

12-8-2019

The Link Between Depression and Alzheimer's Disease

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NORTHERN ILLINOIS UNIVERSITY

The Link Between Depression and Alzheimer's Disease

A Capstone Submitted to the

University Honors Program

In Partial Fulfillment of the

Requirements of the Baccalaureate Degree

With Honors

Department Of

Biological Sciences

By

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DeKalb, Illinois

December 2019

**University Honors Program
Capstone Faculty Approval Page**

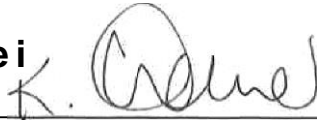
Capstone Title

The Link Between Depression and Alzheimer's Disease _____

Student Name Ania Waclawiak _____

Faculty Supervisor Dr. Katja Wiemer _____

Faculty Approval Signature i

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Department of Psychology _____

Date of Approval 12/05/2019 _____

**Date and Venue of Presentation Honors Capstone Presentations
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ABSTRACT

Depression has been linked to an increased risk of developing Alzheimer's Disease. Depression is a mood disorder that results in low mood, while Alzheimer's Disease is a progressive, neurological disorder that results in memory issues and difficulty with completing everyday tasks. The purpose of this research study was to determine what role depression plays in Alzheimer's Disease, how depression affects mild cognitive impairment, and what brain abnormalities are present in individuals with depression and Alzheimer's Disease.

To find out if depression increases Alzheimer's Disease, certain research experiments were reviewed to see what the results would indicate. After examining several literature sources, it was concluded that depression changes the brain circuitry in people; it causes brain changes in the frontal and limbic circuitry that can lead to amyloid production. Amyloid plaques are the findings in deceased Alzheimer's Disease patients. These changes in depression patients may lead to mild cognitive impairment. When individuals reach this stage of mild cognitive impairment, they have an increased risk of developing Alzheimer's Disease in the future.

The reason this correlation is important is because both disorders, depression and Alzheimer's Disease are genetic. Depression is a mood disorder that can be cured with antidepressants. Alzheimer's Disease, on the other hand, is a neurological disorder that doesn't have a cure. However, if depression really does increase the risk of individuals developing Alzheimer's Disease in the future, this is important to note because depression is something that can be cured. If depression can be cured, the risk of Alzheimer's Disease can be decreased.

To conclude, all these researchers were able to find out that depression indirectly affects Alzheimer's Disease. Depression causes mild abnormal brain dysfunctions that may lead to mild cognitive impairment. When individuals reach this stage, they have a higher risk of developing Alzheimer's Disease.

Alzheimer's Disease is a neurological disorder that stems from brain cell loss. It is a specific type of dementia. In fact, 60-80% of dementia cases are, specifically, cases of Alzheimer's Disease ("What is Alzheimer's?", 2019). People who experience Alzheimer's Disease tend to experience memory loss, confusion, difficulty with completing daily tasks, mood changes, and behavioral changes. Although this is not a normal stage in the aging process, it is the sixth leading cause of death in the United States ("What is Alzheimer's?", 2019). The worst thing about this disorder is that it progressively gets worse.

Depression is a type of mood disorder that affects many lives. It is characterized by sad mood, lost motivation, irritability, sometimes sleeping abnormalities, and sometimes eating abnormalities. It is commonly expressed in Alzheimer's patients during the early stages ("Depression", 2019). People who suffer from depression are prescribed selective serotonin reuptake inhibitors (SSRIs), most of the time. These medications help keep serotonin in the synapses for longer durations of time to help regulate happiness and anxiety.

There are some people who must live with depression, yet others must live with Alzheimer's Disease. Furthermore, another group of people are unfortunate enough to suffer from both depression and Alzheimer's Disease throughout their lives. About 40% of Alzheimer's Patients suffer from depression ("Depression", 2019). The problem is that people with Alzheimer's Disease have some cognitive impairment, so it is not necessarily easy for them to articulate their feelings when they are having symptoms of depression ("Depression", 2019). This means that more patients that suffer from Alzheimer's Disease may, also suffer from depression, but because of the lack of ability to communicate or distinguish these feelings, it is difficult to group them into separate categories.

The objective of this study is to figure out the link between depression and Alzheimer's Disease. Several key questions need to be answered to figure out this correlation, such as: does depression increase the risk of developing Alzheimer's Disease? What role does depression play in cognitive decline? Looking deeper into the brain, it is, also, important to distinguish the areas of the brain that are affected by depression and Alzheimer's Disease. To answer these questions, I first plan on reviewing the risk of Alzheimer's Disease in depression patients. Then, I plan on reviewing how depression affects cognitive decline. Finally, I plan on studying the different areas affected in depression and Alzheimer's Disease patients, individually.

