Current Treatments of the Mechanisms of Alzheimer’s Disease

Elizabeth Haltiwanger

Wofford College

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Abstract

Treatments of Alzheimer’s disease can vary based on the numerous mechanisms and pathologies of the disease. The focus of this review is to better understand the treatments of Alzheimer’s disease and which mechanisms of the disease the treatments are targeting. The connection of type 2 diabetes and Alzheimer’s disease is explored to further understand how insulin may be an effective treatment of the symptoms of Alzheimer’s disease. Pharmaceutical treatments that are also effective in treating the symptoms of Alzheimer’s disease are explored. It is noted that these treatments do not stop the progression of the disease, and an effective treatment would be a vaccine that intervenes early. The current research to find an effective vaccine is also explored.
Current Treatments of the Mechanisms of Alzheimer’s Disease

Alzheimer’s Disease is the most common neurodegenerative disease today. It is most likely found in individuals over the age of 65 and is one of the leading causes of death that cannot be prevented or cured (Kumar & Ekavali, 2015). In America alone, six million people have Alzheimer’s disease and it is expected that by 2050, a new case of Alzheimer’s is expected to develop every 33 seconds totaling to one million cases per year. The disease is not only found in elderly people and it has been found that about 200,000 cases are found in patients under the age of 65. The survival rate of the disease can last from four to twenty years, and there are over 60,000 deaths per year caused by the mechanisms of the disease which include neuronal death, amyloid beta plaques, and neurofibrillary tangles caused by tau proteins. If the onset of the disease is delayed with a treatment, cure, or prevention, the death rate is estimated to cut in half. This would be because the mechanisms that are hallmarks of the disease will be prevented (Weller & Budson, 2018). Alzheimer’s places a large burden on the health care system in America with annual costs exceeding a quarter of a trillion dollars. This demonstrates how the necessity to find a cure for Alzheimer’s disease is not only health motivated, but also financially motivated (Weller & Budson, 2018).

Alzheimer’s disease is a progressive disease that causes a significant disruption in brain function. The first sign of the disease is recent memory deficiency while the remote memories are preserved until a later stage of the disease. Along with memory deteriorating, other cognitive functions deteriorate as the disease progresses including behavioral disorders, depression, irritability, loss of concentration, slowing of speech, and restlessness. According to the American Psychiatric Association’s Diagnostic and Statistical Manual, “Dementia of the Alzheimer’s type” involves significant memory impairment and cognitive deficits. The
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symptoms must not be due to other neurological disorders or substance abuse. The impairments must be severe enough to significantly interfere with social or occupational functioning. The impairments must have a gradual onset with a progressive decline and must represent a significant decline from a previously higher level of functioning (American Psychiatric Association, 2017). The ultimate diagnosis of Alzheimer’s disease requires a post-mortem evaluation of the brain tissue, but looking at the clinical criteria listed previously along with examination of cerebrospinal fluid and positron emission tomography biomarkers, such as deposits of amyloid beta proteins into plaques can help to make a diagnosis in a living patient experiencing Alzheimer’s symptoms (Budson & Solomon, 2012).

There are so many different causes of Alzheimer’s disease, but the disease is primarily a result of an increase in the accumulation of amyloid beta proteins that cause improper folding of the protein which forms plaques in the brain tissue leading to inflammation of the brain and cell death (Chen, Xu, Yan, Zhou, Jiang, Melcher, & Xu, 2017). The disease is also a result of an increase in the accumulation of tau proteins which causes neurofibrillary tangles in the brain. The plaques tend to develop earlier in the disease while the tangles tend to develop more as the disease progresses (Pesini, Lacosta & Sarasa, 2008). Also, patients with Alzheimer’s disease also show degeneration of cholinergic neurons and a reduction of the enzymes cholin-acetyltransferase and acetylcholinesterase. The treatment of Alzheimer’s is varied due to the varying pathology of the disease. As previously mentioned, the pathologies of the disease include amyloid plaques which are an accumulation of amyloid beta protein in the brain, neurofibrillary tangles which is tau build up in the brain, and inflammation. All of these pathologies cause the cognitive decline and neuronal death that is associated with Alzheimer’s
The treatments aim to slow the progression of these characteristics and ultimately prevent them (Weller & Budson, 2018).

The purpose of this literature review is to focus on the treatments of Alzheimer’s disease and more importantly, what is the most effective method for treating Alzheimer’s disease. The literature review will summarize current trends and future therapies for treating patients with Alzheimer’s disease. The literature review will explore the link found between type 2 diabetes and Alzheimer’s disease to determine if insulin could be a beneficial treatment for Alzheimer’s. The current types of medications used to treat Alzheimer’s as well as the new developments in a vaccine to prevent the development and onset of Alzheimer’s will also be explored in order to determine what the best treatment option for Alzheimer’s is and what research needs to focus on for the development of a beneficial treatment.

**The Relationship between Diabetes and Alzheimer’s Disease**

A disease that potentially increases the susceptibility to develop Alzheimer’s disease is type 2 diabetes. Research has found that individuals with type 2 diabetes have an increased risk of developing Alzheimer’s disease (Allen, Frier, & Strachan, 2004). Type 2 diabetes is a disease in which a high blood glucose level results from increased glucose production and impaired insulin production and release, or insulin resistance (Akter, Lanza, Martin, Myronyuk, Rua, & Raffa, 2011), Type 2 diabetes is very prevalent and accounts for many health problems that are significant in society today. Both type 2 diabetes and Alzheimer’s disease are common among the elderly population and are both progressive diseases. The two diseases have been thought to share pathology of cognitive decline. This has been demonstrated in past research conducted by Nooyens, Baan, Spijkerman, and Verschuren (2010), in which they examined cognitive functioning through memory and recognition tasks in 2,613 patients with type 2 diabetes and
without type 2 diabetes over a period of five years. They found that the patients with type 2 diabetes showed a greater decline in cognitive functioning over the five-year period than the healthy patients. Another study by Ruis, Biessels, Gorter, Donk, Kappelle, and Rutten (2009) examined cognitive functioning in type 2 diabetic patients and healthy patients, and they found that cognitive impairments are present in the early stages of type 2 diabetes. The cognitive functioning impairment in type 2 diabetes may be a result of diabetes-specific abnormalities such as hyperinsulinemia or hyperglycemia which can cause damage from oxidative stress to areas of the brain that are essential for cognitive functioning (Ruis et al., 2009). The links of the shared pathology are still not entirely clear, and this section will attempt to summarize the connection of Alzheimer’s and type 2 diabetes by examining current studies.

