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Exploring Alzheimer's Disease (Alzheimer's Type Dementia)

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Dementia is considered to be a progressive, static, and remitting disease that is associated with changes in an individual's personality, behavior, and mental abilities over time. The most common observable characteristic of dementia is the loss of memory and the skills that are needed to carry out everyday activities. There are various types of dementias (e.g. Alzheimer's disease (AD), vascular disease, Lewy body dementia, Huntington's disease, AIDs-Related Dementia, dementia caused by Parkinson's disease, dementia cause by Creutzfeldt-Jacob disease etc.,), but the focus of this final paper will provide a concise overview of Alzheimer's disease (AD) or Alzheimer's type dementia. Firstly, dementia has the ability to cause significant impairments as it relates to the performance activities of daily living and functioning. As it stands, dementia affects as many as 10% of people that are older than 65 years and more than 24% of those people that are older than 85 years of age. As the lifespan of humans continue to lengthen the incidence of dementia is increasing. With the progressive nature of dementia an individual may have about only 7 years to live after diagnosis. The history of Alzheimer's disease stems from its description in 1901 by the German psychiatrist Alois Alzheimer. He gave a lecture in 1960 that identified the unusual disease of the cerebral cortex that affected a woman in her fifties, Augustine D, which lead to memory loss, disorientation, hallucination, and eventually her death at the age of 55. As of today, the pathologic specifics of Alzheimer's disease are still not clearly understood but the hypothesis is that it is attributed to the blockage of information by neurofibrillatory tangles. The presence of neurofibrillatory tangles, amyloid plaques, and neuron loss tend to occur throughout the brain with particularly prevalent in the medial temporal lobes.

Keyword: Alzheimer's Disease; Risk Factors; Disease Management; Pharmacological And Non-pharmacological Interventions

INTRODUCTION: Dementia is considered to be a progressive, static, and remitting disease which is generally characterized by a notable decline of mental abilities accompanied by changes in an individual's personality and behavior over time (Moczymski, 2005).

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Dementia can be associated with a loss in memory and skills that are required to carry out or fulfill every activities of daily living. There are various types of dementia (e.g. Alzheimer's disease (AD), vascular disease, Lewy body dementia, Huntington's disease, AIDs-Related Dementia, dementia caused by Parkinson's disease, etc.,) but the focus of this paper will be on an overview of Alzheimer's disease (AD) or Alzheimer's type dementia (Hahn, Albers, & Reist, 2008). Dementia of any type has the

potential to cause significant impairment in any individual who is afflicted with the disorder a diagnosis most certainly can prove to be terminal with time.

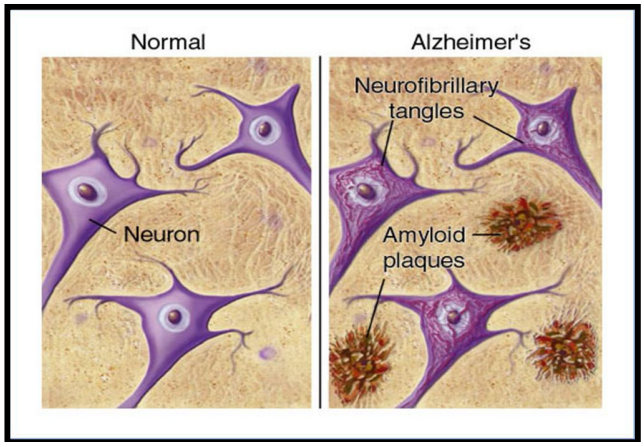

Fig 1: Comparison between Normal and Alzheimer's State

Firstly, dementia is recognized as a serious medical condition that afflicts as many as 10% of individuals older than 65 years and more than 24% of those older than 85 years of age. The incidence of dementia is increasing as lifespan continues to lengthen as the population ages. The prevalence rate of dementia can vary from 2.5% to 24.6 % of the population over 65 and this prevalence tends to double every 5 years after the age of 65 (Moczymski, 2005). The average life expectancy after diagnosis is about seven years. The progressive nature of the disorder ultimately lead to death within a few years after a diagnosis is made. Alzheimer's disease is considered to be one of the most common cause and form of dementia. It is thought to be associated with more senile dementia than vascular dementia (Hersen, Turner, & Beidel, 2007).

