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Alzheimer's and Patient Caregiver Burnout: A Comprehensive Review of the Literature

An Honors College Project Presented to

the Faculty of the Undergraduate

College of Health and Behavioral Sciences

James Madison University

by Madeline Jane Hekeler

April 2021

Accepted by the faculty of the Management Department, James Madison University, in partial fulfillment of the requirements for the Honors College.

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PUBLIC PRESENTATION

This work is accepted for presentation, in part or in full, at The Honors Symposium on April 23, 2021.

“You are my sunshine, my only sunshine

You make me happy when skies are gray

You'll never know dear, how much I love you

Please don't take my sunshine away’

-Johnny Cash

To my beautiful grandma, my sunshine, who

is currently suffering with Alzheimer’s

and to the rest of my family who have shown nothing

but grace, hope, and unconditional love during this time.

To all the families out there hoping to find a cure.

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Acknowledgements

I would like to begin by thanking James Madison University Honors college for pushing me out of my comfort zone and igniting a new found love for research in the medical community. Next, this project would not have been possible without the unconditional guidance and support from my thesis advisor, Dr. Audrey Burnett. Dr. Burnett has been my favorite professor since my sophomore year when I took her infectious disease class. Getting the opportunity to work with her on the project was an extreme honor. She has shown me nothing but kindness, support, and wisdom through the craziness of writing my thesis during COVID-19. I would also like to thank my readers, Dr. Erika Metzler Sawin and Ms. Laura Blosser, for their feedback and support. Their unique perspectives and insights strengthened my thesis and they have been so encouraging throughout the entire process!

Lastly, I would like to thank my family and friends, especially my amazing parents. Thank you for always believing in me and fostering a confidence and passion in me to work hard and pursue my biggest dreams with no boundaries.

Abstract

The term ‘silent epidemic’ has become fitting for Alzheimer’s disease, as it is now the sixth leading cause of death in the US. Caring for AD patients at home in the US costs billions of dollars each year. The current comprehensive literature review discusses the background/history of AD, pathology and modes of transmission of AD, behavioral and natural risk factors, prevention and treatment options, and how the aforementioned factors contribute to caregiver burnout and subsequently affect the AD patient. The extensive examination of the literature determined several gaps to be addressed. More specifically, burnout among AD caregivers has become an epidemic of its own, and caregivers are experiencing increasing fatigue, stress, and financial burden. There have been several means identified to assess caregiver burnout, as well as associated interventions that have shown effectiveness among patients and their families. Nevertheless, further longitudinal research is warranted on the implementation of more effective interventions specifically for caregivers, including stress management and social support mechanisms.

Chapter One: Introduction

Imagine yourself looking into a mirror, staring at your reflection. Upon reflection, you see the basic outline of a human being, but everything else is unfamiliar to you. You rack your brain trying to put the pieces together, grasping at any hindrance of a memory. Every fiber of your being that makes you a unique individual in this world has slowly disappeared. The aforementioned scenario describes a terrifying thought and is what the five million Americans who are living with Alzheimer's disease, AD, have to go through on a daily basis. AD is "a progressive disorder that causes brain cells to waste away (degenerate) and die; it is a continuous decline in thinking, behavior and social skills that disrupts a person's ability to function independently" (Mayo Clinic, 2018, para.1). According to the Alzheimer's Association (2019), it is the sixth leading cause of death in the United States, which means the disease has high prevalence and incidence rates in the US. In a study conducted by Cambridge University, it was determined that "the overall point prevalence of dementia due to AD among individuals 60+ was 40.2 per 1000 persons (Cl95%: 29.1-55.6), and the incidence rate was 15.8 per 1000 person-years ($CI_{95\%}$: 12.9-19.4)" (Fiest, Roberts, Maxwell, Hogan, et al., 2016, para. 3).

AD is the most common type of dementia, not only in the United States, but in other parts of the world. It is important for individuals to understand the difference between AD and dementia. The term *dementia* serves as an umbrella term for when "a cognitive skill becomes impaired so much that a person can no longer get along independently; cognitive problems are acquired meaning that the person was functioning at a higher level prior to developing dementia" (Alzheimer's Association, 2019, para. 1). There is a lot of confusion between dementia and AD, since AD can be suspected in a patient, but cannot be officially diagnosed until after the patient has died and an autopsy of the brain has been performed. During an autopsy, the coroner

examines the brain thoroughly, specifically looking for ‘plaques’ and ‘tangles’ in the brain that will ultimately confirm the diagnosis (Ellison & Center, 2019, para. 4).

Even after an autopsy, it is difficult to know if AD is what killed the patient, since most patients have at least one comorbidity. Due to the many unknown facts about the disease, a significant question that doctors face is when to blame death on AD. In an interview with Susan Mitchel, a professor of medicine at Harvard and a scientist at Hebrew SeniorLife Institute for Aging Research, she states “many death certificates still list pneumonia or some other disease as the cause of death, even when the underlying problem is Alzheimer’s. So even the statistics that show dementia increasing as a cause of death are a gross underestimate” (Hamilton, 2013, para. 8).

The fight against AD began over 100 years ago, the first case being diagnosed in 1906 by Dr. Alois Alzheimer. Since then, countless hours have been devoted to laboratory and clinical research pertaining to the disease in an attempt to gain a better understanding of its pathology, modes transmission, and possible risk factors. The number of deaths this disease causes has had a continuous increase since the first diagnosis. The Alzheimer's Association (2019) states that “since 2000 and 2018, deaths from Alzheimer’s have increased 146%” (para. 1). The Alzheimer's Association (2019) also determined that, “one in three seniors dies with Alzheimer’s or another dementia and almost two-thirds of Americans with Alzheimer's disease are women” (para. 1).

For over a hundred years, this disease has inflicted tremendous suffering on the global population with still no cure to be found. Maria Carillo, a neuroscientist with the Alzheimer’s Association, describes this disease as, “an epidemic, it’s on the rise, and currently there is no way to delay it, prevent it, or cure it” (Hamilton, 2013, para. 3). More recently, the term epidemic has

been applied to chronic disease or even behaviors (e.g., opioid abuse). While AD is not an infectious disease, the nature of the chronic disease continues to increase and infect more people over time.

AD not only has a tragic impact on the individuals who have been diagnosed with the disease, but also on the individual's family, friends, and loved ones who are faced with the pressures of providing physical care, emotional support, and dealing with the financial burdens that are associated with chronic illness. The caregiving experience can be very overwhelming at first, particularly since most caregivers are related to the individual suffering with the disease and have no prior training. The main role of a caregiver is to develop the necessary skills that are needed to deal with the interpersonal demands of the individual due to their cognitive decline. Watching a loved one diminish before one's eyes takes a toll on one's physical and mental health (Sörensen & Conwell, 2011, para. 1).

The medical community uses the term *compassion fatigue* to describe caregivers who experience burnout. Compassion fatigue is "the physical and mental exhaustion and emotional withdrawal experienced by those who care for sick or traumatized people over an extended period of time" (Merriam-Webster, n.d, para. 1). Burnout is the "prolonged response to chronic emotional and interpersonal stress on the job that is often the result of a period of expending excessive effort at work while having too little recovery time" (Chuang et al., 2016, para. 1). According to the Alzheimer's Association (2019), "there are more than 16 million caregivers of people living with Alzheimer's and other dementias in the United States" (para. 6). It is imperative that caregivers take care of not just their loved ones, but also themselves, especially dementia and AD caregivers. In a study conducted by Sörensen & Conwell (2011), they found

that “dementia caregivers report higher levels of stress, more depression and anxiety symptoms, and lower levels of subjective well-being, self-efficacy, and anxiety” (para. 3).

Over the last decade, the baby boomer generation has been reaching retirement age, meaning that 15 percent of the United States population is now considered senior citizens (Froese, 2009). Since age is still the greatest risk factor known for developing AD, there is an exponential increase in the numbers of possible cases due to the baby boomer generation reaching age 65. The increase in cases also increases the number of caregivers, professional or family-related, which are needed to aid the affected individual through their cognitive decline. According to the Alzheimer's Association (2019), “50% of primary care physicians believe the medical profession is not ready for the growing number of people with Alzheimer's or other dementias” (para. 7).

In a report from UsAgainstAlzheimer’s (2017), AD is the most expensive disease, with the United States having “vastly underestimated the public costs and consequences of the Alzheimer’s epidemic, and major social trends have direct and adverse implications for our capacity to cope with the Alzheimer’s epidemic in the years ahead” (para. 5). In 2020, the total cost for caring for AD patients in the United States is around $305 billion dollars, and that number is expected to increase to $1.1 trillion dollars by 2050 (Alzheimer's Association, 2019). Family-related caregivers also do not usually receive a salary, which is “an estimated 18.6 billion hours of unpaid care, a contribution to the nation valued at more than $244 billion” (Alzheimer's Association, 2019, para. 8).

Insurance companies have been working hard to do their part in aiding individuals who experience financial burdens associated with AD. However, “Medicare and Medicaid only cover $175 billion, or approximately 68% of the out-of-pocket healthcare costs"

(UsAgainstAlzheimers, 2017, para. 6). AD patients also pay 23 times more in Medicaid payments, and that cost is expected to increase by 330% by 2050; that is three times greater than individuals who do not suffer from AD (UsAgainstAlzheimers, 2017). Clinical trials and research are constantly being conducted in hopes of finding a cure in order to reduce the out-of-pocket health care costs and reduce the projected $1.1 trillion cost for the United States (UsAgainstAlzheimers, 2017, para. 6).

A significant issue with the research to find a cure for AD is that federal funding is low compared to funding research for other major health issues. In fact, “for every dollar the federal government spends today on the costs of Alzheimer’s care, it invests less than a penny in research to find a cure.” (UsAgainstAlzheimers,2017, para. 7). An increasing number of people are being diagnosed with AD; in fact, every 65 seconds, a person in the United States is diagnosed with a stage of AD (UsAgainstAlzheimers, 2017, para.1). AD funding needs to become a priority for the United States in order to slow the epidemic.

While a cure is being examined, it is imperative that prevention measures are being implemented and that communities are being properly educated on all aspects of this disease. AD is a very unique and dynamic disease with a vast diversity in different symptoms each patient experiences. Educating communities is important for early identification of the disease, as well as starting the slowing down of progression with the five medications that have been approved by the Food and Drug Administration to treat AD (UsAgainstAlzheimers, 2017). Increasing epidemiological surveillance is imperative to finding a cure, and many organizations have been formed to help.

The National Institute on Aging (NIA) was established in 1974 by Congress and has been fundamental in the progress of AD research. The organization is responsible for declaring the

month of November as the National AD month, which has helped educate communities all over the United States. In 2003, the National Institute on Aging conducted a genetic research study to find genetic markers that are associated with AD. This study was important because it allowed individuals to know if they were genetically inclined to developing AD. President Barack Obama signed the National AD Project Act in 2011, which connected the nation in providing support and funding towards AD research (History of Alzheimer's, 2019). There is still a lot of progress that needs to be made, but there have been plenty of successful steps in the right direction.

The objective of this project is to create a comprehensive literature review and systematic review of: a) background/history of AD, b) pathology and modes of transmission of AD, c) behavioral and natural risk factors, d) prevention and treatment options, and e) how the factors above contribute to patient caregiver burnout and subsequently affect the AD patient. Education is key in stopping this epidemic and finding a cure for a disease that affects 5.7 million people in the US (UsAgainstAlzheimers, 2017).

Chapter Two: Comprehensive Overview of Alzheimer's Disease

History of AD

Alois Alzheimer was a neurology research assistant at Munich medical school, where he conducted clinical and research practices to study all parts of the brain. In 1906, he was studying a middle-aged woman's brain when he first discovered:

> an unusual disease of the cerebral cortex which causes memory loss, disorientation, hallucinations, and ultimately death. The cerebral cortex was thinner than normal and senile plaque, previously only encountered in elderly people, was found in the brain along with neurofibrillary tangles (Alzheimer's Disease International, 2020, para. 3).