One study looked at a population of 918 patients over the age of 65 years old with no signs of Alzheimer’s disease or cognitive impairment (Luchsinger, Reitz, & Patel, 2007). They asked each participant to indicate past health history, including type 2 diabetes. They studied the patients over a period of time and found that the patients who had type 2 diabetes showed signs of cognitive impairment significantly faster than the patients who did not report having type 2 diabetes. This indicates that the participants who had a history of type 2 diabetes had faster cognitive decline than the participants without a history of type 2 diabetes. In another study, a population of 1488 people in Manhattan over the age of 65 were randomly recruited through the Medicare system to study cognitive decline in patients with type 2 diabetes (Cheng, Noble, Tang, Schupf, Mayeux, & Luchsinger, 2011). The results showed that the patients that reported having type 2 diabetes showed more cognitive impairments and signs of Alzheimer’s disease than patients without type 2 diabetes (Cheng et al., 2011). Another study examined 23 adults with no prior treatment for diabetes, but who met the criteria of the American Diabetes Association to be
diabetic, with no cognitive impairment (Baker, Cross, Minoshima, Belongia, Watson, & Craft, 2011). The researchers examined the insulin resistance levels of each participant using screening measures and then were given a memory task where they were asked to remember a repeating list of 20 words that were randomly presented. It was found that the participants with greater insulin resistance levels had more Alzheimer’s like patterns such as cognitive impairments during the memory task, performing more poorly that the participants with little to no insulin resistance. This indicates that insulin resistance may be a link between the two diseases (Baker et al., 2011). An important aspect to consider when reviewing these studies is that none of the participants were diagnosed with Alzheimer’s disease, they were only showing signs of cognitive impairment that is associated with Alzheimer’s disease. Therefore, the link between Alzheimer’s disease and type 2 diabetes must be explored further to understand why type 2 diabetes may increase the risk of developing Alzheimer’s disease.

The prevalence of type 2 diabetes in 100 patients with Alzheimer’s disease and 138 healthy patients was examined in a study in Minnesota (Janson, Lawdtke, & Parisi., 2004). The researchers found that 81% of the people with Alzheimer’s disease had type 2 diabetes. They found that type 2 diabetes was not as prevalent among people without Alzheimer’s disease finding that 24% of the people without Alzheimer’s disease had type 2 diabetes. The prevalence of the two diseases co-existing indicates that there may be a link between the two diseases. To further study the link between the two diseases, the researchers did a clinical study of the same community by examining autopsy cases to determine if there was a larger prevalence for amyloid plaques in patients with type 2 diabetes and Alzheimer’s compared to the healthy patients. They found that the patients without Alzheimer’s disease who had type 2 diabetes for a longer duration of time had more plaques than the patients who only had recently been diagnosed with type 2
diabetes and did not have Alzheimer’s disease. Amyloid beta plaques were also much more frequent in the Alzheimer’s patients with type 2 diabetes than in the Alzheimer’s patients without type 2 diabetes. This indicates that the mechanism of the amyloid beta creating plaques may be a link between the two diseases. This linkage between the two diseases and the increase in amyloid beta found in patients with type 2 diabetes may support the idea that having type 2 diabetes can increase the risk of developing Alzheimer’s disease (Janson et al., 2004).

Another possible link between Alzheimer’s and diabetes is associated with insulin processing and insulin resistance (Wan, Xiong, Man, Ackerley, Braunton, Becker, MacDonald, & Wang, 1997). Insulin serves important functions in many brain regions including ones that are associated with memory by increasing glucose uptake into the cells. Insulin receptors are located in the hippocampus, hypothalamus, and amygdala which are all brain regions that are essential in memory. If insulin becomes no longer present, these areas that are essential for memory functioning may be damaged which will lead to a decline in cognitive functioning. It has also been researched that insulin also may play a role in regulating amyloid beta protein and preventing the formation of amyloid beta protein plaques (Watson & Craft, 2003). A study was conducted where the researchers inactivated the IRS1 gene, which is the insulin receptor, in mice (Schubert, Brazil, Burks, Kushner, Ye, Flint, Farhang- Fallah, Dikkes, Warot, Rio, Corfas, & White, 2003). This was done by the researchers permanently changing the rat’s DNA by using a drug resistance marker to replace the IRS1 gene and then breeding the mice to produce a population that does not have the insulin receptor gene and is, therefore, resistant to insulin. They found that the mice without the insulin receptor had neuronal proliferation and more amyloid-beta plaques present in their brain (Shubert et al., 2003). This shows that insulin resistance may play a role in the formation of amyloid beta plaques suggesting that inulin plays an important
role in regulating amyloid beta. Another study examines brain scans of 150 middle-aged adults who had high insulin resistance or who had normal insulin processing and were healthy (Willette, Bendllin, Okonkwo, Rue, Hermann, Koscik, Jonaitis, Sager, & Asthana, 2015). The researchers found that the people who had high insulin resistance used less glucose in the brain especially in the areas of the brain most associated with memory where insulin receptors are located such as the hippocampus, hypothalamus, and the amygdala. Glucose is used as a fuel source in the brain when insulin is not present to provide uptake of glucose into the cells, these areas of the brain can no longer function (Willette et al., 2015).