The incurable, degenerative, and terminal disease was initially described by the German psychiatrist Alois Alzheimer in 1901. In 1906, Alzheimer gave a lecture which would make him famous because in the lecture he identified an unusual disease of the cerebral cortex which affected a woman in her fifties, Augustine, D, and the disease led to memory loss, disorientation, hallucinations, and eventually her death at the age of 55. The post-mortem examination of Augustine D displayed abnormalities of her brain where the cerebral cortex was thinner than normal with senile plaque and neurofibrillatory tangles which had previously only been described in elderly people (Alzheimer's disease International 2008). The loss of intellectual and social abilities in older people had been described throughout history but it was surprising to witness this development in a middle-aged individual. As of today, the pathological diagnosis of Alzheimer's disease is still generally based of the same investigative methods that were used by Alzheimer and other researchers in the early twentieth century. While the cause and process of Alzheimer's cause is not well understood, the proposed pathophysiology or pathologic specifics of Alzheimer's disease is thought to be attributed to the blockage of information by neurofibrillary tangles (threaded like tangles of protein between neuron that are composed of the protein tau). The neurofibrillatory tangles forming within the neurons tend to cause death to the surrounding cells. The existence of neurofibrillatory tangles, amyloid plaques, and neuron loss tend to occur throughout the brain but are particularly prevalent in the medial temporal lobes such as the amygdale and the hippocampus (Pinel, 2009). As the disease progresses the frontotemporal and parietal association area becoming increasing involved and there is also subcortical neuron loss in the nucleus basalis of the mynert (Moczymski, 2005). The significant changes that can occur in the brain in individuals with Alzheimer's disease have been categorized into four basic categories, (1) primary events that are related to genetic factors and some death of nerve cell apoptosis, (2) secondary events that include beta amyloid deposition, cytoskeletal and tau changes resulting in synaptic loss, (3) tertiary changes that can occur with neurotransmitter deficits, tropic alteration and immune dysfunction, and (4) quaternary events that can involve changes in calcium metabolism, free radical formation, and circulatory alternation in the brain after cell death (Gilman,1997).

Clinical Features of Alzheimer's Disease

First of all, when it comes to determining whether or not a person may potentially have Alzheimer's disease there are clinical features that can serve as indicators of the disease process. First of all, a significant feature of the disorder is that it presents with a rapid onset with a gradual progression of the symptoms (Frisoni, Padovani & Wahlund, 2003). One of the dominant features that can be observed early with the disease process is memory loss and patients typically come to their family doctor's office with complaints about their absent mindedness or after it has been brought to their attention by others, and this is followed with forgetting day-to-day events, a tendency to repeat statements or thoughts, and possible word-finding difficulties (Mocznyski, 2005). Also, other early clinical features of Alzheimer's disease include the reduced ability to plan, judge, and organize and relative preservation of remote memory (Reger, 2003). As the disease gradually progress the formation of memory for new event can become problematic and the memory of childhood or early adulthood can remain intact. The intermediate phase of the disease progress consists of the deteroriation of logical, reasoning, planning, and organizing, a worsening of the person's remote memory, and a greater difficult with word finding or deteroriation in language. Over time and during the latter stages of the disease, long-term memory become significantly more impaired and a severe deterioration of all cognitive modality and lack of control of bowel function (urinary and bowel incontinence) and near mutism with the illness eventually leading to death. The basis for diagnosing Alzheimer's disease is found within the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision (DSM-IV-TR). According to the DSM-IV-TR Alzheimer's disease is recognized as a disorder of insidious onset with progressive decline of cognitive function resulting in impairment in social or occupational functioning (American Psychiatric Association, 2000). The impairments in recent memory fall within one or more domains that include aphasia(language disturbance), apraxia (impaired ability to carry out purposeful movements) agnosia (failure to recognize or identify objects), or there is a noticeable disturbance in executive function which includes abstract thinking, planning, and carrying out tasks (Hahn, Albers, & Reist, 2008). The cognitive deficits have the ability to cause significant decline from a previous level of functioning. Another reliable instrument for the diagnosis of Alzheimer disease is the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) which lists Alzheimer's disease into three categories of probable, possible, and definitive Alzheimer's Disease (Yaari et al., 2007). Probable AD is defined as deficits in two or more domain of cognitive, decline of memory, and preserved consciousness. Possible AD is considered to have an atypical onset, presentation or clinical course with a co-existing illness that is capable of producing the dementia, and lasting definitive AD fits meets the clinical criteria for probable AD and tissue diagnosis by autopsy and biopsy can lead to confirmation of the disease.