Several studies have confirmed a connection between depression and Alzheimer's Disease. Certain case studies have confirmed that people that suffer from depression early on in their lives tend to have a higher risk of developing Alzheimer's Disease as they age. About 11% of the elderly suffer from depression, and about 19% of people in the United States suffer from major depressive disorder throughout their lifetimes (Steenland et al., 2012). The reason it is important to establish this linkage between the two is because people with depression should take certain approaches to eliminate their depression. In fact, depression is a treatable mood disorder that can be treated with antidepressants and therapy.

Analyzing family histories may help patients because both depression and Alzheimer's Disease have been linked to genetics, and both disorders seem to run in families. If people who are more prone to getting these disorders are aware of this, then they have a chance to take preventative measures. On the other hand, if they will, inevitably, get either one of these disorders,

they can be prepared, and they can know what to do when that day finally comes. Knowing these facts may, also, help decrease their risks of other disorders or diseases.

Both disorders are caused by abnormalities in the brain. However, the connection between the two disorders, and the decision as to whether depression causes Alzheimer's Disease, or whether Alzheimer's Disease is accompanied by depression is still a matter of discussion. Based off the studies that have been done, depression is a strong correlation factor relating to Alzheimer's Disease later in life.

People with late-life depression have been found to be less responsive to antidepressants and their brain functioning seems to be declining (Diniz B et al., 2013). Diniz and colleagues have found that people who suffer from depression had a higher risk of developing dementia, in general. In fact, vascular dementia and Alzheimer's Disease were the specific types that were more likely to be exhibited, too. However, vascular dementia was found to occur more often than Alzheimer's Disease in people that experienced late-life depression.

Because depression may have negative effects on a person's overall health, it is important to take steps to help decrease these negative effects. This can be an important step in providing an elderly person with a positive and healthy ending in life. Once somebody is aware of what is happening to their health and what measures they can take to stop it from worsening, then they can help themselves stay out of progressive disorders. Depression is found to influence a person's cardiovascular health, along with their mental health. So, if this person were to figure out what they are at risk for, they can treat that condition, and, in fact, help keep themselves from developing dementia, at the same time.

Vascular dementia is a type of dementia that affects the memory of the human brain. Now, Alzheimer's Disease is, also, an efferent factor for memory. The difference between vascular dementia and Alzheimer's Disease is that, in vascular dementia, there is impaired blood flow that deprives the brain of the "food" it needs to function properly. Over time, this may decrease somebody's cognitive capabilities, and, mostly, memory ("Differential Diagnosis of Vascular Dementia", 2019). Alzheimer's Disease, on the other hand, is a progressive type of disease, which, over time, will contribute to memory and cognitive damage.

Several studies have supported the idea that depression increases the risk of developing Alzheimer's Disease (Gracia-Garcia, Barnes, and Benoit). Gracia-Garcia and researchers were able to establish specific factors of people suffering from depression and specific depressive episodes that related to an increased risk of developing Alzheimer's Disease. On the other hand, Barnes and teammates were able to study the difference in the risk of developing Alzheimer's Disease between patients suffering from depression at different time points in their lives. Additionally, Benoit and colleagues studied the amount of people suffering from Alzheimer's Disease that, also, exhibited sign of apathy and depression to see which correlates to Alzheimer's Disease more than the other.

Gracia-Garcia and teammates have summed up certain factors that increase the risk of dementia and Alzheimer's Disease, such as: age, low educational background, apoE genotype, and lifestyle factors (Gracia-Garcia et al., 2015). They studied this correlation over the course of five years on people aged 55 years and older. This study has confirmed that untreated depression and first-time depression are strong correlating factors for developing Alzheimer's Disease. Certain

studies have, also, shown that the number of symptoms somebody suffers from during their depressive states positively correlates with an increased risk of developing Alzheimer's Disease.

When Gracia-Garcia and her team studied how depression might affect the risk of developing Alzheimer's Disease, they found that the patients that suffered from depression were usually: older, female, suffered from functional disabilities, diabetes, and vascular disease. They found that 18.6% of individuals who ended up having dementia were depressed (Gracia-Garcia et al., 2015). The incident rate of Alzheimer's Disease was high amongst individuals with severe depression, non-persistent depression, first-time depression, and untreated depression (Gracia-Garcia et al., 2015).