A study looked at the potential of using insulin as a treatment for Alzheimer’s disease (Park, Seeley, Craft, & Woods, 2000). The researchers used long-Evans rats to see if increasing their insulin would improve their memory. The rats were trained through a step-through passive-avoidance task which is a fear-aggravated task that evaluates memory by exposing the animal to an adverse stimulus when entering an environment in order to teach the animal to avoid entering the environment. In this experiment, the task consisted of the rats being shocked if they entered a dark compartment of their housing which allowed them to learn to not enter the dark component of their housing. After the training, the rats received an injection of insulin or saline as a control and then were retested in the same task. The rats were injected immediately after the training in order to see if the insulin influenced memory formation and consolidation. The rats that received insulin had an increased latency to entering the darkened compartment of their cage compared to the control rats showing that the insulin increased their memory formation of the task allowing them to remember being shocked when entering the dark compartment and have an increased response time to re-entering (Park et al., 2000). This evidence indicates that insulin improved the rat’s memory and positively affected memory consolidation. Another study
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supports the idea that insulin is important in memory consolidation. Schwarzberg, Berstein, Reiser, and Gunther (1989) completed a similar experiment where rats were trained through a step-through passive-avoidance task, but instead of being injected with insulin after the training, they were injected before. The rats injected with insulin entered the dark component of their housing with the same latency as the rats injected with the placebo. This indicates that the injection of insulin prior to learning did not have an influence on the rat’s memory. This suggests that insulin plays a significant role in the formation of memories and the memory mechanism process, long-term potentiation. Another study also looked at insulin as a potential treatment by examining 104 participants with Alzheimer’s disease received either a placebo or insulin through a nasal delivery for four months in order to test the longer-term effects of the treatment (Claxton, Baker, Wilkinson, Trittschih, Chapman, Watson, Cholerton, Plymate, Arbuckle, & Craft, 2013). The subjects participated in cognitive testing the morning after their last treatment of either insulin or the placebo after the four-month time period. The cognitive testing consisted of listening to a recording of a story and then having to repeat the story immediately following listening and then again after a 20-minute delay. It was found that the participants who received insulin performed significantly better repeating the story following the 20-minute delay. This shows that the insulin significantly improved cognitive abilities of patients with Alzheimer’s disease (Claxton et al., 2013).

A study tested the effectiveness and safety of using a nasal spray to administer insulin to Alzheimer’s patients (Craft, Baker, Montine, Minoshima, Watson, Claxton, Arbuckle, Callaghan, Tsai, Plymate, Green, Leverenz, Cross, & Gerton, 2012). The study consisted of 104 patients with mild to moderate Alzheimer’s disease who receive a placebo or insulin administered through a nasal spray for four months. The patients who received the insulin
treatment showed improvements in memory compared to the patients who received the placebo. No adverse side effects of the insulin treatment occurred. Using insulin as a treatment for Alzheimer’s disease could be beneficial in improving cognitive functioning according to the studies previously mentioned. An important consideration is how often and how much the treatment should be administered. Another study looked at whether the effects of insulin administered through a nasal spray to Alzheimer’s patients is fast acting by looking at improvements in cognitive functioning in a shorter time (Reger, Watson, Green, Wilkinson, Baker, Cholerton, Fishel, Plymate, Breiter, DeGroodt, Mehta, & Craft, 2008). This study examined twenty-five patients with Alzheimer’s disease who were either administered insulin or a placebo through a nasal spray. The researchers examined cognitive functioning twenty-one days after the administration and found that the patients who received the insulin treatment showed improvement in attention and memory (Reger et al., 2008).

The previous studies by Park and colleagues (2000) and Schwarzberg and colleagues (1989) administered a single injection into the rats and it improved their memory when administered after learning. Claxton and colleagues (2013), administered insulin to humans daily for a four-month period and it improved their memory, but Reger and colleagues (2008) administered insulin to patients once and it also improved their memory. This suggests that insulin is a fast-acting treatment that does not decrease over time. It also shows that the treatment does not have any adverse side effects. It is important for future research to focus on how long the treatment will last. These study also shows that administering insulin through a nasal spray is effective.

In conclusion, it has been shown that insulin is a link between type 2 diabetes and Alzheimer’s disease as shown through the increased risk of Alzheimer’s disease in people with
type 2 diabetes. Since studies have shown that insulin resistance is associated with a risk of Alzheimer’s disease, more research is being done to determine if increasing insulin is an effective treatment option for Alzheimer’s disease to increase memory and cognitive functioning. Testing for high levels of insulin resistance could also be used to test people who have high insulin resistance and may be at a higher risk for Alzheimer’s disease. Although it has been found through previous studies that insulin does increase memory formation and improved cognitive functioning, the mechanism for which it does is still under-researched and therefore, other treatment options must be explored to find an effective treatment that will not only improve cognition but slow and eventually stop the progression of the disease. Also, the effects of insulin on Alzheimer’s disease have only been researched in few studies with small samples. Future studies should use larger populations and look at the long-term effects of the treatment to determine if any significant adverse side effects are caused by continuous and long-term administration. Also, it is unclear how often the treatment should be administered and for how long it will last. Future studies should focus on the timing and the frequency of the administration of the insulin administration.

**Neuro-therapy Treatment for Alzheimer’s Disease with Pharmaceuticals**

Treatments of Alzheimer’s vary due to the varying mechanisms and pathology of the disease. This section will focus on the treatment for Alzheimer’s disease using pharmaceutical treatments. Pharmaceutical treatments of Alzheimer’s disease consist mostly of acetylcholinesterase inhibitors, which inhibit the acetylcholinesterase that breaks down acetylcholine and allows for the regulation of the production of amyloid-beta proteins. This helps to treat the symptoms of Alzheimer’s disease, most particularly, cognitive decline, because
acetylcholine is a neurotransmitter that is essential for cognitive functioning, such as processing memory and learning.