Since Alois Alzheimer was the first person to discover the strain of nerve tangles that causes severe cognitive decline, his research mentor, Emil Kraeplin, named the disease after him. AD has become one of the most prevalent diseases in the world since its first discovery over 100 years ago (Alzheimer's Disease International, 2020, para. 4)

Pathology of AD

AD is very complex, which is why scientists have a difficult time understanding why it happens. The main factors associated with AD are 'plaques' and 'tangles,' which are found in the cerebral cortex of the brain. Amyloid plaques are "hard, insoluble accumulations of beta amyloid proteins that clump together between the nerve cells (neurons) in the brain" (BrightFocus Foundation, 2020, para. 1). Amyloid plaques are found in all brains; however, in healthy brains, they are able to be broken down and removed naturally since there is no beta buildup. Beta amyloid plaques build up when "the enzyme that cuts APP into beta amyloid is not very precise and can also result in slightly larger strands that do not dissolve" (BrightFocus Foundation, 2020, para. 2). Neurofibrillary tangles are

> insoluble twisted fibers found inside the brain's cells that consist primarily of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another (BrightFocus Foundation, 2020, para. 4).

BrightFocus Foundation (2020) shows that, in AD patients, "the tau forms a C-shape in the core of the tangle with a loose end sticking out randomly and once a tangle has been started, more tau proteins are recruited to make it longer" (para.5).

The beta amyloid plaques and neurofibrillary tangles cause not only a disruption in the connection between neural pathways, but "causes them to die, possibly by triggering an immune response in the immediate area" (BrightFocus Foundation, 2020, para. 6). The nervous system is a complex system of neurons that are electrically excitable, not just in the brain, but throughout the entire body. Neurons are crucial to the overall function of the body's nervous system because they "transmit messages between different parts of the brain, and from the brain to muscles and organs in the body" (National Institute on Aging [NIA], 2019, para. 6).

There are three types of neurons: sensory, motor, and interneurons. Sensory neurons are "responsible for converting external stimuli from the organism's environment into internal electrical impulses," motor neurons "project to the spinal cord or outside of the spinal cord to directly or indirectly control effector organs, mainly muscles and glands," and interneurons "acts as an intermediary in passing signals between two other neurons with no motor or sensory function" (Khan Academy, 2018, para. 9). AD patients will eventually forget how to perform everyday functions, such as eating, walking, and speaking, because the neurons responsible for transmitting those messages are continuously dying.

Vascular issues also contribute to the rapid cognitive decline that AD patients experience. The vascular system, or circulatory system, is an

> organ system that permits blood to circulate and transport nutrients (such as amino acids and electrolytes), oxygen, carbon dioxide, hormones, and blood cells to and from the cells in the body to provide nourishment and help in fighting diseases, stabilize temperature and pH, and maintain homeostasis (Johns Hopkins Medicine, 2020, para. 2).

AD patients have increased inflammation in their arteries and veins because of the beta-amyloid plaques and neurofibrillary tangles. This inflammation weakens the brain-blood barrier, which reduces the flow of blood and oxygen throughout the brain. A lack of blood and oxygen in the brain can lead to other medical complications, such as multiple strokes (BrightFocus Foundation, 2020, para. 9).

AD starts affecting the brain ten years before symptoms present themselves. This early symptom onset is known as the preclinical stage, where undetectable toxic changes occur, such as "abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain" (National Institute on Aging [NIA], 2019, para. 7). The part of the brain that is affected first is the hippocampus and the entorhinal cortex. The hippocampus is "involved in the formation of new memories and is also associated with learning and emotions" (Anand & Dhikav, 2012, para. 1). The entorhinal cortex "plays an important role in pattern recognition and encoding of memories" (Anand & Dhikav, 2012, para. 10). The disease will then spread to the cerebral cortex, which is responsible for language, reasoning, and social behavior. Eventually, all parts of the brain will become diseased, leading to fatality (National Institute on Aging [NIA], 2019, para. 8).

Stages of AD

There are three evident stages of AD that are determined by the level of the individual's function. During the first stage, early-stage AD, an individual can still perform daily functions independently, but feel like they are having memory lapses and increasing forgetfulness. An individual in this stage may experience difficulties with

> coming up with the right word or name, remembering names when introduced to new people, having difficulties performing tasks in social or work settings, forgetting material that was just read, losing or misplacing an object, and experience increased trouble with planning and organizing (Alzheimer's Association, 2019, para. 7).

It is recommended that an individual in this stage makes legal, financial, and end-of-life decisions while they are still cognitive in the decision-making process.

Moderate AD, middle-stage AD, is when symptoms become more prevalent, and the patient is very aware of their cognitive decline. This is the longest stage of the disease, and can last for many years, depending on the individual (Alzheimer's Association, 2019). An individual in this stage may experience difficulties with

> being forgetful of events or personal history, feeling moody or withdrawn, especially in socially or mentally challenging situations, being unable to recall information about themselves, experiencing confusion about where they are or what day it is, having trouble controlling their bladder and bowels, experience changes in sleep patterns, and showing an increased tendency to wander and become lost (Alzheimer's Association, 2019, para. 9)

Since the individual is aware of their cognitive decline, there will mostly be evidence of personality and behavioral changes, such as increased aggravation and anger toward others.

Individuals in this stage will need caregiving as the disease continues to progress (citation needed here).

The last stage of AD, severe (late-stage) AD, is when an individual's memory and cognitive skills have rapidly declined, and they are no longer able to function independently. This is the final stage of the disease, when the patient's symptoms have reached their full potential. An individual in this stage may "require around-the-clock assistance with daily personal care, lose awareness of recent experiences as well as of their surroundings, experience changes in physical abilities, including walking, sitting and, eventually, swallowing, have difficulty communicating, become vulnerable to infections, especially pneumonia" (Alzheimer's Association, 2019, para. 10). Caregivers are most needed at this stage for assisting in daily function, emotional support, and companionship.

Age and Genetic Risk Factors

There are many factors associated with AD that put people at a higher risk of developing the disease during their lifetime. Age is the greatest risk factor known for AD, and as an individual ages, the likelihood of developing AD increases. Susanne Wegmann of the German Center for Neurodegenerative Diseases (DZNE), discovered that older people are more susceptible to the disease, because "certain molecules involved in the disease, termed tau proteins, spread more easily in the aging brain" (Wegmann et al., 2019, para. 1). Wegmann and her colleagues studied tau propagation for years using a gene vector that "channeled the blueprint of the human tau protein into the brains of mice" (Wegmann et al., 2019, para. 3). Wegmann determined that "human tau proteins spread about twice as fast in older mice as compared to younger animals" (Wegmann et al., 2019, para. 3).

While older people are more susceptible to developing AD, people younger than 65 can develop early onset AD. According to the Alzheimer's Association (2019), "up to 5 percent of the more than 5 million Americans with Alzheimer's have younger onset" (para 1). Early-onset AD is related to genetic factors, which is the next most significant risk factor for developing AD. The Mayo Clinic (2018) states, "your risk of developing Alzheimer's is somewhat higher if a first degree relative, parent or sibling, has the disease. An individual is at greater risk if more than one first degree relative has the disease" (para. 27). Risk genes and deterministic genes are the two categories of genes that determine if a disease will develop in an individual. Risk genes "increase the likelihood of developing a disease but do not guarantee it will happen," while deterministic genes "directly cause a disease, guaranteeing that anyone who inherits one will develop a disorder" (Alzheimer's Association, 2019, para. 5).

Scientists have found several risk genes that contribute to AD. The first identified gene was the APOE-e4 gene. The function of the APOE-e4 gene is to "provide instructions for making a protein called apolipoprotein E. This protein combines with fats in the body to form molecules called lipoproteins" (National Institutes of Health [NIH], 2018, para 1). Individuals who have this gene have an increased risk of developing AD, because "researchers have found that this allele is associated with an increased number of protein clumps, called amyloid plaques" (NIH, 2018, para. 3). According to the Alzheimer's Association (2019), "an estimated 20-30% of individuals in the U.S. have one or two copies of APOE-e4; approximately 2% of the U.S. population has two copies of APOE-e4." It is important to understand that not all people who have this allele will develop AD, nor do all AD patients have this allele. An individual does have the option to get genetically tested to see if they are a carrier of the allele (NIH, 2018, para. 4.)

Familial AD is when an individual has a deterministic gene that guarantees the development of AD at some point in life. Scientists have discovered three genetic protein variations that will result in AD: amyloid precursor protein (APP), presenilin-1 (PS-1), and presenilin-2 (PS-2) (Wegerer, 2014). According to the Alzheimer's Association (2019), "these genes, which are estimated to account for 1% or less of Alzheimer's cases, cause familial early-onset forms in which symptoms usually develop between a person's early 40s and mid-50s" (pg. 3, para. 2.).

The amyloid precursor protein (APP) is a "ubiquitously expressed type 1 membrane glycoprotein and is encoded by a single gene on chromosome 21q21" (Ling, Morgan, & Kalsheker, 2003, para. 7). This protein causes AD when

> cleavage of APP by either - or -secretases produces large soluble N-terminal fragments sAPP and sAPP, and C83 and C99 membrane-bound C-terminal fragments, respectively, which can be further cleaved by -secretase leading to the release and secretion of non-pathogenic p3 peptide and AB. Y-Cleavage of APP produces the extracellular AB associated with AD and also releases an intracellular tail fragment (Ling, Morgan, & Kalsheker, 2003, para. 9).

Mutations in the presenilin-1 (PS-1) and presenilin-2 (PS-2) are responsible for 10% of all early-onset familial AD (Thinakaran, 2004). These mutation cause AD because "mutant PS proteins influence the γ-secretase–mediated processing of APP, cause a selective increase in the levels of highly fibrillogenic Aβ42 species, and accelerate Aβ deposition in the brains of transgenic mice" (Thinakaran, 2004, para. 1). These mutations also increase the production of APP, which increases the production of amyloid plaques, and is why "longer Aβ peptides (42 or 43 amino acids in length) are more fibrillogenic than are shorter Aβ peptides (40 amino acids in

length) and are more prevalent in the brain lesions of patients with AD" (Thinakaran, 2004, para. 7).

Biological Risk Factors

There are other medical risk factors associated with AD in addition to age and genetics. Individuals who have suffered from a traumatic brain injury have been shown to have a greater chance of developing AD in their lifetime. A traumatic brain injury is defined as an "impact to the head that disrupts normal brain function and can be mild, moderate, or severe depending on whether the injury causes unconsciousness, how long unconsciousness lasts, and the severity of the symptoms" (Alzheimer's Association, 2019, para. 1). In a study conducted by Dr. Brenda Plassan from Duke University Medical Center showed that "any medical history of head injury more than doubled both the risk of developing Alzheimer's disease and the chances of developing non-Alzheimer's dementia, even after adjustments for the effects of age" (Gottlieb, 2000, para. 2). Gottlieb (2000) also showed that a head injury diagnosed as severe quadrupled the risk of AD, while a moderate head injury had a 2.3% increase of risk. Gottlieb (2000) proved that the "pathogenesis of Alzheimer's disease may be traced to origins decades before the appearance of clinical symptoms" (para. 3).

Chronic traumatic encephalopathy (CTE) is a form of dementia that has also been linked to an increased risk of AD. CTE is "a degenerative brain disease found in athletes, military veterans, and others with a history of repetitive brain trauma" (Concussion Legacy Foundation, 2020, para. 1). Stein, Alvarez, and McKee (2014) have specifically studied CTE and the neurological changes that follow it, and were able to show that "the pathology of CTE is characterized by the accumulation of phosphorylated tau protein in neurons and astrocytes in a pattern that is unique from other tauopathies, including Alzheimer's disease" (para. 1). In other

words, the same tau proteins that are found in AD are also found in patients with CTE, where the tau proteins clump and kill other brain cells. According to Stein and colleagues (2014), the way the disease works is

> hyperphosphorylated tau abnormalities begin focally, as perivascular neurofibrillary tangles and neurites at the depths of the cerebral sulci, and then spread to involve superficial layers of adjacent cortex before becoming a widespread degeneration affecting medial temporal lobe structures, diencephalon and brainstem (para. 1).

This pathology then increases the amount of long-term gray and white matter in the brain, which is an indicator of risk for AD (McKee, & Robinson, 2014, para. 1).