After all, they summed up the fact that people who suffered from depression had double the risk of contracting Alzheimer's Disease, while those who were severely depressed had a quadrupled risk (Gracia-Garcia et al., 2015). Untreated depression and first-time depression were proven to be risk factors, as well.

About 5.3 billion people in the United States suffer from dementia. Barnes and partners have mentioned that people suffering from depression have a doubled risk of developing dementia (E. Barnes et al., 2012). To prove this theory, they studied about 13,000 patients over the course of 45 years to make sure their long-term results confirmed what was believed. 20.7% of the people who did not suffer from depression ended up getting dementia after about 6 years. 23.5% and 31.4% of those who suffered from mid-life and late-life depression, respectively, ended up getting dementia (E. Barnes et al., 2012).

Patients who suffered from both, mid-life and late-life depression ended up increasing their dementia risk by 80%, which is a lot higher risk than either depressive stage, individually (E. Barnes et al., 2012). Barnes' team confirmed that people who suffer from late-life depression have a doubled risk of getting Alzheimer's Disease, along with a 50% chance of getting diagnosed with vascular dementia, as well (E. Barnes et al., 2012). Patients who suffered from both stages of depression remained at a doubled risk of getting diagnosed with Alzheimer's Disease, but a triple risk of getting diagnosed with vascular dementia (E. Barnes et al., 2012).

These results suggest that people who are diagnosed with mid-life depression still can lower their dementia risks if they take the proper precautions because the risk increases with late-life depression. Even so, patients who are diagnosed with dementia earlier have the possibility of helping their memory by taking memory-enhancing drugs which might slow their progressive disorder (E. Barnes et al., 2012). Long-term depression has been proven to cause cerebrovascular disease that may predispose people to dementia (E. Barnes et al., 2012). Damage to the hippocampus can, also, have negative effects on the human brain, and the factors that cause this damage can be prevented to help decrease people's chances of getting diagnosed with dementia (E. Barnes et al., 2012).

Benoit and colleagues have, also, confirmed that apathy and depression are the two neuropsychological symptoms that lead to Alzheimer's Disease (Benoit et al., 2012). Patients who suffer from mild cognitive impairment (MCI) and Alzheimer's Disease (AD) have a fair percentage of apathy as part of their symptoms. They found a couple tell-tale signs that a lot of AD patients experienced (ranging from most experienced symptom to less experienced symptom): fatigue, decreased pleasure, agitation, and depressed mood. About 42% of the patients experienced

apathy, while about 49% experienced depression (Benoit et al., 2012). Even though other groups have been able to establish a concise answer, Benoit and teammates were unable to declare which affects AD more, depression or apathy. However, they were able to note that both were highly prevalent in patients that suffer from AD.

People suffering from depression show a morphological brain change in certain areas, such as the areas affecting mood and memory. The prefrontal cortex is an area of the brain that may decrease in size in depressed individuals, depending on the level of their episodes, and this is the area that lacks function in depression ("Stress, Depression and Brain Structure - Depression and Bipolar Support Alliance", 2019). Dementia is a type of disorder that stems from the loss of brain cells. This brain cell loss in certain areas of the brain is what causes cognitive decline.

People who suffer from dementia end up suffering from memory loss that may incur because of certain areas in the brain that have lost brain cells. The health staff that study this disease have found that dementia occurs when the frontal cortex is affected by brain cell loss, which affects memory and behavior ("Areas of the brain affected by Alzheimer's and other dementias", 2019). The link between depression and dementia is clearly visible as they both affect certain areas in the brain and cause abnormal functioning in these areas that takes on to abnormal behaviors.

Rapp and his teammates have mentioned that 30 to 50% of people who suffer from dementia, also, suffer from depression (Rapp et al., 2011). Depression takes a toll on the brain, and effects its functioning. This, in turn, can possibly lead to abnormal changes in the brain that cause dementia and Alzheimer's Disease. Previous studies have shown that people who suffer from depression later in life have changes in deep frontal white matter and hippocampal structural changes from imaging (Rapp et al., 2011). Studies have, also, shown that people who have taken anti-depressants to treat their depression still have impaired memory function in their elderly age. Increased plasma amyloid levels are shown for people suffering from geriatric depression, which is a connection that can be drawn between depressed people and those suffering from dementia (Rapp et al, 2011).