One study examined the long-term effects of treating Alzheimer’s Disease with two drugs, either donepezil or memantine (Howard, 2012). Donepezil is a type of acetylcholinesterase inhibitor, and memantine is a drug that blocks the NMDA receptor to decrease glutamate. The study looked at 295 patients who were either treated with donepezil, treated with memantine, or not treated with a medication at all in a multicenter, double-blind, placebo-controlled, clinical trial with a two-by-two factorial design. The study found significant improvements in cognitive functioning in the patients who continued taking donepezil and not memantine. The cognitive functioning was based on scores of the Standardized Mini-Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS) which are both common questionnaires that measure the cognitive abilities of elderly people. The patients who continued taking donepezil and not memantine had higher scores on more the SMMSE and the BADLS. These results indicate that an acetylcholinesterase inhibitor is a more effective treatment of Alzheimer’s disease than memantine (Howard, R, McShane, R., Lindesay, J., 2012). A similar study looked at 565 treatments of Alzheimer’s disease with either donepezil or a placebo and found no significant improvements in cognitive functioning or other symptoms associated with Alzheimer’s disease (Courtney, Farrell, Gray, Hills, Lynch, Sellwood, Edwards, Hardyman, Raftery, Crome, Lendon, Shaw, & Bentham, 2000). These results contradict the findings of Howard and colleagues (2012) and suggest that donepezil as a treatment for Alzheimer’s is not effective. There is more research that contradicts Howard and colleague’s (2012) findings. Another study examined the long-term effects of treating Alzheimer’s disease with memantine for a 24-week period (Grossberg, Manes, & Allegri, 2013). The study looked at
677 patients who had a clinical diagnosis of Alzheimer’s Disease who were treated with either memantine or a placebo daily in a double-blind test. The study found that the patients treated with memantine had a significant increase in cognitive functioning. This suggests that the treatment of memantine is a beneficial treatment in improving symptoms associated with Alzheimer’s disease. The could be due to the fact that decreasing glutamate may be more beneficial than inhibiting acetylcholinesterase. The results could also be due to the fact that the drugs are acting in different ways to target cognitive decline, and a combination of memantine and donepezil could show benefits. Another study evaluated the combination of memantine and donepezil in patients with mild to moderate Alzheimer’s disease and found that the combination resulted in improvement in daily behavior and cognition tests (Scarpini, Scheltens, Feldman, 2003). This suggests that the combination of these drugs is more beneficial than using them independently. A problem with using cholinesterase inhibitors is that as the disease progresses, the brain produces less acetylcholine and the drugs become less effective.

High cholesterol has been thought to be a risk for developing Alzheimer’s disease and therefore, the efficacy and safety of using cholesterol-lowering drugs such as simvastatin in treating Alzheimer’s disease has been examined. One study found that cholesterol acts as a catalyst for amyloid beta proteins to form in the brain by sticking to lipids containing cholesterol (Habchi, Chia, Galvagnin, Thomas, Micheals, Mathias, Bellaiche, Ruggeri, Sanguanini, Idini, Kumita, Sparr, Linse, Dobson, Knowles, & Vendruscolo, 2018). This increases the aggregation of the protein by increasing the accumulation into plaques. Another group of researchers did a double-blind test using simvastatin and a placebo to see if the lowering of cholesterol will result in the reduction on amyloid-beta protein levels (Simons, Schwarzler, Lutjohann, Bergmann, Beyreuther, Dichgans, & Wormstall, 2002). The patients were given 80 mg of simvastatin or
placebo daily for 26 weeks. Simons and colleagues (2002), found that patients with moderate Alzheimer’s did see a significant decrease in amyloid-beta protein levels in cerebrospinal fluid, but patients with severe Alzheimer’s disease did not see a significant decrease in Amyloid-beta protein levels. These results suggest the use of simvastatin as a preventative measure since the reduction in amyloid-beta protein levels may be sufficient to slow the progression. The researchers indicate that they chose to use simvastatin instead of another type of statin since it passes through the blood-brain barrier more efficiently than any other (Simons et al., 2002). The efficacy of cholesterol-lowering drugs overall is still not clear because another study found different results (McGuinness & Passmore, 2010). The researchers conducted a randomized trial where they treated patients with severe Alzheimer’s disease with three of the most used types of statins, lovastatin, pravastatin, simvastatin, or a placebo and found no significant decrease in cognitive decline in the patients treated with the statins compared to the placebo. This further supports the point that statins are not a beneficial treatment for severe Alzheimer’s disease, and maybe a better preventative measure (McGuinness & Passmore, 2010). To further support this point, another study looked at individuals who were age 50 or older who were already taking cholesterol-lowering medications for hyperlipidemia, or high cholesterol, and individuals who had untreated hyperlipidemia who were not taking statins (Jick, Zornberg, Jick, Sesbadri, & Drachman, 2000). They found that the individuals who were prescribed statins had a significantly lowered risk of developing Alzheimer’s disease indicated by evaluating plasma levels. More studies should be conducted administering statins at different stages of Alzheimer’s disease and before signs of cognitive decline to further test the benefits of using statins as a preventative measure for Alzheimer’s disease.
Treating the accumulation of amyloid-beta plaques have also been researched. A study tested the effectiveness of the antibiotic doxycycline in reducing the effects of amyloid-beta protein and its effects on the brain and memory processing (Balducci, Santamaria, La Vitola, Brandi, Grandi, & Viscomi, 2018). The anti-inflammatory effect of the antibiotic will interfere with amyloid beta by reducing its neurotoxicity. This will result in the reduction of neuroinflammation which is caused by the amyloid beta and will reduce cognitive decline. The researchers tested 15-week old mice that expressed an amyloid precursor protein. The rats were treated with doxycycline through an injection for 60 consecutive days and were tested with novel object recognition tasks to test memory. The rats were placed in an area with 2 identical objects, and then twenty-four hours later were placed in an area with one familiar object and a new object and the time exploring the objects was observed. The results showed that the mice treated with doxycycline would show preference to the new item indicating that the drug was sufficient in improving and restoring memory. Brain tissue was received from the anesthetized rats following the study and found that there was no reduction in amyloid beta plaques in the mice’s brains (Balducci et al., 2018). Another study treated four hundred and six patients with mild to moderate Alzheimer’s disease with doxycycline or a placebo for a twelve-month period (Molloy, Standish, Zhou, & Guvatt, 2013). The researchers tested the participants after the twelve-month treatment with an SMMSE cognitive test and found that the patients treated with doxycycline did not score significantly higher on the cognitive test than the patients treated with the placebo (Molloy et al., 2013). This suggests that the treatment of Alzheimer’s disease with doxycycline is not a beneficial treatment option in improving cognition. This also suggests that the Alzheimer’s rats should not be used as a final indicator for the benefits of a treatment for Alzheimer’s disease.
because the disease may be expressed differently in rat models than in humans, especially since the disease is mimicked (Marciani, 2017).