Other research has been conducted that shows the correlation between traumatic brain injuries and AD. Li, Risacher, McAllister, & Saykin (2016) showed "a history of traumatic brain injury may accelerate the age of onset of cognitive impairment by two or more years" (para. 15). Another study, conducted by Nordström & Nordström (2018), found that the first year after a brain injury had occurred was when the individual was at highest risk for diagnosis of AD. Nordström & Nordström (2018) also found that the risk became more prevalent as more years passed since the individual's injury, and the individual was four to six times more likely to receive a diagnosis within a 30-year time period ((Nordström & Nordström, 2018). While head injuries do increase the risk factor for individuals developing AD, it is important to understand that not all individuals who suffer traumatic brain injuries develop AD.

Vascular health is another medical factor associated with AD. Brain and heart health are vastly intertwined, "because the brain is nourished by one of the body's richest networks of blood vessels, and the heart is responsible for pumping blood through these blood vessels to the brain" (Alzheimer's Association, 2019, para. 9). Individuals who have had strokes, heart attacks,

diabetes, high blood pressure, and high cholesterol are at increased risk of developing AD later in life. Research has shown that "vascular health had a significant direct and indirect impact on neurodegeneration but not on amyloid; and vascular health, specifically the presence of hyperlipidemia, had a significant direct impact on ERC-tau" (Vemuri et al., 2017, para. 3). Vascular health is important to maintain because, with aging, arterial stiffness, endothelial changes, and blood-brain barrier dysfunction occur. These mechanisms then affect the regenerative capacity of the vascular system. The regenerative capacity of the vascular system correlates with the "accumulation of abnormal proteins such as amyloid β likely disrupt cerebral autoregulation, neurovascular coupling and perfusion of the deeper structures to variable degrees to produce white matter changes and selective brain atrophy" (Akinyemi et al., 2013, para. 1).

Vascular disease is also associated with certain ethnic groups being at higher risk for developing AD. Latinos and African Americans have higher rates of vascular disease than any other ethnic group, and researchers believe this correlates with why "Latinos are about one-and-a-half times as likely as older whites to have Alzheimer's and other dementias, while older African-Americans are about twice as likely to have the disease as older whites" (Alzheimer's Association, 2019, para. 18). This discrepancy is due to the variation of the APOE genotype in different ethnic groups, familial risk, and environmental factors. The Alzheimer's Association (2019) refers to the impact of AD on African Americans as a silent epidemic, and states that in the next 30 years, "the number of African Americans entering the age of risk more than doubles to 6.9 million" (para.19).

The APOE genotype is a protein that has three different alleles: APOE2, APOE3, and APOE4. The APOE4 genotype increases the presence of amyloid plaques and neurofibrillary tangles in the brain. While the APOE4 genotype is present throughout all ethnic groups, research

has shown that it is more frequent in American Americans than among Caucasians (Barnes, & Bennett, 2014). A new gene has also been discovered, ABCA7, and shown to increase one's risk of AD in African Americans. The ABCA7 gene is important in the phagocytosis of white blood cells, macrophages, and microglia. Moreover, the gene has doubled the risk of AD disease in African Americans. The underlying mechanisms of ABCA7 that cause AD are unknown, but research has suggested that it has to do with the gene's ability to regulate APP processing and clearance of Aβ through phagocytosis (Kinoshita & Clark, 2007). The importance of the APOE4 and ABCA7 genes are extremely important in the understanding of AD, because both genes "are involved in cholesterol transport, and given that cholesterol metabolism has been implicated in Alzheimer's disease," which emphasizes certain topics of research that may be important in finding a cure (Barnes & Bennett, 2014, para. 13).

The Centers for Disease Control and Prevention (CDC) has also conducted research, which predicts that, due to population growth in Latin America, Hispanic Americans will have the largest increase in AD cases. The CDC (2018) estimates that by 2060, "there will be 3.2 million Hispanics and 2.2 million African Americans with Alzheimer's disease and related dementias" (para. 8). According to Llibre-Guerra and colleagues (2020), Latinos will have an increase in diagnoses due to the fact that individuals are not dying from other chronic diseases and, therefore, live to the age when AD is more prominent.

Llibre-Guerra and colleagues (2020) specifically looked at dominantly inherited Alzheimer's disease (DIAD) cases in Latin America. The focus was to determine pathogenic variants in the Latin American population that increased their risk for developing AD. According to Llibre-Guerra and colleagues (2020),

> Latin American (LatAm) countries have reported a high dementia prevalence, ranging from 6.2 to 12.1%, among individuals aged 65+ years. Furthermore, the region will experience the greatest impact of dementia in the next decade, and the number of people with dementia is expected to nearly quadruple in this region by 2050 (para. 4).

Llibre-Guerra and colleagues' (2020) findings showed unique characteristics within the Latin American population that increased AD incidence and prevalence rates. The presence of common ancestry and mixed ancestry backgrounds from other countries, such as Africa, Western Europe, and Asia, were a factor that was determined. The founder effect, which is "the reduced genetic diversity which results when a population is descended from a small number of colonizing ancestors," was proven to increase DIAD variants in large extended families of Latin Americans (Oxford Languages, 2020, para. 1.). The early colonization periods of Latin American, and the reduced amount of genetic variation from inbreeding, is ultimately what has created this prevalence rate in this specific population. Specific DIAD variants that were found include amyloid plaques, neurofibril tangles, TDP-43, PSEN1, PSEN2, and APP (Llibre-Guerra et al., 2020).

Psychological Risk Factors

Research has shown that some psychological disorders, such as depression, anxiety, and sleep disturbance, increased one's risk of developing AD (Burke et al., 2018). Depression is the number one psychological disorder that can lead to AD. Individuals with depression have a precursor for dementia because depression can induce clinical disease and can damage the hippocampus of the brain that is responsible for learning and memory (Jorm, 2001, para. 3.). However, there is a lot of discussion in the medical field on whether depression is a risk factor, or if it is a comorbidity. There are several biological similarities between the two disorders that

make it difficult to have a definitive answer. Preuss and colleagues (2009) determined that the first year before and after an AD diagnosis is when depression is most prevalent in the individual's life, which goes along with the hypothesis that depression is a risk factor. Preuss and colleagues (2009) also showed that "depression was found to be a consequence of a patient's realization of beginning cognitive deficits" (para 1). There is an association between depression and memory, however, due to the lack of diagnostic scales, more research needs to be conducted in order to differentiate the two.

Sleep disturbance has a similar controversy in the medical field as depression when related to AD, because researchers are able to see it as both a consequence and a modifiable risk factor. There have been studies that have looked at both hypotheses, and an association between sleep and AD has definitely been evident; however, no definitive correlation has been made. Minakawa and colleagues (2019) showed that "more than 60% of patients with AD develop sleep disturbance, which often occurs at the early stages of the disease or even before the onset of major cognitive decline" (para. 2). Minakawa and colleagues (2019) specifically linked sleep disturbance with cognitive decline because of the overall decline in sleep duration due to insomnia, circadian rhythm-sleep wake disorder, sleep-related breathing disorders, and sleep-related movement disorders that most AD patients experience. When an individual's circadian rhythm is disrupted, they begin to lose their sense of time, and that is what causes sun downing. Sun downing is when the biological clock gets disturbed, and an individual has a difficult time differentiating between day and night. Lack of sleep also affects the galaninergic neurons in the intermediate nucleus of the hypothalamus, which correlates with the sleep fragmentation that AD patients experience (Minakawa et al., 2019,). However, Minakawa and colleagues (2019) also showed that "older adults without dementia, a higher level of sleep fragmentation due to

increased intermittent nocturnal arousal was associated with an increased risk of AD", which relates to the theory of sleep disturbance as a modifiable risk factor (para. 11).

Socioeconomic Risk Factors

Socioeconomic factors, such as education, income, and environment, have been studied to determine if there is an association with increased risk of AD. Evans and colleagues (1997) looked at the three socioeconomic factors and concluded that lower socioeconomic status did, in fact, increase the risk of developing AD later in life. According to Evans and colleagues (1997), "fewer years of formal schooling, lower income, and lower occupational status each predicted risk of incident AD; risk of disease decreased by approximately 17% for each year of education" (para 6). However, there was discrepancy over whether this was an accurate report since the study looked at principal occupation and not occupation duration. Karp and colleagues (2004) conducted a study that looked at education versus main occupation, education versus lifetime number of years spent in occupation, and high education/low occupation-based jobs versus low education/high occupation jobs. The result of the study showed that low education, along with either low occupation or high occupation, served as an increased risk factor for AD. There was no association with higher education with either low occupation or higher occupation (Karp et al., 2004). In relation to time employed at the occupation, Karp and colleagues (2004) also found that "those persons who had a low occupation-based SES at a young age and remained in this category for most of their occupational life had a 70–140 percent increased risk of Alzheimer's disease" (para. 30). Karp and colleagues (2004) acknowledged that there were some limitations to their findings, one being that they did not factor in the stress level of the occupation and how that may have been influential in cognitive decline. Income has not been deemed a risk factor for AD, but instead a consequence after the patient has been diagnosed (Karp et al., 2004).

Borenstein and colleagues also conducted a study that looked at socioeconomic status and IQ. The results of the study were parallel to Karp and colleagues' (2004) and found low socioeconomic status and low education to be a valid risk factor for developing AD. However, Borenstein and colleagues (2006) emphasized how higher educated individuals may be at lower risk, but that it does not mean they will never develop AD in their lifetime. Borenstein and colleagues (2006) also interpreted their results as "such factors are not related to the absolute probability of whether a person will develop AD or not, but rather are related to the timing of symptomatic onset among individuals who are predisposed to the neuropathology of AD" (para. 32). Borenstein and colleagues (2006) related low education and socioeconomic status to developing AD earlier than higher educated individuals. They determined that a low IQ is a factor associated with cognitive decline later in life and believe it is a stronger predictor than education. These results were parallel with the findings of Whalley and colleagues' (2000), which found "higher intelligence measured in early life also has been shown to be related to a lower risk of dementia 66 years later" (para. 4).

Prevention Measures

Since AD has become a 'silent epidemic,' researchers have dedicated time to find ways to prevent developing AD in an individual's lifetime. There are both pharmacological and nonpharmacological interventions that have been studied. Pharmacological interventions include symptomatic treatments, clinical trials, and treatments for comorbidities. Non-pharmacological interventions include lifestyle changes, mental health interventions, and setting a plan to help guide an individual's life. The goal of these interventions is to not necessarily cure AD, but to improve an individual's cognitive function, address depression symptoms, and delay institutionalization. According to the Alzheimer's Association (2019), non-pharmacological

interventions have shown significant results, and elderly patients who take part in these interventions have shown a 25 to 150% improvement of cognitive function.

Direct cognitive intervention has been taken into consideration when it comes to prevention methods for AD. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study conducted in the United States looked at healthy individuals over the age of 65 years old who showed no signs of cognitive decline and separated them into 10 groups. Each group, aside from the control group, received training in memory, reasoning, and speed of processing. The groups were then evaluated after two, five, and 10 years. The results of the study were “after the 10-year follow-up investigators concluded that those who received any intervention showed less functional decline in daily living activities, and those trained in reasoning and speed of processing also showed better performance in the targeted abilities" (Crous-Bou et al., 2017, para. 20). The groups that received the intervention had shown significantly lower rates of developing AD (Crous-Bou et al., 2017, para. 21)

As discussed above, hypertension and cardiovascular health has been shown as a risk factor for developing AD at a later stage in life. Richard and colleagues (2009) looked at the prevention of AD and dementia through intensive vascular care. The goal of the study was to determine if treatment for cardiovascular risk factors in elderly individuals would reduce their risk and prevent new cases of AD in older adults. The trial was conducted over a six-year span and measured mortality rates, cardiovascular events, and cognitive functioning. The Prevention of Vascular Dementia by Intensive Care (PreDIVA) included treatment for hypertension, hypercholesterolemia, diabetes, obesity, smoking, and lack of physical exercise (Richard et al., 2009). Unfortunately, the results showed that:

> vascular care did not result in a reduced incidence of all-cause dementia in an unselected population of older people and did not have an effect on mortality, cardiovascular disease or disability, despite a greater improvement in systolic blood pressure in the intervention group compared with the control (Crous-Bou et al., 2017, para 16).

Crous-Bou and colleagues (2017) believed the results were unsuccessful due to basic baseline measurements and high-quality care that the individuals were already experiencing prior to the trial. However, this leaves a gap in the research and the trial has the potential to be altered to achieve more accurate results regarding prevention of AD and dementia through intensive vascular care.