After studying 313 patients from a nursing home, the results stated that 40.1% of the residents that suffered from dementia made the progression to Alzheimer's Disease, as well (Rapp et al, 2011). There were other residents that suffered from other types of dementia, but Alzheimer's was the most prevalent. The patients who did suffer from major depression at any time during the study, along with dementia have found to have steeper cognitive decline (Rapp et al, 2011). When comparing the results from the mini mental state examination (MMSE), patients who experienced depression lost 2.7 points extra along with the 13.7 points lost in patients suffering from dementia (Rapp et al, 2011). Opposed to other studies, they did note that a history of depression was not enough to alone account for the cognitive decline experienced.

To summarize, Barnes, Benoit, Diniz, Gracia-Garcia, and Rapp all agree that people who suffer from depression may progress to the stage of Alzheimer's Disease at some point in their lives. These studies have proven that people who suffer from depression, at least, double their risks of developing some type of dementia, particularly, Alzheimer's Disease. Now, people who suffer from dementia, may develop depression because of the disease. However, these studies considered previous depressive episodes and their effect of dementia down the line.

Barnes and Yaffe have estimated that about 10% of the people with Alzheimer's Disease can attribute the disease to their depression (Steenland et al., 2012). Steenland and partners concluded that patients who have experienced depression in the past were the ones who experienced the mild cognitive impairment (MCI) in the present. 38% of patients that suffered from MCI progressed to AD (Steenland et al., 2012). However, once the cognitive impairment is present, depression plays less of a role in cognitive impairment. This was shown by decreased progression in people who started from MCI and progressed to AD compared to those people who began at normal cognition (Steenland et al., 2012). This was the only progressive phase; the patients that suffered from MCI and depression during the time of the study were the ones that progressed to Alzheimer's. Past depression and treated depression did not affect this progression.

The connection drawn here is that both, depression and MCI cause cognitive deficits. People that suffer from depression but help themselves in some way lower their chances of progressing to MCI. Depression is a mood disorder that people can grow out of, so to say. However, when patients reach the level of MCI, there is not turning back, necessarily. Steenland and colleagues were trying to make it noted that depression might not play a direct role in causing Alzheimer's Disease, but it can affect somebody's cognitive impairment.

Other studies have examined how depression affects the cognitive functioning of its patients (Steenland and Sugarman). First off, Steenland and colleagues were able to study the amyloid plaques associated with depression patients. On the contrary, Sugarman and researchers focused more on MCI in certain patients and how that level of cognitive dysfunction leads to dementia.

Amyloid plaques are said to form about a decade before the cognitive impairment is completely noted (Steenland et al., 2012). The reason this is noteworthy is because if somebody suffers from a risk factor that causes this cognitive deficit, it is important to understand whether something can be done, so that the individual does not progress to the next, worse, level (Steenland et al., 2012). Depression has been found to alter sleep, the frontal, and the limbic circuitry, so that means that this may change the amyloid production. Because of this evidence, depression may be a culprit for the decline in cognitive functioning, that may contribute to Alzheimer's Disease.

Mild cognitive impairment is the second step in a three-step staircase that features normal cognition at the bottom and Alzheimer's Disease at the top. This is the step where cognitive decline begins, but the functional decline that occurs with Alzheimer's Disease is still absent (Sugarman et al., 2018). This is a good method to predict whether a certain person is more likely to progress to Alzheimer's Disease or not. Neuropsychiatric symptoms, such as depression, anxiety, and apathy are more likely to push somebody upward from step one to step two and place them in the MCI range (Sugarman et al., 2018). These symptoms that may take place are usually comparable to the pathology of Alzheimer's Disease.

An interesting observation is that people who fit the following factors: are younger, female, have good memory, are absent of the *APOE ε4* allele, and show more functional engagement, amongst others, are more likely to revert from MCI to normal cognition (NC) (Sugarman et al., 2018). There is instability in the MCI range because of this reversion that may occur in some individuals.

Sugarman and colleagues described the hypothalamic-pituitary-adrenal (HPA) axis, when it functions abnormally during times of stress, glutamate excitotoxicity may occur and signal cell death in the hippocampus. In turn, this produces A β (amyloid beta) in the hippocampus; in fact, people with depression, also, have an increase in their A β levels. Given this information, these neuropathological similarities might be the reason for people with depression having an increased risk of developing AD (Sugarman et al., 2018).

The results that accumulated showed that 1121 out of 6763 patients reverted from NC to MCI, and 242 of those progressed to dementia (Sugarman et al., 2018). Severe depression was found to increase the progression to the AD diagnosis. Patients who rid themselves of depression seemed to return to NC. This shows that anti-depressant treatments can work, and even stop the progression to another worse disease. Patients with MCI are more likely to reverse back to normal cognition if they receive an MCI diagnosis, have a reduction in self-reported depressive symptoms, and experience less anxiety and other mood inconveniences (Sugarman et al., 2018). However, about 30% of patients that reverted to NC from MCI, made it back to an MCI diagnosis in the future.

