems to be an up-regulated production of these prostanoids due to the presence of the incorrectly cleaved amyloid-beta 42. Along with the secretion of inflammation-inducing cytokines, amyloid-beta 42 increases the production of the prostaglandin E2 (Cudaback et al, 2014), increasing levels of inflammation while also providing direct neurotoxic damage.

Through the inhibition of these COX enzymes, NSAIDs may decrease the biosynthesis of these prostanoids that lead to inflammation. In fact, Cudaback et al (2014) cite evidence of clinical trials in which COX-inhibitors reduced the instances of amyloid-beta plaques and neuroinflammation. In some AD models, the subjects showed improvements in cognitive testing, as well. This finding supports the idea that inflammation caused by the presence of amyloid-beta
may directly relate to the pathological symptoms that inflict individuals with AD. More directly, NSAIDs also inhibit gamma secretase, a protein complex that cleaves the amyloid-precursor protein (APP), inhibiting the production of amyloid-beta and its subsequent plaques (Cudaback et al, 2014).

Other evidence exists of the effects of NSAIDs on the protein tau, which is integral in the production of the neurofibrillary tangles (NFTs) that normally accompany AD pathology. Carreras and colleagues (2013) cite ibuprofen’s benefits as an NSAID in the decrease of tau pathology in mice. Through further study of another drug, R-flurbiprofen, which possesses similar levels of gamma-secretase mediation but lacks the anti-inflammatory action of ibuprofen, Carreras and colleagues (2014) found that the drug significantly decreased the levels of tau aggregation in the brain. The drug produced little-to-no effects on the production of the neurotoxic amyloid-beta 42. However, the mice still showed cognitive improvement in a water-maze learning task, suggesting that the protein tau and its NFTs may actually be the main sources of AD pathology. This evidence also counters previous research that elevated levels of amyloid-beta 42 activate the kinases involved in the production of phosphorylated tau (Carreras et al, 2014).

Given this evidence for the benefits of NSAIDs in affecting tau phosphorylation, increased production of amyloid-beta and the subsequent inflammation and NFTs associated with both, NSAIDs have arisen as a significant treatment option for those individuals that possess mild-to-moderate levels of AD. However, some skepticism still remains concerning the time during AD development at which the drugs are the most effective in the treatment of AD symptoms. Breitner and colleagues (2011) found that individuals who already exhibited Alzheimer’s pathology, though did not have dementia, were adversely affected by the reception
of NSAID treatments. That is to say, the onset of AD dementia in these individuals actually seemed to be accelerated by almost an entire year due to these treatments.

These results were only found in individuals that had already expressed AD symptomatology. Individuals who did not express AD symptoms, when given clinical treatment with NSAIDs, showed reduced instances of Alzheimer’s disease (though only longitudinally) after two or three years (Breitner et al, 2011). These findings suggest that some aspect of Alzheimer’s pathology causes the NSAIDs to have a negative effect once symptoms have already arisen, while they are beneficial if prescribed in significant advance of the onset of pathological symptoms. Explanations for this temporal difference are relatively unknown. The unselective COX-inhibitory effects of NSAIDs may decrease the efficiency of some neural signaling, stressing neurons that are already dysfunctional (e.g. weakened neurons in symptomatic patients) (Breitner et al, 2011). In asymptomatic patients, this decrease in signaling should not have adverse effects due to the remaining efficiency of the healthy neurons in their brain.

In practical application, doctors may need to find a way to assess an individual’s risk for the development of AD to better prevent its onset. Breitner and colleagues (2011) suggest that a high ratio of tau to amyloid-beta present in an individual’s cerebrospinal fluid indicates the imminent pathogenesis of AD, giving at least one biomarker that may aid in preventative treatment. However, as these studies have been performed in rat subjects, the results’ generalization to human trials is not necessarily known. As the most easily facilitated form of AD treatment NSAIDs have a wide range of benefits.

Overall, NSAIDs seem to be effective in treating some of the symptoms of AD. They can reduce neural inflammation through the inhibition of COX enzymes, decreasing inflammation-
causing prostanoids. Also, they have been shown to inhibit gamma-secretase, targeting one specific aspect of the amyloid-beta cleavage pathway, and treatment with NSAIDs has shown to reduce levels of tau aggregation in the brain. Interestingly, treatment with NSAIDs seemed to accelerate AD symptoms in individuals who already exhibited some type of AD symptoms. As such, although NSAIDs are effective in treating some AD symptoms, they may only work as preventative treatments that target the onset of the disorder.