The Multidomain Alzheimer Preventive Trial (MAPT) was a trial conducted over the span of three years to investigate the relationship between the interventions of a multidomain lifestyle and omega-3 supplementation on physical activity in elderly individuals experiencing cognitive decline. The implementation of a multidomain lifestyle included nutritional and exercise counseling to help with increased physical activity, along with cognitive training for memory repair. Unfortunately, "both the multidomain intervention and polyunsaturated fatty acids, either individually or in combination, had no significant effects on cognitive decline over 3 years in older people with memory complaints" (Crous-Bou et al., 2017, para. 17). The results of the study show an increase in physical activity for only a short period of time, since patients returned to baseline status once the trial was over. This treatment would have no long-term effects for the individuals (Barreto et al., 2018). Baretto and colleagues (2018) determined that the treatment was not effective since the patients were already experiencing cognitive decline and, therefore, these preventative interventions were too late. However, Baretto and colleagues

(2018) results leave room for researchers to explore these interventions on individuals who have not yet experienced cognitive decline and have associated risk factors.

With the increase in technological advancements throughout the last century, eHealth has become an up-and-coming form of patient care. The term eHealth refers to "intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies" (Eysenbach, 2001, para. 4). Since eHealth has become more prevalent in today's society, it has created a new platform for research. The Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study examined the relationship between a coach-supported intervention over the Internet and the effects on cardiovascular disease and cognitive decline (Richard et al., 2019). The goal of the study was to look at individuals over 65 years old and create a platform that would be easy to use with very little knowledge of technology. This ease of use was important, since older generations are not as privy to advances in technology. Richard and colleagues (2019) showed that eHealth intervention was effective in reducing the risk of cardiovascular disease in an elderly population. However, the results were inconclusive when looking at cognitive decline (Richard et al., 2019).

Researchers (e.g., Rosenberg et al., 2018) have shown certain lifestyle changes, such as exercise, quitting smoking, low-fat and high vegetable and fruit diets, and adequate sleep, to be helpful in the prevention of cognitive decline. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial was a two-year study conducted by the Finnish Geriatric Intervention that looked at multidomain lifestyle interventions and their effect on cognitive improvements. The multidomain interventions that were studied were diet, exercise, vascular risk management, and cognition exercises. Rosenberg and colleagues (2018) used a Neuropsychological Test Battery (NTB) scale to show overall improvement in cognition.

The results showed that these multidomain lifestyle interventions are not only effective for elderly patients, but those of all ages. This means that the results can be generalizable to multiple different populations and should be implemented in many clinical practices (Rosenberg et al., 2018).

McGough and colleagues (2017) looked at the possibilities of integrating physical therapy practices to prevent AD. The results of the study showed that physical therapy has been able to improve brain health through exercise, which strengthens an individual's cardiovascular and neurovascular systems (McGough et al., 2017). Quinn and colleagues (2017) resembled these findings and emphasized the need for physical therapists to take control and promote rehabilitation of the brain, and truly promote the need for innovation in exercises in elderly patients to help aid in the prevention of cognitive decline. However, more research still needs to be conducted to understand the mechanisms behind this reasoning (Brown et al., 2013). It is known that exercise improves vascular health, but that it is beneficial for all individuals and not only those with AD.

Low-fat and high vegetable and fruit diets have been shown to aid in the prevention of AD. Specifically, the Mediterranean diet is recommended because Omega-3, antioxidants and polyphenols associated with the diet have been found to inhibit the neuroinflammatory mechanism that occurs in AD (McGrattan et al., 2019). Some foods increase cognitive decline through several immune pathways in the gut microbiome and systemic system. Anti-inflammatory diets essentially redirect those pathways and reduce neuroinflammation (McGrattan et al., 2019). The Dietary Approaches to Stop Hypertension (DASH) diet has also been shown to slow down cognitive decline by improving cardiovascular health. The goal of the DASH diet is to reduce hypertension by reducing sodium intake, which is done through

increasing the intake of other elements, such as potassium, calcium, and magnesium. According to the Mayo Clinic (2019), "the top number of your blood pressure (systolic blood pressure) could drop by eight to 14 points, which can make a significant difference in your health risks" (para. 3).

As discussed above, sleep disturbance is a risk factor for AD, since there is an interruption in the individual's circadian rhythm. Researchers have been looking at ways to restore an individual's circadian rhythm before any long-term effects become evident. Ying-Hui and Swab (2007) found that:

> pineal melatonin secretion and pineal clock gene oscillation were disrupted in AD patients…and observed functional disconnection between the SCN and the pineal from the earliest AD stage onwards seems to account for the pineal clock gene and melatonin changes and underlies circadian rhythm disturbances in AD (para. 1).

Ying-Hui and Swab (2007) then studied therapies, such as melatonin and bright light therapy, which would hopefully aid in both the restoration of the circadian rhythm and prevention of interruption in the circadian rhythm. The production of melatonin is affected when sleep disturbance occurs. Melatonin is "a hormone produced at night and in darkness and is believed to be a timing messenger to the body, indicating to all cells that it is circadian night" (Hanford et al., 2013, para. 5). Melatonin therapy increases the production of melatonin within the body and, therefore, increases an individual's productivity, alertness, and performance that will help them stay on-track (Hanford et al., 2013). Light therapy is when an individual is exposed to a synthetic form of light that mimics daylight. However, studies have not found light therapy to be a means of prevention, but rather a means to slow cognitive decline after an individual has been diagnosed with AD. According to Hanford and colleagues (2013), "it has been suggested that

light therapy's effect on sleep in those with Alzheimer's Disease Related Dementia (ADRD) is only measurable after 6 months of treatment possibly because these patients are slower to respond to the stimulus" (para. 18). In conclusion, more research needs to be conducted to determine if light therapy will be beneficial to individuals who may be predisposed to developing AD because of their genetic and family history.

Meditation is the act of practicing mindfulness in order to achieve a clear mentality and an emotionally stable state of mind. Khalsa (2015) highlighted the importance of individuals practicing Kirtan Kriya. Kirtan Kriya (KK) evolved from the Kundalini yoga tradition and is a type of mediation that "involves singing the sounds, Saa Taa Naa Maa along with repetitive finger movements, or mudra" (Alzheimer's Research and Prevention Foundation, 2017, para. 1). This meditation only requires 12 minutes of an individual's day and has been successfully shown to improve memory in patients who have already been diagnosed with AD, and has been successful in prevention. According to Khalsa (2015), "KK has also been shown to improve sleep, decrease depression, reduce anxiety, down regulate inflammatory genes, upregulate immune system genes, improve insulin and glucose regulatory genes, and increase telomerase by 43%; the largest ever recorded" (para. 1). Khalsa (2015) also stated that KK has been known to improve spiritual well-being, which is primitive in the prevention of AD when associated with other prevention methods.

Available Pharmaceutical Treatments for AD

While there is no known cure for AD, there is a lot of research dedicated to treatment options, and researchers are hopefully one step closer to finding a cure. There are both molecular and therapeutic approaches for treatment. Molecular approaches focus on modifying the mutations that are associated with the disease with the goal of lowering the susceptibility for

these mutations to actually occur. Therapeutic approaches focus on drugs that have the potential to slow disease progression and give the individuals a longer cognitive life span. With more advances in technology, there is hope in finding a cure, as the pathology pathway of the disease is becoming more understood (Mayeux & Sano, 1999).

There are currently five medications that are approved by the FDA in North America and some European countries for treating AD. Cholinesterase inhibitors, such as tacrine, donepezil, galantamine, and rivastigmine, are the main forms of treatment, along with the NMDA receptor antagonist memantine. Cholinesterase inhibitor treatment coincides with the 'cholinergic hypothesis', which posits that treatment for the disease is based on the replacement of neurotransmitters that are absent in patients with AD. The neurochemical function of AD occurs when there is a deficit of cholinergic transmission in the basal forebrain nuclei, along with a loss of nicotinic receptors, acetylcholine-synthesizing enzyme, and choline acetyltransferase (Herrmann et al., 2012). There has been controversy in the scientific community over whether this deficit actually occurs. Researchers who support this hypothesis have been looking at the relationship between increasing "acetylcholine synthesis, the augmentation of presynaptic acetylcholine release, the stimulation of cholinergic postsynaptic muscarinic and nicotinic receptors, and the reduction of acetylcholine synaptic degradation with cholinesterase inhibitors" and cognitive improvement (Scarpini et al., 2003, para. 5). The goal is to improve cholinergic transmission through the elevation of acetylcholine in the synaptic cleft and block the hydrolysis of acetylcholinesterase (Scarpini et al., 2003, para. 6)

The drugs tacrine, donepezil, and galantamine have similar mechanisms when inhibiting acetylcholinesterase. Galantamine has also been shown to improve cholinergic transmission by increasing presynaptic acetylcholine release and postsynaptic neurotransmission. Galantamine

also “allosterically modulates nicotinic acetylcholine receptors to improve nicotinic transmission — another pathway implicated in the pathogenesis of neurodegenerative disorders” (Herrmann et al., 2012, para. 16). Donepezil is a second-generation drug that acts in a non-competitive reversible manner, which binds to acetylcholinesterase and hydrolyzes instead of acetylcholine. Donepezil also binds to plasma protein and has a long half-life, which “protects cortical neurons against glutamate toxicity, prevents apoptotic cell death, increases expression of nicotinic receptors and decreases Aβ production and Aβ-induced toxicity” (Herrmann et al., 2012, para. 14). Rivastigmine is different from the other cholinergic inhibitors because it is ‘pseudo-irreversible’ and is persistent in action, which inactivates acetylcholinesterase enzyme for more than 24 hours. Rivastigmine also inhibits butyrylcholinesterase, which has been shown to increase when acetylcholinesterase decreases. Therefore, rivastigmine acts on both enzymes in order to improve cognition (Herrmann et al., 2012). While these treatments are not effective in targeting the main pathway of pathology, they have been shown successful in slowing down the progression of cognitive decline at different stages.

There are some side effects associated with cholinesterase inhibitors, including headache, nausea, vomiting, diarrhea, insomnia, and abnormal dreams. Some patients may experience even more severe side effects, such as hallucinations, hypertension, and polyuria. Cholinesterase inhibitors can interact with other drugs, so it is important to cross-reference all medication with a doctor before starting any prescriptions. Adverse effects have been reported as the drug has been implemented more in the scientific community. A study using the Pharmacovigilance Databases of the United States and Canada showed that Donepezil was associated with muscle-related adverse effects and acute renal failure. However, after discontinuation of the drug from the patients’ routine, muscle atrophy and renal failure improved (Ali et al., 2015). Ali and colleagues

(2015) concluded that cholinesterase inhibitors are effective in treating AD patients; however, drug profiles need to be updated in order to monitor the side effects of the drug and create the safest atmosphere for patients.

Herrmann and colleagues (2012) looked at the differences of all four cholinergic inhibitors and overall functional outcomes for patients to determine which one was more successful among patients who showed forms of mild to severe AD. The results showed that "ChEIs are beneficial for the treatment of behavioral disturbances, though more so for mild than for severe AD" (Herrmann et al., 2012, para. 17). Other researchers have questioned whether this form of treatment was actually successful due to the unknown pathologies of the disease. Further research has shown cholinergic inhibitors to have other mechanisms of action, such as to "influence the expression of various isoforms of acetylcholine, increase expression of nicotinic acetylcholine receptors, mediate amyloid precursor protein (APP) processing and attenuate Aβ-induced toxicity" (Herrmann et al., 2012, para 11). It is believed that these treatments are being implemented too late in the stages of the disease, and that if they were applied earlier, there might be more successful interventions.

Memantine is an NMDA-receptor partial antagonist that is specific and non-competitive. The NMDA receptors have multiple binding sites for glutamate and phencyclidine. Glutamate is the main neurotransmitter in the central nervous system. The functions of the NMDA receptors increase the concentration of calcium into the neuron that affects learning and memory. In patients with AD, there is an increase of glutamate and NMDA receptors that increases the concentration of calcium and causes neuron death. The goal of memantine is to protect the neurons from cell death. The NMDA antagonist blocks glutamate levels in both receptors and pathologically (Hynd et al., 2004). Clinical trials have shown memantine to be successful in

increasing learning and memory in mild AD patients. More research does need to be conducted to determine memantine's effects when mixed with other drugs associated with AD, and to determine if the drug has an effect on function or behavior. According to a study conducted by the Cochrane Collaboration, "treatment of mild to moderate AD with memantine does not generate improvement in function and behavior, but slightly improves cognitive and global status" (Herrmann et al., 2012, para. 54).