Treating other mechanisms of Alzheimer’s disease such as the oxidative damage to the neurons in the brain has also been researched. One study did a trial on a drug called selegiline combined with vitamin E to treat Alzheimer’s disease (Sano, Ernesto, Thoomas, Klauber, Shafer, Grundman, Woodbury, Growdon, Cotman, Pfieffer, Schneider, & Thai, 1997). The selegiline is an antioxidant that inhibits the oxidative deamination in order to reduce neural damage. The vitamin E traps free radicals in the cell membrane. Free radicals cause extreme oxidative stress to cells leading to cell death. This treatment of trapping the free radicals in the cell membrane was proven to be beneficial because by trapping the free radicals in the membrane, lipid peroxidation cannot occur which is when free radicals are released from the cell membrane and cause oxidative stress and cell death. This treatment proved to slow the progression of the disease by preventing cell death (Sano et al, 1997). Another study tested the benefits of treating Alzheimer’s with selegiline. Birks and Flicker (2003) examined patients with mild to moderate Alzheimer’s disease who had been administered selegiline or a placebo. The researchers assessed daily living and tested cognition with memory and cognition tests eight weeks and then again seventeen weeks after the treatment was first administered. They did not find any differences in improvement in cognition in the patients treated with selegiline and the patients treated with the placebo (Birks & Flicker 2003). In another study, a double-blind randomized clinical trial using 613 subjects with mild Alzheimer’s disease tested the effectiveness of vitamin E for the treatment of Alzheimer’s disease (Belitskaya-Levy, Dysken, Guarino, Sano, Asthana, & Vertrees, 2018). Half of the subjects received a placebo and the other half received vitamin E and the results show that the patients receiving vitamin E showed a significantly slower decline
in cognitive functioning. The results also did not show any adverse side effects of the vitamin supplement (Belitskaya-Levy et al., 2018). These results further support the evidence that the effect vitamin E has on the free radicals is effective in slowing the progression of Alzheimer’s disease. Another study testing vitamin E as a treatment for Alzheimer’s disease looked at the effects that vitamin E has on the progression of Alzheimer’s disease. Farina, Llewellyn, and Tabet (2017) examined 516 people with mild Alzheimer’s disease who were taking vitamin E as a supplement. The researchers found that the vitamin E supplement showed no evidence in improving cognition of learning and memory or slowing the progression of the disease. The results also did not point to any adverse side effects of the vitamin supplement (Farina, Llewellyn, & Tabet, 2017). This suggests that there is no benefit or harm in treating Alzheimer’s disease with a vitamin supplement, but when used with selegiline, there might be benefits. Another study by Filip and Kolibas (1999) examined the combination treatment of vitamin E and selegiline for patients with mild to moderate Alzheimer’s. They examined 173 patients who were treated with selegiline alone, selegiline and vitamin E or a placebo for 24 weeks and found that the patients treated with selegiline and vitamin E performed better on cognition and memory tasks than the patients treated with the placebo (Filip & Kolibas, 1999). This suggests that the combination of the two treatments is more beneficial than solely treating with vitamin E or selegiline.

In conclusion, no single drug treatment has been proven to be significantly effective at treating Alzheimer’s disease, however, as shown previously many of these treatments, such as cholinesterase inhibitors and statins, have been shown to maintain the progression of the disease by improving cognition and everyday behavioral abilities. These treatments are aimed at targeting the mechanisms in order to treat the symptoms. The treatments aim at improving
cognition and do not show any success in stopping the progression of the disease or preventing the disease. These symptomatic treatments are beneficial in improving the quality of life, but it is still important that a preventative or curing treatment is still discovered in order to stop the disease entirely.

**Alzheimer’s Disease Vaccine**

Since a cure or treatment has not been discovered for Alzheimer’s disease, many preventative treatments have been researched recently. This section will focus on the vaccine to prevent Alzheimer’s disease. The current treatments that were explored above are thought to be used too late when the features of the disease are already present, therefore the development of a vaccine that will intervene earlier is important. The type of vaccine that is currently being explored is an active vaccine, which involves the patient receiving an injection of the antigen itself (Lambracht-Washington & Rosenberg, 2012). Most of the vaccines focus on using an immunotherapy treatment in which the vaccine induces an immune response where antibodies are made to protect the body from the antigen that was introduced through the vaccine. By doing this, the body is exposed to the foreign antigen and can produce a protective immune response to the antigen if exposed to it again. The safety and effectiveness of Alzheimer’s vaccines are still being tested in clinical trials. Clinical trials test new treatments through four phases before being approved by the U.S. Food and Drug Administration (FDA) (Marciani, 2017). They are ultimately the way that researchers find out if a new treatment, such as a vaccine, in this case, is safe and effective to use in people. They are aimed to find treatments that are more effective with less harmful side effects than current and available treatments. Clinical trials are split into four phases. The first phase consists of testing the treatment on a small population to test for its safety and potential side effects. The second phase also tests for safety and possible side effects
but on a bigger population. The third phase studies the safety and effectiveness on different populations and in different dosages and in combination with other medications to see possible interactions. The fourth phase takes place after the drug has been approved by the FDA and is done to monitor the treatment in large populations over a longer period of time (Marciani, 2017). Since it has been found that amyloid beta protein and tau protein are the likely causal agents of Alzheimer’s disease, clinical trials are constantly being done to test the safety and effectiveness of vaccines that target these two proteins.