**Acetylcholinesterase (AChE) Inhibitors.**

Acetylcholinesterase (AChE) inhibitors may prove to be a treatment that, unlike NSAIDs, is effective when administered to individuals who already exhibit AD symptomatology. Acetylcholine (ACh) is proven to be involved in many aspects of cognitive activity. Thus, researchers have explored the connections between decreasing levels of ACh and Alzheimer’s pathology. Indeed, Alzheimer’s disease has been associated with decreased activity in neurons that involve ACh (Ansari & Khodagholi, 2013). AChE is an enzyme that degrades ACh. As such, the inhibition of AChE increases the levels of ACh in the brain, which would theoretically aid in the cognitive symptoms that plague AD patients.

Some research, like that of Benzi and Moretti (1998) focuses on the role that acetylcholine directly plays in cognition in the brain. ACh is thought to be an important neurotransmitter that modulates cognitive abilities, and lower levels of ACh are often observed in the brains of patients with Alzheimer’s disease. Benzi and Moretti (1998) suggest that this decrease in levels of ACh occurs in response to neuronal loss that characterizes the disorder. Pittman (2014) suggests that ACh may play a significant part in monitoring the excitotoxicity of neurons through the management of voltage-gated calcium channels. AChE inhibitors work to increase the amount of extracellular ACh in the brain, allowing the ACh to bind to voltage-gated
Ca2+ channels, regulating the irregularities in intracellular calcium that are caused by amyloid-beta proteins.

Other research suggests that the exact neural mechanisms that underlie the importance of ACh in AD pathology mostly pertain to glutamate and glutamate receptors. Glutamate works as a neurotransmitter and excitotoxin in the brain. While glutamate is integral in the plasticity of the brain, it also causes neuronal death, or apoptosis (Takada-Takatori et al, 2006). AChE inhibitors may work to prevent some of this glutamate-induced neurotoxicity, reducing the amount of neuronal loss in AD brains (Takada-Takatori et al, 2006). More specifically, there seem to be connections with nicotinic ACh receptors, as proven antagonists of these receptors antagonize the neuroprotective effects of the ACh inhibitors while in the presence of glutamate (Takada-Takatori et al, 2006). Takada-Takatori and colleagues (2006) also cite evidence that the AChE inhibitors work through the phosphatidylinositol 3-kinase pathway via stimulation of a specific nicotinic ACh receptor, alpha-7.

Another drug, donepezil has been effective in reducing amyloid plaque density and increasing synaptic density in transgenic mouse models (Dong et al, 2009). These findings support acetylcholine’s effects on the level of apoptosis in the brain, as it decreases programmed cell death through modulation of excitatory glutamate.

As we have said previously, acetylcholine is an important neurotransmitter in cognitive activity. AChE inhibitors prevent the enzyme Acetylcholinesterase from breaking down ACh, leading to greater amounts of ACh present extracellularly in the brain, allowing ACh to regulate transmembrane irregularities in calcium caused by amyloid-beta. AChE inhibitors may interact with the aforementioned glutamate excitotoxicity, reducing the levels of neuronal loss.
specific AChE inhibitor, donepezil, reduces amyloid plaque density, suggesting the effectiveness of these types of drugs in treating some aspects of AD pathology.

**Neurofibrillary Tangle (NFT) Treatments.**

As previously stated, Alzheimer’s disease is often characterized by the aggregation of bundles of tau proteins that cover the brain. These bundles of proteins are called neurofibrillary tangles (NFTs), and they may negatively affect the neurons on which they develop, weakening their function or even causing their death. Current research focused on treating the presence of neurofibrillary tangles focuses on inhibiting the aggregation of tau into microtubules, decreasing the overall levels of tau and decreasing the levels of extracellular tau that may be toxic to brain neurons.

Medina and Avila (2014) cite evidence that davunetide, an eight amino acid peptide may actually aid in the prevention of tau phosphorylation, damaging the stability of the microtubules that are associated with it. Through in vitro measures, Brunden, Trojanowski and Lee (2009) found evidence for the role of a specific kinase called glycogen synthase kinase-3 (GSK-3) in the hyperphosphorylation of tau. In animal models using mice, the specific tau kinase inhibitor LiCl, which targeted this specific GSK-3 kinase, resulted in improved behavior, a reduction in tau pathology and a reduction in levels of insoluble tau in the brains of mice after only four months of treatment (Brunden et al, 2009). Further research by Brunden and colleagues (2010) focuses on the binding of tau proteins that leads to fibrillation and aggregation of tangles. A cyanine dye molecule called N744 has been found to positively affect already existing aggregations of tau filaments.
Amyloid-beta Inhibitors.