Side effects of memantine include dizziness, confusion, aggression, depression, fatigue, constipation, vomiting, and weight gain. The patients who participated in the clinical drug trials of memantine did not experience any severe side effects, which proved the drug to be well tolerated in the body. However, since the population of the trials were rather small and short-term, there is a gap in the research to determine whether memantine has any long-term effects on patients taking it every day. There is also a lack of research of drug interaction between memantine and other drugs used to treat AD (Institute for Quality and Efficiency in Health Care, 2017).

Cerebrolysin is another drug used to treat AD in Europe and Asia, and it protects neuron function in the brain by releasing small peptides and amino acids that can cross the blood-brain barrier. Clinical trials have shown Cerebrolysin to be successful in "β-amyloid- and tau-related pathologies, neuroinflammation, neurotrophic factors, oxidative stress, excitotoxicity, neurotransmission, brain metabolism, neuroplasticity, neuronal apoptosis and degeneration, neurogenesis and cognition" (Alvarez & Fuentes, 2011, para. 1). The results also showed the Cerebrolysin was effective with other drugs, such as donepezil, and that the two drugs have similar properties that might form a synergistic relationship. The drug was also effective with neurotrophic and cholinergic treatments. The United States currently does not approve treatment

using Cerebrolysin. Cerebrolysin is derived from pigs' brains, which increases the risk of bacterial, fungal, and viral infections. Side effects gathered from clinical trials include anxiety, agitation, weight loss, headaches, and hypertension. The clinical trials of the drug determined that Cerebrolysin is safe to use for three years with minimal-to-mild side effects present. There is a gap in the research in that the drug needs to be examined among larger sample groups to determine if it has an effect on the behavior of AD patients, and to determine any drug interactions that would cause more adverse effects (Rockenstein et al., 2003).

Emerging Treatments for AD

There are various emerging therapies that are in testing stages in hopes of finding a cure for AD. Amyloid-*Beta* intervention is the primary method associated with most clinical trials because it is known that patients with AD have an excessive amount of Amyloid-B plaques and neurofibrillary tangles in the brain. Many researchers believe that intervening with the amyloid-B plaques in some manner is the key. The pathology of AD is still unknown, which makes it difficult for researchers to know how to target the amyloid-B plaques.

Reducing amyloid-B production via B-secretase inhibition is one method being studied in clinical trials. β-site APP-cleaving enzyme 1 (BACE1) is the enzyme that activates the amyloidogenic pathway. It is hypothesized that drugs, such as rosiglitazone and pioglitazone, which are used to treat type II diabetes, may also be successful in reducing amyloid-beta levels. Diabetes is a known risk factor for AD, and insulin resistance may be an underlying mechanism that contributes to the pathology pathway of AD. There are currently trials in preliminary and phase II stages that are studying the effects of rosiglitazone in AD patients. The results of phase II stages showed "significant improvements on the ADAS-cog occurred in the apolipoprotein E (APOE) ε4-negative patients given rosiglitazone 8 mg compared with placebo, while no efficacy

was found for APOE ε4 carriers" (Herrmann et al., 2012, para. 68). Phase III trials have started, but cardiovascular safety issues among patients arose and prolonged any further phase III trials (Herrmann et al., 2012, para. 70)

Y-secretase inhibition is another method being studied in clinical trials. The mechanism of y-secretase is important in the production of amyloid-Beta plaques. Y-secretase cleavage is important in other substrates in the body, so it is difficult to only isolate the mechanism associated with amyloid-beta formation. The drug semagacestat is a y-secretase inhibitor that reaches phase II clinical trials. The goal of semagacestat was to lower the central nervous system amyloid-beta level through a daily dose. Preliminary trials of the drug did not show a significant decrease in amyloid-beta plaques, and multiple patients experienced damage to their skin tissue. The trials ultimately ended when the large population studies, IDENTITY AND IDENTITY-2 trials, lacked efficacy and showed that patients taking semagacestat were at increased risk for skin cancer and lower cognitive functioning (Herrmann et al., 2012). Another drug, avagestat, is another y-secretase inhibitor that made it to phase II trials. Avagesat was believed to divert y-secretase from binding to the notch receptor site. Patients involved in the trial clinically worsened, and the trial ended in 2012 (Nygaard, 2013).

Alpha-secretase enhancement is believed to block amyloid-beta plaque expression because it is "the competing enzyme of β-secretase for APP, initiates a non-amyloidogenic pathway, which results in a protein with lower propensity to aggregate" (Herrmann et al., 2012, para. 70). Clinical trials of stimulating alpha-secretase have shown increased neuroprotectivity, memory enhancement, and reduced apoptosis. Drugs such as etazolate have made it to phase III trials, but since the neural pathway is still being researched, all phases have concluded (Herrmann et al., 2012).

Research shows that amyloid-beta plaques build up when there is increased neuronal activity in the brain, which is mostly caused by sleep deprivation. Most AD patients experience insomnia, which contributes to the increased plaques found in the brain. The drug levetiracetam is an anticonvulsant, which means it is used to treat epileptectic episode or other convulsions in the body. Recent studies have been examining levetiracetam as a way to lower amyloid-plaque formation and neuronal activity in the brain. In human trials, a low dose of levetiracetam was able to reduce neuronal hyperactivity and increase memory function in the hippocampus. More research needs to be conducted to prove effectiveness in AD (Nygaard, 2013).

Blocking Fyn kinase is another method researchers are exploring in order to block amyloid-beta production. Fyn kinase is a 59 kDa protein that plays a role in t-cell receptor signaling, cell division, platelet function, and synaptic plasticity of the central nervous system. Synaptic plasticity is important in the ability of neurons to communicate during memory formation. AD patients have altered Fyn expression, which suggests an "increase in tyrosine phosphorylated proteins in cell culture, [further] suggesting the importance of tyrosine kinases in AD" (Nygaard et al., 2014, para. 10). Since Fyn is involved in multiple physiological mechanisms, it is unknown what might occur if a Fyn inhibitor is given to AD patients. Fyn inhibitors, such as Masitinib and Saracatinib, are currently in the clinical phase in Europe. Masitinib was given to mild-moderate AD patients, and results showed improvement in cognitive functioning in just 12 weeks. The trial supported the theory that Fyn inhibitors might be a key in the pathology of the disease, because "Fyn represents a unique therapeutic target in AD as it is central to Aβ signal transduction, and has major functional interactions with Tau, thereby unifying the two major pathologies in AD," and further trials were launched to study the drug in a larger population (Nygaard et al., 2014, para. 13). Saracatinib is a drug that inhibits

members of the Src family kinases, such as Fyn. Although Saracatinib has shown promise with tumor degradation therapy, there are no studies demonstrating increased cognitive functioning using Saracatinib. (Nygaard et al., 2014).

The hyperphosphorylation of tau proteins that leads to neurofibrillary tangles in the brain is the other main pathology besides amyloid-beta plaques associated with AD (Avila et al., 2010). Another approach to finding a cure is to attack the formation of neurofibrillary tangles by inhibiting the phosphorylation of tau proteins and stimulating filament deconstruction. Glycogen synthase kinase 3β is a protein kinase that is associated with tau phosphorylation, neurofibrillary tangles, and neuronal death in the brains of AD patients. Researchers believe that Glycogen synthase kinase 3β inhibitory is a possibly successful therapy. Lithium is a noncompetitive mood stabilizing drug that inhibits glycogen synthase kinase 3β and blocks the accumulation of amyloid-beta plaques. Lithium has been tested in mouse models and has been able to prevent tau phosphorylation in the early stages and reduce the hyperphosphorylation of tau in the later stages of the disease. Lithium was unsuccessful in reversing any damage that had already occurred in mouse model brains. Clinical trials for lithium treatment in humans are underway, but researchers are hoping to discover another Glycogen synthase kinase 3β inhibitor that will be more specific and not have other functional mechanisms in the body (Avila et al., 2010).

A modified version of methylene blue, compound TRx0237, is another tau inhibitor that may be effective in "disrupting PHFs isolated from AD brain tissues at the concentration at 0.16 μM" (Panza et al., 2016, para. 6). There are currently three phase III placebo controlled studies underway examining the effects of TRx0237 on all forms of dementia patients with probable AD, mild-to-moderate AD patients, and frontotemporal dementia patients. There is no current

data from humans released to the public from these trials, and phase III trials have been prolonged due to a failure in study design (Panza et al., 2016).

For over two decades, researchers have been working on AD vaccination development. . In 1999, Dr. Schwenk and colleagues developed a vaccine for AD in mice models. Two strategies for immunotherapy were being studied: (1) active immunization through amyloid-beta peptides, and (2) passive transfer of amyloid-beta specific antibodies (Lemere, 2009). Mice were injected with the vaccine (AN 1792) for 11 months, and six weeks after the vaccination was administered, there was evidence of amyloid-beta deposition and slower cognitive decline. According to Schenk and colleagues (1999),

> the almost complete absence of plaques in the brains of Aβ42-treated mice indicates that a fundamental mechanism of amyloid plaque formation has been disrupted... and the above results clearly indicate that Aβ42 immunization essentially prevents the development of AD-like neuropathology in the PDAPP mouse (para. 8).

Phase I of the clinical trial showed immunotherapy to be effective in improving cognitive decline and decreasing amyloid-beta levels in mouse models. In another study, Weiner and colleagues (2001) supported Schenk and colleagues' (1999) findings by testing chronic mucosal administration of amyloid-beta peptide and its effects on the inflammatory response in the brains of AD patients. The results showed a "50–60% reduction in amyloid burden in the brains of PDAPP mice immunized intranasally with freshly solubilized Aβ1–40" (Weiner et al., 2001, para. 1).

In 2002, Phase IIa in the clinical trial researching the active immunization AN 1792 in humans was stopped when 17 of the 360 patients enrolled in the study showed symptoms associated with meningoencephalitis. The autopsy of the patients who passed away were useful

in studying the mechanism associated with the vaccine and will help researchers to design future studies that have the potential to be more successful. A scientific finding during the study was "that not all of the affected individuals in the Phase IIa study had a measurable antibody titre against Aβ, indicating that the presence of immunoglobulin-γ was not a prerequisite for the development of meningoencephalitis" (Schenk, 2002, para. 13). Schenk's (2002) findings forced researchers to question if the action of antibodies in the human body had any effect on why some patients developed meningoencephalitis, thereby paving the way for immunotherapy research to treat AD.

Other researchers, such as Frederique Bard and colleagues, extended Schenk's (2002) vaccination research. Bard and colleagues (2000) studied passive immunization associated with monoclonal and polyclonal antibodies as a way to reduce amyloid-beta formation in AD patients. A mouse model was used for the study, and amyloid-beta peptide antibodies were injected in mice over a period of six months. The results showed that "the passively administered antibodies were able to enter the central nervous system, decorate plaques and induce clearance of preexisting amyloid" (Bard et al., 2000, para. 1).

The AADvac, an active vaccine against tau proteins, made it to phase I in clinical trials. The vaccine uses immunotherapy to target the production of tau proteins. Phase I of the study was a 12-week, randomized, double-blind, placebo-controlled experiment among mild-moderate AD patients. Out of the 30 patients who received the vaccine, only two withdrew due to adverse effects in the injection site from the vaccine, one developed microhemorrhages, and 29 showed an IgG immune response. Further research needs to be conducted to determine if this vaccine is successful in preventing cognitive decline; however, this trial did show a high immunogenicity and was safe for patients (Novak et al., 2017).