Vaccines Targeting Tau Protein

AADvac1 is currently the only known vaccine that targets abnormal tau proteins by inducing an immune response against the proteins in the hopes to inhibit the progression of neurofibrillary pathology and stop the progression of the disease entirely (Godyn, Jonczyk, Panek, Malawska, 2016). Multiple phase 1 clinical trials have been conducted to test the safety and effectiveness of the vaccine. The first phase 1 trial to test the tolerability of the vaccine in humans was completed in 2014. In the study, thirty participants who had Alzheimer’s disease received either the vaccine or the placebo once monthly for three months (Kontsekova, Zilka, Kovacech, Novak, & Novak, 2014). The researchers performed MRI’s, cognitive tests, blood tests, and urine tests to investigate how well the vaccine is tolerated and how safe it is, as well as test the immune response to the vaccine. The researchers found the vaccine to be safe with no adverse side effects occurring. They also found that the vaccine is capable of recognizing the tau proteins in the brain of the patients because the vaccine stimulating an immune response to attack the tau protein component of the vaccine. This indicates that this response could be beneficial in preventing the progression of the disease by illuminating the tau protein (Kontsekova et al., 2014). The follow-up trial continued to assess the tolerability of the vaccine
in the patients who were treated in the first study for another additional eighteen months in order to test the long-term safety and effects of the vaccine. The vaccine was continued to be administered once monthly. The researchers did not find any adverse, long-term effects of the vaccine and continued to find that the vaccine recognized the tau proteins in the brain by initiating an immune response towards tau protein (Kontsekova et al., 2014).

The next phase 1 study that was more recently conducted consisted of a randomized double-blind study with 54 patients who were 50 to 85 years of age and who had moderate Alzheimer’s disease (Novak, Schmidt, Kontsekova, Zikla, Kovacech, Skrabama, Vince-Kazmerova, Katina, Fialova, Prcina, Parrak, Dal-Bianco, Brunner, Staffen, Rainer, Ondrus, Ropels, Smisek, Sivak, Winblad, Novak, 2017). The participants were randomly assigned with 30 patients receiving a placebo and 24 patients receiving the vaccine for a 12-week period, one dose every 4 weeks. The goal of this study was to further test the tolerability of multiple administrations of the vaccine by testing the adverse side effects. Again, no significant adverse side effects related to the vaccine were found. The patients who received the vaccine produced an antibody against tau which was discovered through western blot analyses. The researchers then did cognitive assessment tests on the participants by asking the participant to produce as many words fitting into a specific category as possible in one minute. No difference was found in cognition when comparing baseline performance to performance after receiving the vaccine. Since the participants were already diagnosed with Alzheimer’s disease and no cognitive abilities were seen to improve, the vaccine does not prove effective as a treatment for already existing symptoms, but could potentially be a preventative treatment, especially since it was found that the vaccine causes antibodies against the accumulation of tau to form. This could allow the
vaccine to be more effective as a preventative measure to prevent accumulation of tau by administering it before signs of cognitive impairment appear (Novak et al., 2017).

The most recent phase 1 study to test AADvac1 was a 72-week study in patients with mild to moderate Alzheimer’s disease who completed the previously mentioned studies (Novak, Schmidt, Kontsekova, Smolek, Katina, Fialova, Prcina, Parrak, Dal-Bianco, Brunner, Staffen, Rainer, Ondrus, Ropels, Smisek, Sivak, Zilka, Winblad, & Novak, 2018). The patients either received six doses of the vaccine at monthly intervals or received three doses at monthly intervals. The patients were then treated with booster doses at the 24-week interval. The booster dose was to assess the required frequency of administration of the vaccine. Again, the researchers were testing the long-term safety of the vaccine, the presence of antibodies, and cognitive improvements. No adverse side effects were found and all the patients showed an antibody response towards the tau protein component of the vaccine. The researchers also found through MRI evaluations of the patients that there was slower atrophy in the brain when the vaccine was administered, which indicates that the vaccine is helping to slow down the neuronal death caused by the neurofibrillary tangles (Novak et al., 2018). Currently, a 24-month safety phase 1 study is being investigated to continue evaluating the safety and efficacy of the vaccine in the treatment of patients with mild to moderate Alzheimer’s disease as well as cognitive improvements from the vaccine. The study is estimated to complete in June of 2019 (clinicaltrials.gov, NCT02579252). This study is being completed to further expand the safety database of the vaccine (Novak et al., 2018).

Overall, these studies show promising and encouraging results that the developing AADvac1 may be a beneficial treatment option for Alzheimer’s disease. As shown in the study by Novak and colleagues (2017), the vaccine may be best used as a preventative treatment in
which the body can become exposed to the tau protein and develop an immune response towards it in order to prevent future build up that will cause neurofibrillary tangles and neuronal death. Further clinical trials in each phase are still required in order to continue testing the safety of the vaccine and to show proof of the clinical effectiveness of the vaccine in order for the vaccine to be approved by the FDA.

Vaccines Targeting Amyloid Beta Protein

Currently, three vaccines are undergoing clinical trials to test the safety and effectiveness of the vaccines in treating patients with Alzheimer’s disease. The vaccine is composed of amino acids from the amyloid beta proteins and is designed to initiate an immune response by creating antibodies against amyloid beta protein in hopes to prevent the accumulation of the protein into plaques in the brain. The three vaccines are CAD106, UB-311, and ABvac40.

CAD106 was designed in hopes that antibodies against amyloid beta protein would be produced to prevent the accumulation of amyloid beta plaques in the brain (Farlow, Andreasen, Riviere, Vostiar, Vitaliti, Sovago, Caputo, Windblad, & Graf, 2015). The first clinical trial to test the effectiveness and safety of the vaccine consisted of fifty-eight patients with mild to moderate Alzheimer’s disease. The patients were administered either a placebo or the vaccine four times in order to assess the tolerability of repeated injections. The researchers monitored the patients for any adverse side effects as well as evaluating the plasma levels of the antibodies by sampling plasma of different brain sections in order to determine if the vaccine created the proper immune response they were hoping for. The researchers did not find any adverse side effects that were not already expected in Alzheimer’s disease patients. The researchers also found that multiple administrations of the vaccine produced the specific antibodies against amyloid beta which indicates that multiple exposures of the protein to the body through increased injections may be a
beneficial treatment for Alzheimer’s disease (Farlow et al., 2015). The second clinical trial examined 121 patients with mild to moderate Alzheimer’s disease who received 7 injections of the vaccine or placebo over a 60-week time period (Vandenbergh, Riviere, Caputo, Sovago, Maguire, Farlow, Marotta, Sanchez-Valle, Scheltens, Ryan, & Graf, 2016). The researchers did find serious adverse side effects, such as irritation at the vaccination site, headache, and hypertension in nineteen of the cases that received the vaccine. These side effects were thought to be potentially related to the vaccine. The researchers did detect an immune response in the patients treated with the vaccine indicated by evaluating plasma levels. This trial demonstrated that the vaccine was safe and mostly tolerated in humans (Vandenbergh et al., 2016). Another trial called the Generation Study is currently recruiting people who are at risk for Alzheimer’s disease by having the APOE4 gene (clinicaltrials.gov, NCT02565511). This gene is thought to increase the risk of developing Alzheimer’s disease because it has been found to promote the accumulation of amyloid beta protein which causes the plaques characteristic of the disease (Kim, Basak, & Holtzman, 2009). The study will compare people given the vaccine or a placebo for up to eight years and is thought to be completed in 2024. The study will further test the tolerability and the effectiveness of the vaccine as well as whether the vaccine can slow down the onset or progression of Alzheimer’s disease. This study will be very beneficial in studying a preventative treatment in people who are at risk of developing Alzheimer’s disease.