While the aforementioned treatments may indirectly affect levels of amyloid-beta in the brain, it may be more efficient to directly target amyloid-beta and its residual plaques to decrease AD pathology. Recently, the effectiveness of a relatively new drug called Alzhemed (or Tramiprosate) has been studied in clinical trials. Evidence exists that treatment with tramiprosate is correlated with reduction in hippocampal volume loss (Aisen et al, 2010). This finding suggests that Alzhemed is at least somewhat effective in reducing amyloid-beta levels and their subsequent neurotoxicity.

In further human clinical trials, Alzhemed has shown to effectively reduce levels of soluble amyloid-beta in the cerebrospinal fluid (Aisen et al, 2004). The fact that Alzhemed was able to affect levels of amyloid-beta in the CSF demonstrates its ability to cross the blood-brain barrier, making it a more effective treatment option as a smaller molecule. Perhaps more importantly, in these clinical trials, Alzhemed has shown to have no significantly detrimental side effects (Aisen et al, 2004), making it a treatment that lacks many negative aspects. As a drug treatment, Alzhemed is a simple way of treating many AD symptoms through its modulation of amyloid-beta. However, there is more evidence for the effectiveness of immunotherapies in the treatment of the amyloid-beta pathology of Alzheimer’s disease.

Immunotherapies.

While drug therapies can be very effective in the treatment of AD, it is important to administer the proper drugs at the proper timing for each unique individual. In addition, it is difficult to anticipate Alzheimer’s symptoms, resulting in the disease reaching a critical point before treatment is sought. At more developed stages of AD, drugs may only be helpful in terms of numbing the symptoms of the disorder, rather than treating it directly. In these situations,
immunotherapies are more effective ways of treating the disorder. Alzheimer’s vaccinations and antibodies that target tau and amyloid-beta are just a few of the immunotherapeutic targets that have been studied in recent years (Wisniewski & Goñi, 2014).

Researchers have performed several vaccination trials targeting the existence of the amyloid-beta peptide in the brain. Nemirovsky and colleagues (2011) performed a vaccination trial with wild-type transgenic mice. Using a vaccination consisting of amyloid-beta 1-15 complexed with heat-shock protein 60 (HSP60), the researchers were able to create amyloid-beta specific antibodies in the mice (Nemirovsky et al, 2011). While this study did not directly examine the behavioral and biological benefits in mice with AD symptoms, the findings suggest that it is possible to create specific amyloid-beta antibodies that may combat the toxic amyloid plaques seen in AD.

In other research, vaccines consisting of synthetic amyloid-beta peptides resulted in significant inhibition of amyloid fibril formation in guinea pig, baboon and mouse models (Wang et al, 2007). Guo et al (2013) found both behavioral and biological efficacy of an amyloid-beta vaccine with their research of mouse models. Using an injection comprising of the minimal effective fragment of amyloid-beta, amyloid-beta 3-10, and cDNA encoding mouse genes, the researchers were able to significantly reduce the presence of amyloid plaques in the brains of the mice, resulting in improved cognitive function as well (Guo et al, 2013). It seems that these amyloid antibodies do most of their work through direct dissociation of the amyloid plaques. However, it is also possible that levels of amyloid-beta antibodies in plasma drive a reduction in soluble levels of amyloid-beta in the brain that are usually responsible for plaques (Guo et al, 2013).
There exists less research regarding tau-directed vaccines for the treatment of AD. However, some studies have experimented with small injections of phosphorylated tau, testing their effectiveness against the development of NFTs. Old mice that exhibited NFT burden were shown to exhibit significantly reduced levels of NFT burden in areas such as the hippocampus, cortex, striatum-thalamus and brain stem following body injections of phosphorylated tau peptides (Boimel et al, 2010). The mechanism that controls this decrease in NFT burden due to immunization is not fully understood. However, the phosphorylated tau antibodies that are created may enter neurons via surface receptors and bind to tau aggregates, causing their degeneration (Boimel et al, 2010). Also, direct injections of tau antibodies from mice have been proven to decrease tau pathology (Asuni et al, 2007).