The reason why there is still no fully functioning vaccine for AD is because the mechanism of the vaccine itself is still unknown. There are several hypotheses regarding the mechanism and pathology of an AD vaccine. Schenk and colleagues (1999) hypothesized that amyloid-beta peptide antibodies enter the central nervous system and bind to the amyloid-beta plaques, which are then phagocytized by microglia. Solomon and colleagues (1996) hypothesized that monoclonal antibodies target the terminal end of amyloid-beta peptides and dissolve associated fibrils. Demattos and colleagues (20001) hypothesized the idea of a 'peripheral sink' in which the equilibrium between amyloid-beta peptides and the central nervous system is altered by amyloid-beta antibodies to adjust the outflow of amyloid-beta in the brain. Lastly, several researchers have hypothesized the idea of a soluble pool of amyloid beta as a probable mechanism. Mclean and colleagues (1999) hypothesized that "several interacting pools of Aβ, that is, a large relatively static insoluble pool that is derived from a constantly turning over smaller soluble pool" due to the fact that soluble amyloid-beta is three times more prevalent in AD patients and contributes to the severity of the disease.

The 'soluble pool' hypothesis has led researchers to further study the binding and isolation of soluble amyloid-beta through a passive immunization. More specifically, Dodart and colleagues (2002) studied the effects of monoclonal antibody m266 on memory deficits in mouse models. The results

> indicate that passive immunization with this anti-Aβ monoclonal antibody can very rapidly reverse memory impairment in certain learning and memory tasks in the PDAPP mouse model of AD, owing perhaps to enhanced peripheral clearance and (or) sequestration of a soluble brain Aβ species (Dodart et al., 2002, para. 4).

The interesting aspect about this study was that the results contrasted with multiple previous findings that showed active immunization as a way to reduce amyloid-beta production.

Amyloid antiaggrent therapies is an emerging therapy built on the foundation of the 'amyloid hypothesis' that states soluble amyloid-beta conforms into a fibril-rich beta-pleated sheet structure. Conformational changes promote diseases such as AD, because it alters the secondary or tertiary structure without altering the primary structure, causing a gain in toxic functionality. Amyloid antiaggrent therapies focus on disrupting the beta-pleated sheet formation and reverse the conformation changes that occur in the protein. In an experiment conducted by Soto and colleagues (2001), short synthetic peptides were used to correct the protein misfolding and disrupt beta-pleated sheet formation through a self-recognition design. The synthetic peptides are similar to the sequence of the protein that favors folding, and when they bind, they instead inhibit the beta-pleated sheet formation. The synthetic peptides have only been tested in animal models of AD, but have been successful in destabilizing beta-sheet formation. The ability to manipulate the synthetic peptides is in the forefront of AD research, and further research is needed to generate synthetic peptides as a functioning therapeutic approach for AD (Soto et al., 2001).

The plasma protein, Serum Amyloid P (SAP), has the ability to bind to amyloid-beta plaques found in AD, which prevents proteolysis of the fibrils. According to Tennent and colleagues (1995), "SAP is not an enzyme inhibitor and is protective only when bound to the fibrils" (para. 1). Therefore, the interference of SAP is hypothesized to be a potential therapeutic method for AD patients. The interference of SAP would ultimately stop the progression of amyloid deposits. The drug CPHPC was designed to act as an inhibitor for SAP when binding to amyloid-beta deposits, and the mechanism of the drug depletes the overall production of SAP

circulating the body. Human clinical trials were successful, and patients who took the drug had lower SAP concentration levels in their blood. There is evidence that "coupled with direct inhibition of SAP binding by CPHPC, this leads to rapid and extensive removal of SAP from the amyloid deposits' (Pepys, 1995, para. 15). While CPHPC has great potential, further trials need to be conducted to determine the longevity of the drug, and whether it has any effects associated with memory enhancement and cognitive decline.

Intravenous Immunoglobulins (IVIG) have natural antibodies against amyloid-beta that are hypothesized to affect biomarkers associated with AD and manage symptoms in moderate-to-severe patients. The intravenous immunoglobulins come from purified plasma from a larger number of donors and are converted into a serum. In a clinical trial conducted by Dodel and colleagues (2002), seven patients received IVIG for three consecutive days every four weeks for six months. Dodel and colleagues (2002) "confirmed the ability of the affinity-purified anti–Aβ antibody from plasma to bind Aβ by immunoprecipitation of synthetic Aβ peptide," meaning there was evidence that intravenous immunoglobulins have the potential for being a successful therapy (para. 10). In phase II of the trial, a larger population was studied, and IVIG was delivered to patients every four weeks for 24 weeks. The results of the study were not in sync with the first study, and multiple patients suffered adverse effects. It was determined that more safety measures need to be applied in the next clinical trial, and that there is a need for a longer trial to assess the effects of intravenous immunoglobulins on memory enhancement and cognitive functioning (Dodel et al., 2013). In 2013, phase III placebo-controlled trials were conducted among 390 patients who received treatment every two weeks for 18 months, the results of which showed no significant effect on cognitive decline (Loeffler, 2013). There are two clinical trials that are currently in-progress studying intravenous immunoglobulins. A Phase

III trial conducted by Sutter Health is studying Flebogamma, a type of intravenous immunoglobulin, and its effects on mild cognitive impairment (MCI) patients in terms of their risk for developing AD. The other study is a retrospective study analyzing patients over 65 who have taken IVIG and their risk of developing AD or other related disorders (Loeffler, 2013).

Amyloid-Beta plaques have a high affinity for copper and zinc, which means that metal ions play a functional role in the pathogenesis of AD. Therefore, metal chelators are hypothesized as a potential treatment. Metal chelators aim to restore metal ion imbalance without disrupting homeostasis. In 1999, Cherny and colleagues were the first to test this hypothesis by examining post-mortem brains of AD patients. Cherny and colleagues (1999) injected patients' brains with copper and zinc chelators, and found the choletors to be effective in extracting amyloid-beta and solubilizing it. Two years later, Cherny and colleagues (20001) conducted another study in mice models to test the effects of metal chelators on the inhibition of amyloid-beta accumulation. Cherny and colleagues (2001) used the drug clioquinol, which is a copper and zinc chelator, the results of which were similar to those in the post-mortem brains, as the drug increased solubility in amyloid-beta. The most promising metal chelator that has been tested is a multi-target drug called 8-Hydroxyquinoline hybrids (8HQ). 8HQ has the ability to cross the blood-brain barrier, moderate affinity with copper and zinc, is approved by the FDA, and has dissolved amyloid plaques in post-mortem AD brains. Phase II clinical trials of the drug were halted due to the inability to produce the drug in large quantities. However, 8HQ is still being studied by researchers and modified to address the dangerous factors associated with metal chelators, such as the ability to cross the blood-brain barrier, toxicity, redox potential, thermodynamic, and lack of research (Santos et al., 2016).

Insulin dysregulation in AD pathology is another measure being researched. The main function of insulin involves glucose and affects synaptic function in the central nervous system. In a study conducted by Pedersen and colleagues (2004), the effect of stress responses on insulin resistance in the Tg2576 mouse model of AD was examined. The results showed "a relationship between insulin resistance, impaired regulation of insulin and glucose levels, and aberrant stress responses in Tg2576 mice", which opened up further research for insulin being a method for cognitive improvement (Pedersen & Flynn, 2004, para. 1). AD patients tend to have lower insulin levels, so the goal of the study conducted by Craft and colleagues (2012) was to examine the effects of intranasal insulin on cognition in mild AD patients. Phase II of the study examined patients receiving nasal insulin over a period of four months. Craft and colleagues (2012) provided evidence that insulin improved daily cognition and delayed memory loss, as well as "changes in memory and function were associated with changes in the Aβ42 level and in the tau protein–to–Aβ42 ratio in cerebrospinal fluid" (para. 7). Overall, the study was promising and left room for a longer and more populated trial to be conducted, and a Phase III multisite trial using intranasal insulin in AD patients was initiated (Craft, 2012, para. 8).

A medical food product, Souvenaid, was developed for AD patients, which is a drink containing fatty acids and vitamins that are precursors for healthy neuron function. Souvenaid is designed to improve synapse formation in the central nervous system and enhance memory function. The first clinical trial testing of Souvenaid showed evidence for improvement in memory for up to 48 weeks in AD patients, but no significant cognitive benefits were evident. The EEG results from the trial suggest "that Souvenaid has an effect on brain functional connectivity, supporting the underlying hypothesis of changed synaptic activity" (Scheltens et al., 2012, para. 1). It is suggested that the patients who would benefit most from this medical

drink are patients with a mild case of AD, and that the drug should be used as a form of management in mild cases. It is not recommended for patients with severe AD, and patients should stop their dosage if intolerance develops and cognition continues to decline. Nevertheless, current research shows continued benefit among mild cases (Cummings et al., 2019).

Organizations Dedicated to Emerging AD Therapies

Several organizations are dedicated to AD research and towards building a framework for clinical trials to maximize efficiency and develop outcomes that are progressive in finding a cure. The Dominantly Inherited Alzheimer Network (DIAN) is an organization combined of several AD research centers that focus on autosomal dominant Alzheimer's disease (ADAD). ADAD is a rare form of AD that is caused by a genetic mutation in presenilin 1 (PSEN1), presenilin 2 (PSEN2) , or amyloid precursor protein (APP). Several centers combine their research to form a comprehensive journal associated with information about ADAD, such as "standard protocols from asymptomatic and symptomatic ADAD mutation carriers and their non-carrier family members to determine the pathochronology of clinical, cognitive, neuroimaging, and fluid biomarkers of AD" (Morris, 2011, para. 1). DIAN focuses on gaining a comprehensive idea behind the mechanism of ADAD in order to gather more information on the common form of AD. Several clinical trials are conducted through DIAN. For example, one study is testing participants who are offspring of ADAD patients to determine the functionality of the gene to determine successful prevention methods that have the possibility of applying to other populations. The goal of the organization is "successful prevention trial that yields the approval of the first disease-modifying drug, bolsters interest in developing improved drugs and demonstrates a clear pathway to prevent AD in the general population" (Crous-Bou et al, 2017, para. 26).

The international collaborative, Alzheimer's Prevention Initiative (API), is an organization dedicated to finding successful preventative AD treatments for presymptomatic AD patients that will reduce the risk and/or prevent the development of AD. Clinical studies under API evaluate people based on age, genetics, and imminent risk factors, and study their brain imaging, cerebrospinal fluid levels, and cognition to determine an amyloid-modifying treatment. Members of the API receive information regularly about new clinical trials in progress and data collected from previous trials. The goal of the API is to: (1) develop an AD modifying treatment; (2) analyze brain imaging and biomarkers that have received treatment and determine the clinical benefits that can be expanded upon in other trials; (3) provide a better testing method for symptomatic patients, so they can receive treatment as soon as possible; (4) expand upon their prevention registries to support current clinical trials; and (5) provide patients with imminent risk priority in treatments being studied in clinical trials (Reiman et al., 2011).

The Innovative Medicine Initiative funded the European Prevention of Alzheimer's Dementia (EPAD), which focuses on secondary prevention methods and developing successful treatments through new interventions. The goal of the EPAD is to: (1) test different agents associated with pre-dementia populations; (2) develop a registry of 24,000 people at risk of developing AD in their lifetime; (3) create a longitudinal cohort study of 6,000 people and track there progression over time; (4) develop a concept trial of 1,500 participants; and (5) coordinate with other organizations in order to play a crucial role in the worldwide epidemic (Ritchie et al., 2016, para. 1).

The Global Alzheimer's Platform (GAP) was initiated by the United States to address several challenges associated with clinical trials dedicated to AD research. The GAP has four mainstream goals to address the challenges: (1) develop a registry-cohort recruitment 2) clinical

trial network construction through GAP-Net; (3) create proof-of-concept design in trials; and (4) fundraise and gain sponsorships to maintain finances. The GAP-Net was the most significant project developed to address one of the mainstream goals, and it focuses on developing 'trial-ready network sites' all over the United States. Each trial-ready site is standardized with "increase trial efficiency and quality, decrease trial redundancy, accelerate cohort development and trial recruitment, and decrease trial costs" (Cummings et al., 2016, para. 1). GAP-Net is also associated with the forefront of new drug development for AD because of its ability to test drugs quickly and efficiently. Since the design of GAP-Net has a quick response rate, it allows researchers, pharma companies, and sponsors to make an educated decision on drug investments based on a drug's projected success rate. GAP-track is another initiative developed with the goal of

> establishing a global standing, trial-ready platform to reduce clinical testing cycle times by 2 years or more and achieve greater efficiency and uniformity in trial populations through large, well-characterized trial-ready cohorts, certified clinical trial sites and an adaptive proof-of-concept trial mechanism (Crous-Bou et al, 2017, para. 27).