Etiology of Alzheimer's Disease

Secondly, the etiology of Alzheimer's disease still remains elusive and unclear but considerable progress has been made to gain a better understanding of its biochemical and genetic mechanisms (Sloane, 1998). Alzheimer's disease is typically characterized by the presence of neuritic plaques and the degeneration of specific nerve cells. There are approximately 4.5 million people living with Alzheimer's disease. The incidence of Alzheimer's disease sharply increases with age with the most notable being the ages between 65 and 95. The prevalence appear to rise from ~2% in ages 65-69 to 4% in age 70-74, to 8% in age 75-79, to 16% in age 80-85, and to ~35%-40% age >85%(National Institute of Health, 2003).

For Alzheimer's disease, the clinical feature that sets it apart from other types of dementia is defined in the Diagnostic and Statistical Manual

of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), which is that is consists a gradual onset with continuation of cognitive decline and the symptoms are not attributed to medical condition or psychiatric disorder. Vascular dementia, previously called multi-infarct dementia, involves meeting the criteria for dementia but also consist of the presence of focal neurological signs and symptoms. Unlike Alzheimer's disease, the changes with vascular dementia can be sudden with highly variable deficits that are dependent on the location of the lesion (Hahn, Albers, & Reist, 2008). AIDS-related dementia is caused by the effects of the HIV virus on the brain which can bring about apathy, flat affect, or psychomotor retardation. Frontotemporal dementia (frontotemporal lobar degeneration) is characterized by atrophy of portions of the lobes or the lobes shrink. While the signs and symptoms tend to vary one distinctive characteristic is an observable changes in an individual's personality and overtime the person become impulsive, emotionally blunted, and socially inappropriate and in these changes behavioral interventions have to be employed to appropriately manage the individual. Also, Lewy-Body Dementia is characterized by a decline in a person's cognition along with fluctuations in their attention and alertness. In general, Lewy-Body Dementia is associated with repeated falls, delusions, and hallucinations (Hahn, Albers, & Reist, 2008).

Additionally, delirium is another type of cognitive disorder that be mistaken for dementia because delirium is often times superimposed upon dementia because these patients can be sensitive to the effects of medical and physical illness. Delirium is defined as a confusional state that is generally associated with a medical or neurologic disorder. Unlike dementia where the patients are alert people with delirium demonstrate an altered level of consciousness or a reduced awareness of their environment attention, and concentration (Hahn, Albers, & Reist, 2008). There tends to be a waxing and waning of delirium symptoms throughout the day but it is to be treated as a medical emergency because if may be fatal if left untreated. Mental retardation and amnestic disorder are examples of other cognitive syndromes and disorders that can be confused with dementia. Mental retardation involves concurrent deficits or impairments in adaptive functioning and amnestic disorder can involve severe and persistent memory loss but cognitive and perceptual functioning can be intact (American Psychiatric Association, 2000).

When it comes to performing an assessment for Alzheimer's disease it is important to go through a battery of tests that help to rule out other differential diagnoses and possibly lead to the diagnosis of Alzheimer's disease. The routine laboratory evaluations that should be performed for an evaluation of Alzheimer's disease include a complete blood chemistry, complete blood count with differentials, thyroid function tests, a urine drug screen and urinalysis, vitamin B12 level (potential for sequelae), and EKG, and brain imaging (CT, MRI) to identify potential lesions in the brain. All of these laboratory tests can help a clinician to either lean towards the potential diagnosis of Alzheimer's disease or another disorder that may be the culprit for the impairment.

Risk Factors for Alzheimer's disease

There are specific risk factors that have been associated with the development of Alzheimer's disease. Alzheimer's disease has a major genetic component. A genetic or positive family history is a second risk factor for the development of AD. People with an Alzheimer's victim in their immediate family have a 50% chance of being stricken with the disease if they survive into their 80s (Pinel, 2009). Additionally, first-degree relatives with Alzheimer's disease have a 3-4 fold age-corrected increase in risk and there is an increase in relative risk to 7.5 in persons with 2 or more first-degree relatives (Herbert et al., 2003). Much of the research on genetic of Alzheimer's disease has primarily focused on rare-early-onset familial forms of the disease and several gene mutations have been identified as being associated with early-onset Alzheimer's disease. Most cases of Alzheimer's disease actually do not exhibit familiar inheritance but genes may act as