Unfortunately (and unlike amyloid-beta immunizations), it seems that immunotherapy procedures targeting NFT aggregates lead to some severe negative side effects. For example, injections of phosphorylated tau, though leading to an increase in tau antibodies, were correlated with an increase in microglial cells, as well (Boimel et al, 2010). There also seems to be a relatively low threshold for the number of effective immunizations. Research has shown that mice, when immunized with phosphorylated tau as many as seven times, display increased numbers of brain infiltrates and microglial cells (Rozenstein-Tsalkovich et al, 2013). As we have previously stated, these microglial cells are one of the main causes of neuroinflammation, a serious symptom of AD pathology that may cause some of the cognitive impairments associated with the disorder. However, it is possible that tau immunotherapy could be paired with a strong NSAID prescription in order to balance the benefits and costs of both treatments.

Calcium channelopathies represent a unique immunotherapy for AD (Chakroborty and Stutzmann, 2013). As we have stated before, some AD pathology may be explained by
glutamate-mediated neuronal death due to modulation of intracellular calcium levels. Though not much research exists regarding the efficacy of specific calcium treatments, there is evidence that the administration of calcium channel blockers is correlated with decreased amyloid-beta pathology (Chakroborty and Stutzmann, 2013). These correlations suggest that the blocking of calcium channels may stimulate the release of neurotransmitters like acetylcholine.

**Conclusion**

As is evidenced by this literature review, Alzheimer’s disease is a complex disorder with many different risk factors and pathological mechanisms. While there are a significant number of treatment directions aimed to reduce or cure AD symptoms, the disease remains as the most prevalent type of dementia in existence. Difficulties in treatment of AD often focus on the timing and prevalence of symptoms. Although many of the treatments we have discussed are effective in treating AD pathology, some of them are more effective preventatively and need to be administered when AD is in its earlier stages. Unfortunately, this is often difficult because symptoms are not always apparent until they reach their later stages. Also, many individuals are not knowledgeable of what symptoms to look for when dealing with individuals at risk for developing AD.

Pre-symptom screening may be beneficial in the targeting of Alzheimer’s symptoms. As we have stated previously, genetic risk factors, like mutations in the presenilin-1 and -2 genes and the presence of the apoE4 allele, have shown to be biomarkers for the future development of AD symptoms. With family history of AD, individuals should be able to seek screening for genetic risk factors like these in their own genome, giving them the opportunity to attack symptoms early, before the disorder has become chronic and invasive. As has been said previously, early identification is important for the effectiveness of several types of AD
treatment, as well. Drugs like NSAIDs, for example, seem to only be effective preventatively, rather than as post-symptom treatment. Early identification of an individual’s expression of apoE4 may allow that person to seek some type of immunotherapy, decreasing his/her symptoms in the long run.

There are some clear pathways for the treatment of Alzheimer’s disease. Although we do not fully understand whether the existence of amyloid-beta plaques and neurofibrillary tangles in the brain are causes of the disorder and the cognitive deficits that are paired with it, our knowledge of the ways in which these affect brain mechanisms is substantial. Drug treatments are often effective in dulling symptoms: AChE inhibitors improve cognitive functioning and decrease amyloid-beta pathology; Alzhemed directly inhibits the binding of amyloid-beta into plaques; NSAIDs, like typical ibuprofen, reduce neuroinflammation and its associated cognitive impairments.

The effectiveness of some drugs gives some hope to the ease of treatment of the disorder, and the immunotherapies that are also available could lead to even more discoveries of effective AD treatments. It seems that many treatments target amyloid-beta specifically, as it has been implicated as a possible causal factor in almost all phases of AD pathology. Perhaps more unique treatments could be created that target the alpha- and beta-secretase step of the amyloid pathway in order to prevent the production of toxic amyloid-beta before the onset of the disorder. In regard to this, an effective vaccine that targets the productive factors of amyloid-beta could prevent the onset of AD symptoms, reducing the effort that it may take to treat more advanced levels of the disorder.

With the existence of effective AD treatments, the remaining factor in the reduction of AD prevalence is widespread knowledge of the disorder and its risk factors. With such a
significant prevalence of AD, one should question why so few AD sufferers, or their families, seek out treatments for their condition. With increased knowledge of the disorder and the treatments that exist for it, families should be more able to informally diagnose their loved ones and seek treatments for them. Furthermore, with more knowledge of the disorder’s risk factors, the families would be able to seek treatment earlier on in the life span of the pathology, increasing the likelihood that the affected individual may recover from AD symptomatology and live an improved life for a longer time.