Fernandez and colleagues have mentioned that the prevalence of depression in AD is about half. Among the most common symptoms that highlight cognitive decline are lack of concentration, tremors, and depression with each symptom occurring in about half of the population. More than 90% of AD patients experience, at least, one of the symptoms that relate to cognitive decline. However, this team noted that no correlation has been found between MCI and depression, which is something the other researchers stipulated. Now, depression may be an indirect factor throughout any time of the process of AD. (Fernández et al., 2010)

Fernandez, Steenland, and Sugarman, agree that depression might not necessarily, directly, contribute to Alzheimer's Disease. However, depression does have some cognitive effects that may contribute to the brain morphologies that can lead to mild cognitive impairment. Depression and apathy can change the brain to a form that will lead to mild cognitive impairments. A lot of times, the people that do move from normal cognition to mild cognitive impairment may revert to normal cognition when their depressive symptoms get better. However, a lot of times, these reversions will correct themselves and these people will end up suffering from some sort of cognitive impairment in the future that can cause other disease states at the end.

To compare, MCI is a step in the continuum to Alzheimer's Disease. All these researchers successfully demonstrated that MCI can lead to Alzheimer's. However, preceding this step, certain changes must take place in the brain for cognitive decline to occur. For the occurrence to be present, people either must suffer from depression or another neurological impact that may cause abnormal changes in the brain, and the synapses that control the functioning.

Finally, the last groups of studies that have been done investigated the brain abnormalities that lie amongst patients suffering from depression and Alzheimer's Disease (Chakroborty, Palop and Mucke, and Van Mussele). Chakroborty's team took their studying to the brain's synaptic functions and their dysfunction in Alzheimer's Disease. Second, Palop and Mucke considered the amyloid plaques that occur in Alzheimer's Disease patients and their relationship to Alzheimer's Disease symptoms. Lastly, Van Mussele and his team studied the differences between the risk of developing Alzheimer's Disease in amnesic versus non-amnesic patients. They, also, related certain biomarkers to developing Alzheimer's Disease.

Alzheimer's Disease is a neurodegenerative disease that has been affiliated with endoplasmic reticulum (ER) calcium signaling impairments (Chakroborty et al., 2012). Synapses of the brain are areas where a lot of molding takes place that is calcium-dependent; these are, also, the areas that encode for memory and learning dysfunctions when they function abnormally (Chakroborty et al., 2012). The degree of synapse impairment relates to the different degrees of Alzheimer's Disease. Chakroborty and colleagues did some research on mice and found that mice showing symptoms before the onset of AD had reduced calcium induced calcium release (CICR) (Chakroborty et al., 2012). The point researchers were trying to make is that, even though this calcium signaling is abnormal compared to other mice, they don't experience any other symptoms and their brain pathology seems quite normal.

Even though this reduced calcium ability in synapses may create little worry, they can have detrimental cognitive consequences later when other synaptic breakdowns begin to take place. To start, the pre-synapses can lose their efficacious properties and reduce the ability of calcium to help release neurotransmitters in the synapse. When the brain is functioning under normal consequences, the CICR helps move vesicles from the storage area to the releasing area; this helps keep vesicles on hand for rapid release whenever releasing is needed. When CICR becomes sensitive, it begins to do this at a faster pace, which removes vesicles from storage quickly, but then reduces the probability of these vesicles ever being released (Chakroborty et al., 2012). With this process taking place long-term, this becomes a metabolic stressor that may, potentially, degrade synapses. Since there is this degradation of these synapses, new memories and learning are unable to take place, so cognitive decline occurs (Chakroborty et al., 2012).

Palop and Mucke are two other researchers that explained that amyloid- β ($A\beta$) plaques may gather in the brain, and then cause synapse dysfunction. These plaques are formed by amyloid oligomers. Synapse dysfunction is prevalent in Alzheimer's patients (Palop & Mucke, 2010). Evidence suggest that high glutaminergic synaptic transmission loss is caused by these plaques. These plaques reduce the efficiency of the pre-synapses, and depress the post synapses (Palop & Mucke, 2010). Any abnormal working of synapses can be devastating as these firings have to be modulated, so that neuronal activity is controlled.