The GAP initiatives require effort from other global corporations in order to be successful in their worldwide expansion and have relied on Chinese, Japanese, and South American leaders and other national organizations for help in disease prevention (Cummings et al., 2016).

Chapter Three: Patient-Caregiver Burnout

Comprehensive Overview of Caregiver Burnout

The severity of AD disease does not only affect the diagnosed individual, but also the person taking on the role of caregiver. As defined above, caregiver burnout is "the physical and mental exhaustion and emotional withdrawal experienced by those who care for sick or traumatized people over an extended period of time" (Merriam-Webster, n.d, para.1) Caregiver burnout is prevalent in many chronic diseases, - with the demographic shift and aging population of the baby boomer generation - associated with dementia patients, and is becoming a global issue. Caregivers are an integral part in finding a cure for AD, as they are active members in treatment plans for patients and witness possible adverse effects, monitor progress, and report back to doctors, since most patients with AD cannot advocate for themselves. It is imperative that caregivers are supported in their roles to ensure the best possible outcome for both individuals.

There is no certification necessary to take on the role of caregiver for an AD patient. The role can be satisfied by a spouse, child, sibling, or professional caregiver. According to Brodaty and Green (2002),

> Most persons with dementia live at home and are cared for by family and friends, of whom approximately 77% are women, 73% are over 50 years of age, 33% are the sole providers of care, 45% are children of the patient, and 49% are spouses (para. 5).

The implementation of the caregiver into the patient's lifestyle varies and depends on family comfort and financial position. A caregiver can be live-in, half-time, paid, or unpaid.

There are multiple factors that contribute to caregiver burnout, such as psychological, physical, social, and financial burdens. Psychological morbidity refers to the stress, depression,

and anxiety that a caregiver may experience. According to Jorge and colleagues (2019), psychological morbidity is the number one predictor in determining quality of life among caregivers. In a recent meta-analysis, it was determined that "compared to non-caregivers, dementia caregivers report higher levels of stress, more depression and anxiety symptoms, and lower levels of subjective well-being, self-efficacy, and anxiety' (Pinquart & Sörensen, 2003, para. 1). The reason why AD caregivers experience higher psychological issues is associated with the vast variety of symptoms patients can display. Behavior patterns in AD patients are unpredictable and challenge caregivers. Three risk factors for depression in caregivers of AD patients were determined to include depression in the dementia patient, an ADL score of 12 or greater, and presence of hallucinations, which contributed to depression in caregivers (Shua-Haim et al., 2001). The ADL scale is an assessment that measured the functionality of the AD patient and their ability to perform everyday tasks. Patients have the tendency to wander during the day and at night, have emotional outbursts, and can act in inappropriate ways (Pinquart & Sörensen, 2004). While their behavior is unintentional, it can be mentally draining on caregivers, especially when there are more negative moments than positive. Mahoney and colleagues (2005) analyzed anxiety and depression among family caregivers of AD patients. In the study, 153 patient-caregivers were interviewed, and it was determined that females are more at risk for developing psychological morbidity, as 23.5% of caregivers reported significant levels of anxiety and depression (Mahoney et al., 2005). Family caregivers are at even higher risk of anxiety and depression, as they experience an extended grieving time. They experience grief twice, first watching their loved ones lose their unique personality, and later during the physical death of their loved one.

Physical health of caregivers in another factor highly associated with caregiver burnout, because there is evidence that it is poorer than non-caregivers. There is a symbiotic relationship between stress and physiological human responses and, therefore, alters the body. Stress induces elevated levels of stress hormones in the body, which can cause "hyperglycemia (elevated levels of blood sugar), hyperinsulinemia (elevated levels of blood insulin), higher blood pressure (BP), and poorer immune functioning" (Vitaliano, Young, & Zhang, 2004, para. 6). Hyperglycemia and hyperinsulinemia can lead to diabetes if not managed, which can then increase coronary risk and cause low levels of high-density cholesterol and obesity. A meta-analysis was conducted by Vitaliano and colleagues (2003) and determined six categories of physiological responses that were associated with caregiver burnout, including antibody response to vaccines and viruses, number of immune cell markers, functional cellular immunity, cardiovascular levels, metabolic measures, and stress hormone levels. The results of the analysis showed that "caregivers reported poorer global health and took more medications for physical problems than non-caregivers did. Furthermore, they had 23% higher levels of stress hormones, and a 15% lower level of antibody responses" (Vitaliano et al., 2003, para. 6). Caregivers' reduced resistance to viruses was an important discovery, because they are constantly around a population of people who are at high risk of acquiring viruses and spreading them faster, as compared to their counterparts.

Social isolation in caregivers of AD patients is rather common, especially among females. The continuous progression of the disease requires more effort from caregivers as time goes on. The ability of caregivers to take time for themselves diminishes, and eventually social interactions and leisure activities that were once enjoyed are limited. According to Brodaty and Pavlovic (1990), caregivers reported not seeing another person besides their patient for more than a week. Females rely on social support and social interaction for their own self-efficacy,

and the social isolation experienced while caregiving takes a toll on their ability to cope with their emotions. Etters and colleagues (2008) found that male caregivers "experience a lack of positive outlook and a need for social support, while females reported increased CB in their relationships with other family members as well as an increase in their own health problems" (para. 6). Men do not rely on relationships for social support as much as females do, which is why male caregivers do not have as many reported health issues or psychological morbidities as female caregivers.

The financial burden associated with AD is a main stressor for a family caregiver, such as a spouse or adult child. In this case, the caregiver is responsible for all financial needs of the patient, such as doctors' appointments, medication, and certain therapies, while not getting paid for their hard work. The average caregiver works 50 to 286 hours per month and works close to 36-hour days (Brodaty & Green, 2002). This constitutes a lot of hours of unpaid work dedicated to the care of another person and a notable disruption in their ability to find paid employment. In a report by Howard and Gibson (2008), "an estimated 52 million caregivers, or 19% of the U.S. adult population, provide unpaid care to family and friends aged 18 years and older over the course of a year" (para. 3). In addition, the annual economic value associated with informal caregivers is $375 billion in 2007 alone (Howard & Gibson, 2008). Even if the family chooses a professional caregiver instead of taking on the role themselves, it is still a financial burden. The national average cost of assisted living facilities or a live-in caregiver for AD patients is $4,000 a month. A high percentage of patients placed in a nursing home facility is due to their informal caregiver experiencing caregiver burnout. The kinship between patient and caregiver places a higher burden on the caregiver. Even after patient relocation to an assisted living facility,

caregiver burnout remains for at least a year after, because they question whether or not they made the right decision (Elmstahl et al., 1998).

Cultural background and socioeconomic status have been deemed as a potential risk factor for developing patient-caregiver burnout. As the baby boomer generation continues to age, there will be a shift in demographic among ethnic groups. According to Hinton and colleagues (1999), "by the year 2020, the percentage of White older adults will decline by 10%, and the proportion of minority older adults will increase to 23% of senior households" (para. 2). It is suggested that different ethnic groups handle and cope with stress differently in their roles as caregiver. Knight and colleagues (2000) have suggested that this difference in coping mechanisms among ethnic caregivers is associated with background variables, severity of illness among different groups, social support, and cultural values. For instance, there are higher divorce rates among African American and Native Americans and higher birth rates, creating less spouses and more children available to take on the caregiver role. There is also a higher rate of female caregivers due to the gender-role socialization among minorities. African Americans, Hispanics, and Native Americans have statistically lower education and income, which has led ethnic caregivers to lack knowledge about the disease and overestimate their ability to be able to take care of their loved one (Pinquart & Sorensen, 2005). Pinquart and Sorensen (2005) provided evidence that Asian Americans and Latinos do not differ from Caucasians in burden but report more depressive symptoms than Caucasians. Ethnic minority caregivers also report more physical health issues than whites, which indicates an increase in risk of becoming caregivers (Sörensen & Conwell, 2001).

Cultural norms and values also influence caregiver burnout in minority groups. Western cultures tend to emphasize individualism, meaning they prefer freedom among individuals

instead of a collective state of control. Non-western cultures emphasize collectivism and familism, meaning that the needs of the family are more important than a single individual. White caregivers tend to follow a more individualistic routine versus minority caregivers emphasizing family (Pinquart & Sorensen, 2005). According to Lee and Sung (1998), Asian Americans require the oldest son and his wife to be the caregiver. In a report from Lawton and colleagues (1992), African Americans and Hispanic caregivers follow more traditional familial ideology and receive more support from relatives and children than whites. In terms of formal services, such as assisted living or a live-in caregiver, African Americans and Hispanics are less likely to use them, because of their ideology and possible lack of accessibility due to societal factors, the United States' healthcare system, and individual factors. Some minority groups also believe that it is unacceptable to put their loved ones in a nursing home, and instead use community-based services that are provided. The differences between ethnic groups are very dependent on samples and subgroups that are studied; therefore, there is research that supports both sides of formal and informal caregiving among various ethnic groups (Williams & Wilson, 2001).

Assessment of Caregiver Burnout

Symptoms of caregiver burnout include emotional and physical exhaustion; changes in sleep patterns, appetite, and weight; loss of interest in activities; withdrawal from family and friends; and suicidal tendencies (Pathak, 2020). Screening and monitoring tools have been established since caregiver burnout has become so prevalent in relation to AD. It is important to note that, given the emerging nature of the field of caregiver burnout, additional research is warranted to develop more all-encompassing assessment tools to fully gauge the depth and

breadth of the AD caregiver experience. Nevertheless, there are several effective assessment tools currently available upon which future research may build.

The Zarit Burden Interview (ZBI) is the most common scale used for assessing burnout among AD caregivers. The ZBI is a "22-item questionnaire measuring subjective burden, which has demonstrated high consistency and validity, and a higher score indicates greater burden" (Zarit et al., 1986, para. 1). The caregiver strain index (CSI) is another easily accessible tool that consists of 13-questions related to employment, finances, physical health, social health, and time. A score of seven or higher positive items suggests further follow-up with a doctor to receive more in-depth assessment and treatment (Sullivan, 2002). Therefore, it is important for families to be aware of the symptoms associated with burnout, so they can obtain the help they need before their health takes a detrimental toll. A healthy caregiver is imperative for fostering healthy patients.

The ZBI was used successfully in Thailand to compare quality of life and subjective burden among AD patient caregivers at the Psychiatric Outpatient Unit of Siriraj Hospital in Bangkok, Thailand. Along with the ZBI, the Pictorial Thai Quality of Life (PTQL) scale was used, and questionnaires were distributed among 155 dementia caregivers (Sittironnarit et al., 2020). The results indicated that 40 percent of caregivers who answered the questionnaire experience some type of burden from their job. Individuals who were from high education, income, and showed a passion towards caregiving were less likely to experience burden because of their high-quality lifestyle. Individuals who experienced more characteristics of burnout and a lesser quality of life were mostly female with financial problems, illnesses, low income, low education, and responsible for taking care of multiple family members. Consequently, caregiver

burnout was highly associated with caregivers' overall quality of life, socioeconomic status, and passion for their job (Sittironnarit et al., 2020).

The Caregiver Guilt Questionnaire was created to measure feelings of guilt among caregivers, especially caregivers of dementia patients. Development of the questionnaire was done through face-to-face interviews with 288 dementia caregivers (Losada et al., 2010). Five main factors were retained from the interviews and were variables found most often: 1) guilt about doing wrong for the patient, 2) guilt about not being good enough, 3) guilt about personal care, 4) guilt about neglecting other family members, and 5) guilt about hatred towards the patients. Validation of the questionnaire was determined through associations with the ZBI. Higher scores on the Caregiver Guilt Questionnaire relate to higher scores of depression, anxiety, and behavioral issues. Those respondents who also score higher on this scale tend to be women caring for an ailing parent. The importance of this scale is that it can be used as a means to acknowledge and validate caregivers' feelings, and to let them know that they are not alone in their feelings of guilt. The scale is also helpful in determining useful psychological interventions to reduce caregiver burnout (Losada et al., 2010).