Another clinical trial is examining the safety and effectiveness of the active vaccine called UB-311. Similar to CAD106, UB-11 also contains a peptide from amyloid beta protein that is to elicit an immune response that targets the amyloid beta proteins that form plaques in the brain. Phase one of the clinical trial evaluated the safety of the vaccine in animals. The researchers tested injections of the vaccine in baboons to show the safety of the vaccine and to
determine whether the vaccine would elicit an antibody immune response (Wang, Finstad, Walfiled, Sia, Sokoll, Chang, Fang, Hung, Hutter-Paier, & Windisch, 2007). The researchers found that the vaccine did generate an immune response in the baboons and found that specific antibodies were created against amyloid beta. The second study tested the tolerability of the vaccine in humans. The study consisted of nineteen patients with mild to moderate Alzheimer’s disease (Wang, Wang, Chiu, Finstad, Lin, Lynn, Tai, De Fang, Zhao, Hung, Tseng, Peng, Wang, Yu, Kuo, & Frohna, 2017). The patients were immunized with 3 doses of the vaccine and were studied for 48 weeks. No adverse side effects of the vaccine were found, and the researchers also found that there was a slower rate of cognitive decline in the patients that received the vaccine from the baseline to the 48th week. The researchers also found that the vaccine produced antibodies against amyloid beta proteins (Wang et al., 2017). This showed that the vaccine was safe and could be tolerated and that it has the potential to improve cognition in patients with early signs of Alzheimer’s disease, which could be due to the fact that the vaccine created an immune response to target the amyloid beta plaques in the brain. The second phase of the clinical trial is still being conducted in order to further test the antibody response of the vaccine and the safety and tolerability of the vaccine (clinicaltrials.org, NCT02551809). Also, since the first phase showed a slower rate of cognitive decline in patients with Alzheimer’s who were administered the vaccine, the second phase is also evaluating the vaccine’s effect on cognition by evaluating the patients’ cognitive test scores. The study is administering up to seven doses of the vaccine in patients with mild to moderate Alzheimer’s disease in a 78-week time period and the results from this trial are expected by 2019.

The vaccine ABvac40 is the most recently developed vaccine targeting amyloid beta proteins and therefore does not have as many clinical trials completed yet. The only trial
completed thus far tests the safety and effectiveness of the vaccine in people over the age of 50 with Alzheimer’s disease (Lacosta, Pascual-Lucas, Pesini, Casabona, Perez-Grijalba, Marcos-Campos, Sarasa, Canudas, Badi, Monleon, San-Jose, Munera, Rodriguez-Gomez, Abdelnour, Lafuente, Buendia, Boada, Tarrage, Ruiz, & Saeasa, 2018). Twenty-four patients received three doses of the vaccine and eight patients received three doses of a placebo for four-week intervals. The researchers evaluated any adverse side effects that might be related to the vaccine such as seizures, gait impairment, hallucinations, hypertension, and disorientation by completing laboratory assessments and physical examinations of the patients. No significant adverse side effects were found in the group that received the vaccine that was not already expected to accompany the patients’ old age and Alzheimer’s disease. The researchers also assessed the plasma levels in the patients to see if the vaccine was causing an antibody response against amyloid beta proteins. They found that the levels of specific antibodies against amyloid beta in the patients treated with the vaccine were significantly higher than they were at baseline and compared to the patients treated with the placebo (Lacosta et al., 2018). This study shows that the vaccine is safe and tolerable since no significant adverse side effects were present in the patients treated with the vaccine. The study also shows that the vaccine is capable of creating an immune response since 88% of the patients receiving the vaccine showed specific antibodies that were able to recognize amyloid beta protein and the formation of plaques. Since this study was the first-in-human test of the vaccine to assess the safety and tolerability of the vaccine, only a limited number of participants were used and therefore more tests are required to further assess the safety of the vaccine and the ability that the vaccine has to elicit an immune response. Currently, a second test is recruiting participants to further confirm the safeness and tolerability of the vaccine as well as better understand the immune response (clinicaltrials.org,
NCT03461276). The researchers will administer six doses of the vaccine or the placebo once every four weeks for two years to patients with mild to moderate Alzheimer’s disease. The study is estimated to complete in 2021.

In conclusion, it has been shown previously that the vaccines AADvac1, UB-11, CAD106, and ABvac40 have been proven to be safe and effective in the first phases of the clinical trial. It was even shown that UB-311 has the potential to improve cognition in patients with mild to moderate Alzheimer’s disease. These studies prove that there are two types of vaccines that work to create antibodies against the two main hallmarks of Alzheimer’s disease, amyloid-beta proteins, and tau proteins, is a good first step in the development of a vaccine for Alzheimer’s. The clinical trials must continue to confirm these results and to explore the clinical efficacy of the vaccines. Something to consider when developing vaccines that elicit an immune response is that there has to be an appropriate amount of immune response because the vaccine should not elicit an autoimmune response. An important aspect of all these studies previously mentioned is that they used human studies as opposed to mice. Although mice are extremely helpful, they should not be used as the final indicator for the value of the vaccine before it undergoes a clinical study since the mice are not accurate models of human Alzheimer’s disease (Marciani, 2017). Another important aspect to consider is that these vaccines are being tested on patients that already shows signs of Alzheimer’s disease. It will be important to test the vaccine on healthy patients as well to see if they show the same immune response. Vaccines are more effective when used as a preventative treatment as opposed to a therapeutic treatment and therefore a vaccine that prevents the onset of Alzheimer’s disease should be the ultimate goal and would be a tremendous benefit to the human population (Marciani, 2017).