risk factors. One of the best know risk factor is the inheritance of the €4 allele of the apolioprotein E (APOE) which is implicated in up to 50%of late onset sporadic Alzheimer's disease. Since the release of the first studies in 1993 identifying a connection between the allele ApoE and the late form of Alzheimer's disease, it has been confirmed in other numerous studies that about 65% of all pathologically confirmed Alzheimer's patients carry at least one €4 allele and 12-15% are homozygous for €4 (Mayeux, Saunders & Shea,1998). The exact mechanism by which ApoE4 influences the pathogenesis of Alzheimer's disease is still being researched but the present theory is that APoE4-€4 gene product could potentially be involved in the production and disposal of senile plaques made of b-amyloid and degenerated nerve cells (Civeira et al., 1996). What is known about the APoE-€4 is that is it can serve as a risk factor for Alzheimer's disease, especially in €4 homozygous individuals. Another significant risk factor for the development of Alzheimer's disease is being of female gender. When Alzheimer's disease was first studied it was initially thought the women were had a higher risk of developing the condition because they lived longer than men but further research has shown that women are more likely to be affected by Alzheimer's disease than men due to gender not longevity. It is believed that women are at higher risk because of estrogen deficiency after menopause and estrogen is noted to protect against the loss of mental function and memory loss (Pinel, 2009).Furthermore, estrogen is suggested to block the production of bet amyloid which is the main part of the amyloid plaques found in the brain of people with Alzheimer's disease (Galasko et al.m 1994). Along with the female gender, being a women who is over the age of 75 years increases one's chances of developing Alzheimer's disease and this risk increases as one ages. Advancing age is recognized as the number one risk factor for developing Alzheimer's disease. One out of eight people over the age of 65 have a diagnosis of Alzheimer's disease and almost one out of every two people over the age of 85 years have Alzheimer's disease so this disease is generally associated with the older population but does not mean that it only develops in this population. The probabillity of being diagnosed with Alzheimer's disease nearly doubles every five years after the age of 65 (Herbert et al.,2003). Additionally risk factors that have also been linked to Alzheimer's disease include educational level meaning if a person has a lower educational level they are more likely to develop the disease. It is recommended that people should engage in intellectually stimulating activities (e.g. playing chess) or regular social interactions because these have been shown to have a protective effect against Alzheimer's disease. Furthermore, a connection has been identified between serious head injury/trauma and the development of Alzheimer's disease in the future so those who get into the habit of practicing safety measures and not engaging in activities where there is a high risk of falling at a significant advantage. There are also cardiovascular risk factors, such as hypercholesterolemia, hypertension, diabetes, and smoking which are associated with a higher risk of onset and clinical course of Alzheimer's disease. As it currently stands, there is no definitive evidence to support the theory that certain ethnic or racial groups are predisposed to suffering more severely from Alzheimer's disease than others. Further extensive studies are needed before definitive statements can be made about the predisposition to the development of Alzheimer's disease in a specific group. Certain nutritional deficiencies have been closely associated with dementia with the most identifiable being B vitamins and the hallmark of B-vitamin-deficiency dementia is memory loss with possible coordination problems (ataxia)/. While several studies have shown that individuals with dementia and B-12 deficiencies recover once they are given vitamin by injection other studies have shown mental improvement when folate and niacin deficiencies have received supplemental vitamins. Only about 25% of people with dementia as a result of thiamine deficiency recover while 50% of people only show partial recovery.

While researchers do not know what specifically causes Alzheimer's disease it is theorized that is

can be attributed to a variety of environmental factors. When it comes to the environmental factors, migration effects have shown that this can exist in high incidence Alzheimer's disease areas during adult life (Whalley, 2001). Most of the studies that focus on the possible role of environmental factors in Alzheimer's disease have been from case-control methodologies that intended on determining the relate differences in risk of Alzheimer's disease to exposure to different environmental insults. As it currently stands there is no one single environmental factor that has been robust enough to be detected in several studies but the most studied environmental factors include aluminum, zinc, viruses, and food-borne poisons. One of the most controversial theories surrounded aluminum when researchers discovered trace amounts in the brain of patients with Alzheimer's disease but studies that have followed have not been able to confirm or replicate this finding. Zinc has also been implicated in Alzheimer's disease because the suggestion was made that too little zinc was located in the brains, specifically the hippocampus of Alzheimer's disease patients but recent studies have also suggested that too much zinc can also be a problem as zinc caused beta amyloid from the cerebrospinal fluid to form clumps that resemble the plaques found in Alzheimer's disease (The Cleveland Clinic, 2006). The presence of food-borne poison is a cause for concern because certain amino acids that can be found in the seeds of certain legumes may cause neurological damage but while this may not be considered to be a common cause of dementia it could potentially shed some light on the mechanism behind neuron degeneration. Lastly, the presence of virus or other infectious processes in Alzheimer's disease has produced very little hard evidence so further research is needed to explain the connection between viruses and Alzheimer's disease.