The Screen for Caregiver Burden (SCB) is a 25-item questionnaire that is used as a means to determine caregiver burnout among AD caregivers. The test measures the amount of negative experiences and the caregiver's response to those negative experiences that results in overall burden (Vitaliano et al., 1991). A rapid screening test for caregivers became high in demand over the past couple decades with the continued increase of AD patients and the continued decrease in available caregivers. Hirschman and colleagues (2004) developed a faster and shorter version of the SCB that gave clinicians the ability to rapidly assess suspected cases of caregiver burnout among AD caregivers. The development of the test took place in the memory

disorders clinic of an AD center and analyzed 251 AD patient-caregiver dyads. The rapid test used measurements of Screen for Caregiver Burden (SCB), Center for Epidemiologic Studies Depression scale, Medical Outcomes Short Form, Mini-Mental Examination, and characteristics of depression, anxiety, and fatigue amongst the AD patient-caregiver dyads. The results showed seven factors with a high association and correlation, which were then used to create the shorter scale for the rapid test. The rapid test has been used in multiple clinical diagnoses since its development. One patient claimed that the rapid test was more enjoyable, because the questions are straightforward and aim towards the main themes of social, emotional, and physical well-being. Physicians have also reported that they prefer the rapid test because it allows them to diagnose and treat specific causes of burden faster and gain all the information necessary to do so (Hirschman et al., 2004).

A psychological examination is an instrumental part in the diagnosis of caregiver burnout. The Perceived Change Index (PCI) consists of 13-items analyzing caregivers among different demographics and measures their acknowledgement in the importance of or decline in their own self-care (Gitlin et al., 2006). The National Institute of Aging-Funded Resources for Enhancing Alzheimer's Caregiver Health Initiative administered the test to 255 caregivers, and determined three underlying factors among caregivers, including somatic well-being, affect, and ability to manage. Individuals with higher scores on the PCI tend to be less depressed because of their acknowledgement of the importance of self-care and social interaction with others. In terms of demographics, groups that had lower PCI scores and higher scores of depression were among African Americans, males, and spouses of ailing patients. This index is valid to use in further studies, as it functions as a way of determining caregiver acknowledgement of well-being and how the lack of acknowledgement contributes to burnout (Gitlin et al., 2006).

A physical health examination is another instrumental part in the diagnosis of caregiver burnout. The Swedish National Study on Aging and Care (SNAC) conducted a longitudinal general population study called Good Aging in Skane. This group was then used in another study that examined the health of informal caregivers versus non-caregivers. Ekström and colleagues (2020) used several measurement tools to determine the health of caregivers versus non-caregivers and included 5457 individuals who answered questionnaires based on socioeconomics, demographics, health, life circumstances, and whether they are a caregiver. The Gothenburg QoL instrument was the measurement tool used to determine the symptoms scale, because it is a psychometric evaluation of assessment of symptoms and well-being among women in the population. The questionnaire asked the individual questions related to 23 somatic symptoms and 10 psychological symptoms. Thirty-three self-reported symptoms were recovered from questionnaire answers and divided into seven domains, including depressive, musculoskeletal, gastrourinary, cranial pain, cardiopulmonary, tension, and metabolic rates. Ekström and colleagues (2020) determined that caregivers had higher rates of depression, tension, gastrourinary symptoms, and fatigue compared to non-caregivers. While this trend has been evidenced in previous studies, the use of a different assessment tool confirms that multiple assessment tools can provide the same results.

Islam and colleagues (2017) used several assessment tools that were not necessarily designed for caregiver burnout, but combined them to collect data that related to caregiver burnout. The goal of the study was to analyze the characteristics of caregivers in care facilities (e.g., nursing home) and associated stress levels compared to caregivers in residential facilities (e.g., retirement home) and associated stress levels. Questionnaires were given to 212 caregivers from 72 care facilities. The assessment tools used for the questionnaire were

general health and wellbeing (SF-12); stress (Work Stress Inventory); job content (Karasek Job Content); approach to, and experience of, working with people living with dementia (Approaches to Dementia Questionnaire; and Experience of Working with Dementia Patients); and Productivity and Health Status (SPS-6) (Islam et al., 2017).

Islam and colleagues (2017) determined that caregivers who worked in a nursing home experienced more burnout than caregivers who worked in a residential home. The multiple patients' caregivers were responsible for in the nursing home increased pressure and caused them to report that their mental health inhibited their ability to perform job-related tasks. The results edified how important it is for caregivers to be trained in dementia caregiving in order to more adequately prepare them for the emotional and physical demands of the job (Islam et al., 2017).

Caregiver Burnout Intervention

Establishing a community of resources and interventions to aid in the alleviation and prevention of caregiver burnout is a priority for families around the world. Once caregiver burnout is clinically diagnosed, it is the role of health care providers to provide resources and treatments to address and treat burnout. It should also be the job of the physician to educate individuals, especially family members, on interventions that can be done before starting their role as caregiver to reduce developing burnout. Counseling, education, preplanning, self-care, and professional caregiving are all types of interventions being investigated to determine if they are effective methods in treating burnout, ex. Counseling can benefit caregivers by giving them an outlet to vent their feelings, and then, in return, have those feelings validated by a specialized neutral individual. Educating caregivers on what to expect when taking care of an individual with AD is important, because it can increase their confidence and enable them to perform better as caregivers. In addition, educating caregivers on the signs and symptoms associated with

burnout will encourage them to seek professional help. Hiring a professional caregiver is not taking the easy way out, but instead allows the family caregiver to maintain their own identity. Self-care of the caregiver themselves is imperative for their own mental health, which is why more support groups are being developed to avoid the social isolation some caregivers may feel (Kasuya et al., 2000).

A study conducted by Spruytte and colleagues (2006) researched the dyadic relationship between patient and family caregiver and determined risk factors that led to the institutionalization of the AD patient. The results showed that making home improvements that included assisted living devices, such as stair chair lifts, reduce the risk of family caregivers institutionalizing their loved ones. Spruytte and colleagues (2006) suggested that practitioners should be educated in home improvements and make those suggestions to caregivers during visits. Pinquart and Sorenson (2006) also determined that psychoeducational interventions, such as active role playing, showed caregivers what their reality would be like and reduced depression because they were more prepared. Acton and Kang (2001) conducted a meta-analysis to determine effective treatments for caregivers that experience burnout, specifically counseling, psychoeducation, and respite care. The meta-analysis was inconclusive in determining effective treatments but did suggest that a combination of interventions could have a significant impact (Acton & Kang, 2001). Family intervention programs that address stress management and coping skills have been found to have significant benefits in reducing depression in caregivers and improving the overall quality of life for both patient and caregiver (Marriott et al., 2000).

Some researchers have suggested that a clinical belief set should be implemented more in caregivers in order to reduce burnout. In a study conducted by Hepburn and colleagues (2001), caregivers were randomly assigned to an immediate training group or a wait-list control group.

The training program focused on teaching caregivers stress management and coping mechanisms and was provided for seven weekly two-hour sessions. Hepburn and colleagues (2001) concluded that the caregivers who went through the training program were more emotionally stable, less depressed, and had a better understanding of the knowledge and skills needed to take care of their loved ones. The implementation of a collaborative care model among AD caregivers has also been a topic of study in the medical community. A collaborative care model is a

> systematic approach to the treatment of depression and anxiety in primary care settings that involves the integration of care managers and consultant psychiatrists, with primary care physician oversight, to more proactively manage mental disorders as chronic diseases, rather than treating acute symptoms' (Eghaneyan et al., 2014, para. 1).

Callahan and colleagues (2006) studied the effects of burnout when a collaborative model was implemented with the aid of geriatric nurse practitioners. Caregivers were randomly assigned to groups: one group receiving collaborative care management and the other traditional care management. Those patients who received collaborative care management received the intervention for one year and integrated a geriatric nurse into their everyday lifestyle. Ultimately, “collaborative care for the treatment of AD resulted in significant improvement in the quality of care and in behavioral and psychological symptoms of dementia among primary care patients and their caregivers" (Callahan et al., 2006, para. 7).

The Resources for Enhancing Alzheimer’s Caregiver Health (REACH) was one of the largest randomized trials studying effective interventions for burnout in AD caregivers funded by the National Institute on Aging and the National Institute on Nursing Research. The study analyzed nine interventions and two control conditions across six REACH sites with a sample of 1,222 caregivers. Each REACH site provided interventions that focused on family systems,

psychoeducation, group support, skill training, home management adaptations, technological advances, and individual knowledge. The goals of the study were to

> (a) to test diverse theory-driven caregiving interventions, (b) to develop a standardized outcome protocol to assess the impact of different strategies on caregivers and their care recipients, and (c) to create a common database that would enable the pooling of data across sites' (Wisniewski et al., 2003, para. 3).

After six months, the results showed that the intervention groups had lower burnout rates than the control groups. Nevertheless, it is important to note that not all interventions would work for each caregiver, which is why a broad range of interventions was implemented. Caregivers can then adapt the interventions to their routine and to the individual needs of the patient (Wisniewski et al., 2003).

The German adaptation of REACH II was a study developed by the United States to adapt their REACH program to the German health care system (Berwig et al., 2017). The initiation of the REACH intervention led the German health care system to realize a gap in their coverage when it comes to caregiver burnout. REACH II, Resources for Enhancing Alzheimer's Caregiver Health II, is a multicomponent intervention that analyzed 92 informal caregivers of AD patients. The multicomponent intervention occurred over 12 two-week sessions of five modules. The goal of the intervention was to reduce caregiver burnout in a short period of time and teach caregivers effective coping mechanisms. The results of the study showed that burnout only decreased slightly. However, after a three-month follow up, caregivers reported that they experienced an increased quality of life through applying the coping mechanisms that they learned during the intervention period (Berwig et al., 2017).

A ‘memory club’ is an emerging intervention for both early-stage dementia patients and their caregivers. A ‘memory club’ is a program with 10 group sessions that educate patients and caregivers about what to expect along their journey. The goal of these sessions is to provide emotional support for both individuals, and to allow the patient themselves to be educated on their illness while they are still able to make decisions. During the sessions, caregivers meet with other caregivers, patients meet with other patients, and then conclude each session collectively. The setting allows each individual to receive the emotional support they need and then share the information they learned within their dyad to form a cohesive relationship between caregiver and patient. Early evaluations of the ‘memory club’ were positive, although further longitudinal research is needed to determine whether they are effective in preventing burnout (Zarit et al., 2004).

There are several gaps in the research associated with effective interventions for caregiver burnout in AD patients. According to Sörensen and Conwell (2011), the first gap is that more research needs to be conducted to determine the characteristics of caregivers that make them the most vulnerable to burnout. Sörensen and Conwell (2011) suggested that a pre-intervention assessment needs to be created to identify caregivers who should participate in interventions before they start experiencing signs and symptoms associated with burnout. Several screening tools have been examined during testing trials, but none have been shown to have validity. The second gap in the literature is moderator and mediator factors that explain the variation in caregiver experience. In order to understand why caregivers, have different experiences, “more studies that examine caregiving’s ‘dynamic predictors of change’ to investigate how changes in certain indicators confer long-term risk, describe and compare trajectories and patterns, and identify which subgroups are most distress-prone or resilient”

(Lafortune et al., 2009, para. 5). Longitudinal studies also need to be conducted to investigate emotional behaviors and reactions that lead caregivers to institutionalize their loved ones (Sörensen & Conwell, 2011).

Better understanding of the biological mechanisms of the stress response with associated risk factors among caregivers is another topic that warrants further investigation. Stress plays the most important role in burnout and understanding the biological stress mechanism specifically with burnout can identify interventions that can aid in "cardiovascular reactivity, atypical diurnal cortisol patterns, and increased proinflammatory protein levels that caregivers experience" (Sörensen & Conwell, 2011, para. 19). The biological mechanism associated with sleep disturbance in caregivers also needs to be further investigated. McCurry and colleagues (2005) investigated sleep disturbance among 36 AD patients and their caregivers. The caregivers who received treatment were provided with a sleep hygiene program, sleep management skill training, and were instructed to increase daylight exposure through the use of a light box, while the control group only received general education about caring for a dementia patient. McCurry and colleagues (2005) confirmed that "patients with AD who are experiencing sleep problems can benefit from behavioral techniques (specifically, sleep hygiene education, daily walking, and increased light exposure) that are known to improve sleep in nondemented, institutionalized older adults" (para. 7). While there was improvement in the AD patient, further research needs to be conducted to address caregiver sleep disturbance and sufficient dosage, as well as the cost-effectiveness of treatment (Sörensen & Conwell, 2011).

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