Discussion
Alzheimer’s disease’s complex pathophysiology makes it difficult to find an effective treatment, yet the discovery that amyloid-beta proteins and tau proteins are the central mechanisms of the disease allows for the treatments to be developed to target the main causal agents. As previously stated, a potential treatment could be insulin, more specifically administered as an intranasal treatment. Another potential treatment could be pharmaceutical treatments that manage and improve symptoms. As previously mentioned, neither of these treatments act to prevent or cure Alzheimer’s disease, therefore, the development of a preventative vaccine provides hope in a treatment that cures Alzheimer’s.

Past research has shown a link between Alzheimer’s disease and type 2 diabetes, particularly people with type 2 diabetes have a higher risk of developing Alzheimer’s disease. As shown in Janson and colleagues (2004) study, many people with type 2 diabetes have brain changes that are hallmarks of Alzheimer’s disease such as amyloid-beta plaques. The research suggests that the insulin resistance in type 2 diabetes may fuel the amyloid beta proteins to cause plaques and cause people with type 2 diabetes to have an increase risk of developing Alzheimer’s disease. This may be due to the fact that type 2 diabetes affects the ability of the brain to use glucose and respond to insulin. Glucose is the brain’s main source of energy. The link between type 2 diabetes and Alzheimer’s disease may be due to the effects of insulin resistance on the brain. By studying the link between the two diseases, a potential treatment of insulin is more likely to treat both diseases by clearing amyloid beta plaques from the brain in Alzheimer’s patients. Past research has shown that insulin is an effective treatment in both treating type 2 diabetes and improving cognitive functioning in patients with mild Alzheimer’s disease, but the progression of Alzheimer’s disease is not slowed.
Pharmaceutical treatments have also been shown to be effective in treating the symptoms of Alzheimer’s disease, but not stopping the progression of the disease. As previously mentioned, no single drug treatment has been proven to be significantly effective at treating the disease, just slowing the progression of the disease. As shown previously, there is a variety of treatments that focus on treating different mechanisms of Alzheimer’s disease. This is because as more is understood about the mechanisms involved in the disease, more treatments can be created to combat the disease such as the oxidative damage to neurons, and the lowering of cholesterol to lower the amount of amyloid-beta proteins. These treatments have been effective in targeting the symptoms of the disease, but the progression of the disease is not affected. An effective Alzheimer’s treatment should begin early in the diagnosis, or even before the onset of the disease. This is difficult since there is not an easy test to diagnose the disease, and the diagnosis relies on the clinical evaluation of irreversible symptoms. Further research and findings on the diagnosis of the disease will more likely lead to a treatment that can cure Alzheimer’s disease and stop the progression instead of just slowing it.

Overall, intranasal insulin may be beneficial in treating cognitive impairments associated with Alzheimer’s disease such as memory and cognition by increasing glucose in the brain and decreasing amyloid beta plaques in the brain. Not many studies have been conducted to test the safety and potential side effects that this treatment may have when used long-term, and the studies that have been completed use small sample sizes and the results cannot be applied to a larger population yet. Further clinical trials, which could take years to complete, should be completed in order to see if intranasal insulin will be safe long-term. Another aspect that makes insulin as a treatment for Alzheimer’s not an ideal treatment is that it does not stop the progression of the disease, instead it only slows cognitive decline. This would make the
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treatment beneficial in treating a symptom of the disease, but not curing the disease. The FDA approved pharmaceutical treatments may also be beneficial in helping to treat the symptoms of Alzheimer’s disease, but many adverse side effects can accompany these medications which makes these treatments less ideal. Some side effects that are caused by these medications can include nausea, loss of appetite, weight loss, and vomiting. It would take a trial and error process for the patient to see which medication works best for them which could take a significant amount of time in which the disease is continuing to progress. Another issue with pharmaceutical treatments is that they may become less effective over time, as shown through the use of cholinesterase inhibitors as a treatment. Again, these treatments do not stop the progression of the disease, but only treat the symptoms. An ideal treatment option for Alzheimer’s disease would stop the progression of cognitive decline or prevent the disease from developing. There is hope with finding a preventative or curing treatment with the recent and current research being done to develop a safe and effective vaccine. As mentioned previously, the vaccines are currently undergoing clinical trials to assess the safety effectiveness of the vaccines. Most of the vaccines have been proven effective in safety and in generating antibodies against amyloid-beta proteins. This provides hope that there will soon be a vaccine that can delay or prevent the onset of Alzheimer’s disease available to the general public soon, who is so desperate for a treatment for this disease. In the meantime, the pharmaceutical treatments that have been proven safe and effective should be used to manage the symptoms of the disease. The medications such as cholinesterase inhibitors and statins can be used in combination to further reduce the symptoms and help control some behavioral symptoms. These medications can work better in combination since they are both acting on separate mechanisms, the cholinesterase
inhibitors are preventing the breakdown of acetylcholine, and the statins are lowering cholesterol levels which have both been proven to help increase cognition.

Future studies and research should focus primarily on developing a safe and effective vaccine that works to prevent the onset of Alzheimer’s disease. Continuing to research the safety and effectiveness of intranasal insulin could potentially be beneficial in helping prevent progressive cognitive decline if found safe, but a preventative vaccine would be more beneficial, and therefore, research should focus on the vaccine. A vaccine that targets both the amyloid beta protein and the tau protein would be ideal in order to target both of the hallmarks of Alzheimer’s disease. Also the vaccine should be administered at the early stages of Alzheimer’s disease or in healthy patients in order to prevent the progression or the onset of the disease. The vaccine will be a crucial development since the cure for Alzheimer’s disease is in such high demand.
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