The hypoactivity or the hyperactivity of brain neurons lead to brain dysfunction as they must be modulated accordingly. Imaging shows lowered activity in certain brain areas, which means a decrease in synapse firing (Palop & Mucke, 2010). High concentrations of $A\beta$ lead to excited activity in the brain, but inhibitory activity dealing with learning and memory formation (Palop & Mucke, 2010). This excitation in the brain may, possibly, elicit seizures. However, this excitation is not what causes consequences in and of itself, but it leads to synchrony amongst the glutamatergic synapses that elicit their activities consequently (Palop & Mucke, 2010).

Referencing back to MCI, the middle step between normal cognition and dementia, this introduces amnesic and non-amnesic subtypes. Van Mussele and researchers have found that 5-10% of the population with MCI progresses to dementia. However, they, also, made the distinction that amnesic patients are more likely to progress to Alzheimer's Disease, but non-amnesic patients are more likely to progress to other types of dementias.

When this team put this correlation to the test, they found that 46% out of the 235 patients that had MCI progressed to Alzheimer's Disease in about 2 years (Van der Mussele et al., 2014). Through their investigation, they found out that patients with depression were more likely to

progress to Alzheimer's Disease. Another study tool this team used were cerebrospinal fluid (CSF) lumbar punctures to measure how many had AD biomarkers, and the results stated that 42% of the patients had these signs that would, ultimately, lead to AD (Van der Mussele et al., 2014). Based on testing, verbal agitation and actions that have no purpose may, also, lead to AD in the future. One odd note that should be mentioned is that the diurnal rhythms in patients had no effect on their progression to AD, which is out of the ordinary because people who suffer from AD, typically, suffer from sleep disturbances, as well (Van der Mussele et al., 2014).

To explain why verbal agitation leads to AD, deeper thinking into the brain is a must. Patients that have AD usually have depression present at some point in their continuum. People that suffer from depression have lower serotonergic activity, and because these neurons control dopaminergic neurons, their effects diminish, as well. Because the dopaminergic neurons are present in the frontal-subcortical circuitry and control the functions of the frontal lobe, it makes sense that these impairments cause apathy and agitation (Van der Mussele et al., 2014).

Chakroborty, Fernandez, and Palop all took a deeper look into the underlying brain morphology that occurs that may cause cognitive decline. They all noticed that the signaling pathways in the brain have to do with synapses, and these synapses can decline overtime, which leads to cognitive defects. Certain symptoms, such as depression and apathy take on a huge roll in these circumstances. These symptoms may impact the brain and cause abnormalities in these signaling pathways. In the end, these abnormalities will cause other brain changes that may translate into dementia and Alzheimer's Disease, especially when these downregulated synapses must contribute to memory and mood.

To conclude, these studies have successively shown that patients that suffer from depression may have an increased chance of developing mild cognitive impairment. This impairment may be reverted to normal cognition, however, the presence of it senses that mild cognitive impairment will appear again in a person's lifetime. The impairment that occurs in patients who suffer from depression and apathy is something that interferes with the brains normal functioning. This, then, sets up the brain for a path that goes down a downward slope into the area of dementia, and, ultimately, Alzheimer's Disease. People who suffer from Alzheimer's disease tend to have some form of cognitive impairment plus functional disabilities. People with this disease are no longer able to function independently.

Reviewing the objective questions listed in the beginning of this research study, all three were able to be answered with these researcher's experiments. Depression can increase the risk of developing Alzheimer's Disease, indirectly. However, depression directly affects the cognitive decline of its victims. Lastly, amyloid-beta plaques and dysfunctional synapses may occur in connection with the cognitive decline in Alzheimer's Disease patients.

A lot of these publications have mentioned certain limitations that had to be considered with their experimentations. For the groups who studied the effect of depression on Alzheimer's Disease, most of them mentioned that a lot of depressive symptoms may have been misdiagnosed, or underdiagnosed because people who do suffer from Alzheimer's Disease and depression may have mixed symptoms. The groups that studied the effect of mild cognitive impairment on Alzheimer's Disease mentioned that the sample size of the patients was quite small. Their conclusions were drawn on small sample sizes, which could have erroneously produced unfair results. Antidepressants may have, also, have had an effect, but not everybody takes

antidepressants, solely, for depression. When it came to the details of the brain network that is affected by cognitive impairment, these researchers stated that the next stages in these studies would be to figure out how to manipulate the plaques to see their effects, see the severity of the effects with these manipulations, and test certain drugs to see how they can effect this progression to Alzheimer's Disease.

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