Cultural Considerations and Barriers Affecting Treatment

The decision to treat Alzheimer's disease can be faced with cultural factors and/or barriers. Some cultures are not opposed to the implementation of either non-pharmacological or pharmacological interventions to treat Alzheimer's disease. When it comes to managing the cognitive decline and behavioral disturbances associated with Alzheimer's disease the customary practice has been to use non-pharmacological intervention as first line but when these therapies fail to achieve the desired effect with long-term therapy, providers typically resort to pharmacological interventions (Cohen-Mansfield, 2001). In the American culture it is not uncommon to observe the use of pharmacological interventions after non-medication interventions have not achieve their intended purpose but other culture might be opposed to the use of such intervention in a person who is newly diagnosed with Alzheimer's disease. Once the clinical diagnosis of Alzheimer's disease has been made a plan of action must be developed. The purpose of this plan is to temporarily improve cognitive decline, manage the comorbid condition of Alzheimer's disease, and treat the behavioral and psychological symptoms of the disease (Cumming et al., 2002). While there might be opposition to treatment withholding the necessary treatment in certain patient cases can do more harm than good for the individual. A comprehensive management/treatment plan that consists of both pharmacological and non-pharmacological interventions can achieve the optimal outcome for a patient with Alzheimer's disease. As the disease progresses, modifications may need to be made to the treatment plan to appropriately care for the patient. The final decision to provide treatment or withhold treatment can have a significant impact on the symptoms, course, and progression of Alzheimer's disease but a therapeutic intervention that consists of both pharmacological and non-pharmacological intervention a patient can be effectively managed (Doody et al., 2001). While cultural beliefs and attitudes can play a large role as it relates to the type of intervention that a patient receives it should be collaboration between the patient, the family, and the clinician factoring in the values and preferences of the patient and the family when making a final decision (Cumming et al., 2002).

Behavioral and Neuropsychiatric Symptoms of Alzheimer's Disease

The optimal management of the comorbid conditions in patients with Alzheimer's disease can reduce disability and maximize function (Cummings et al., 2002).The behavioral and psychological symptoms of dementia (BSPD) include the presence of depression, psychosis, anxiety, disinhibition, altered circadian rhythms, apathy, and irritability to name a few (Blaszczyk & Mathys, 2007). For example, disinhibition which occurs early, can lead to poor social judgment such as making inappropriate comments or engaging in inappropriate behaviors (Hahn, R Albers, & Reist, 2008). BPSD is considered to be a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors that result from the development of dementia (International Psychogeriatric Association, 2002). It can have considerable negative impact on the quality of life of both patients and caregivers by causing significant distress. It is important to address BPSD because they can result in burden on caregivers and health care institutions, increased hospitalizations, substantial financial costs, and excess disability (Finkel, 2001). When it comes to diagnosing BPSD the practitioner can use direct interview, direct observation, proxy report, and validated measurements and scales for confirmation. Factor analysis of BPSD has theorized that symptoms complexes (e.g. psychosis, depression, anxiety) can exist within individual patients and among the symptom complexes psychosis is one of the most identifiable. The existence of psychosis in BPSD has been defined by an expert consensus process which states that in order to meet the diagnostic criteria the psychotic symptoms must be present for at least one month or longer with symptoms that are severe enough to cause disruption in the patient's and/or other people's functioning (International Psychogeriatric Association, 2002). Another recognizable BPSD is depression and patients are typically diagnosed with depressive pseudodementia or reversible dementia but about 11-23% of individual who are diagnosed with reversible dementia typically become irreversibly demented every year. Depression is common in older adults, especially those with Alzheimer's disease and often times this condition can be untreated (Cummings et al., 2002). Depression that is diagnosed in dementia patients is different than depression that is diagnosed in patients without depression because dementia patients tend to exhibit more self-pity, anhedonia, and psychomotor disturbances. The depression is also more likely to recur so steps must be taken in order to minimize the symptoms when they do appear once again. Furthermore, while agitation may not be considered a part of the symptom complexes of BPSD it is still recognized as an important aspect of the disease. Agitation is defined as the inappropriate verbal or motor activity that is not judged by an outside observer to result from the needs or confusion of the person (Cohen-Mansfield, 1991). The symptoms of agitation can be divided into physical aggressive behavior (e.g. hitting, putting, kicking, biting, etc.,) physically non-aggressive behaviors (e.g. pacing, inappropriate dressing/undressing, repetitive mannerisms, etc.,), verbally aggressive (e.g. screaming, temper tantrums) or verbal non-aggressive (e.g. chanting, repetitive sentences, or frequent interruptions). Lastly, aggressive episodes can be demonstrates in about 12% of dementia patients with a higher incidence of physical aggression compared to verbal aggression. Lastly, while no definitive definition has been given for what characterizes anxiety in BPSD it typically presents in clinical forms such as pacing chanting, or fear of being alone, etc., ((International Psychogeriatric Association, 2002). When it comes to treating these challenging behavioral and psychological symptoms of dementia the recommendation is to have all non-pharmacological measures exhausted before drugs are to be utilized. When drug therapy is required, concurrent non-pharmacologic interventions can assist with reducing dosages, duration, and possibly the complexity of treatment (Cummings et al., 2002).

Neuropsychiatric disturbances or behaviors are common in people with Alzheimer's disease. The neuropsychiatric disturbances of dementia

typically include agitation, aggression, delusions, hallucinations, repetitive vocalizing and wandering which can be observed in about 68% to 98% of patients with dementia, especially in the later stages of the disease (Blaszczyk & Mathys, 2007). As the disease progress these disturbances begin to cause a significant burden on caregivers and their ability to effectively care for the patients with Alzheimer's disease because it makes both professional and lay caregiving difficult (Dowling et al., 2007). On any given day, patients with Alzheimer's disease can exhibit aggressive behavior and often times it can be directed at the individuals who care for them. The impact that neuropsychiatric disturbances can have on caregivers if not appropriately treated include stress, depression and reduction in employment and income. Also, neuropsychiatric disturbances can be associated with an increase in hospital length of stay and eventually lead to nursing home placement once the people who are for the individual with Alzheimer's disease are not equipped to handle their progressively, worsening condition(Blaszczyk & Mathys, 2007). The large amount of the Federal expenditure goes towards the management of neuropsychiatric symptoms and this is expected to triple in the next 10 years. The ultimate goal is to have the interventions that are specifically targeted to treat neuropsychiatric disturbances should have a significant impact on patients, caregivers, and society as a whole.

Medical Comorbidities and Alzheimer's Disease Treatment

Along with the behavioral and neuropsychiatric disturbances of Alzheimer's disease there are also medical comorbidities that must be treated in order to maintain some quality of life. Recent research and advances suggest that vascular risk factors are connected to cerebrovascular disease as well as stroke in the elderly which increases the risk of developing Alzheimer's disease (Wolfson Research Center, 2000) These vascular risk factors include atherosclerosis, atrial fibrillation, and coronary heart disease to name a few. The performance of various autopsies showed that 60%-90% of AD cases exhibit variable cerebrovascular pathology. Stroke occurs in patients with Alzheimer's disease especially those with significantly worsening cognitive decline and outcome. Out of the vascular risk factors, atherosclerotic heart disease is the most common in the elderly population. It has been proposed through research that the number of senile plaques that are found in the brain of Alzheimer's disease patients is related to the severity of coronary artery disease. There are currently no studies that have identified the outcome of those patients with dementia treated with coronary artery disease, angioplasty, or stint placement (Dementia Education & Training Program, n.d.).

It has been noted the existence of traumatic brain injury can lead to a more frequent and greater rate for the development of Alzheimer's disease. The presence of traumatic brain injury has the potential to worsen Alzheimer's disease. The issue that still exists is whether traumatic brain injury increased a person's risk for the future for the development of Alzheimer's disease. There has been substantial research regarding whether mild, repetitive mild, moderate, or severe traumatic brain injuries actually increase a person's risk of developing Alzheimer's disease (Iverson et al., 2006). For the moment, the research is still mixed so there is currently no clear consensus in the literature. The connection between traumatic brain injury and the risk for Alzheimer's disease is hard to study but the current interest in on whether genetic factors can influence the brain's predisposition to injury and also the ability for recovery (Iverson et al., 2006). Lastly, the presence of diabetes and having to regulate blood sugar level in patients with Alzheimer's disease can be challenging as for physicians to maintain a normal glucose level given that this can change based on food consumption, dietary patterns, and stress. Unfortunately, research has shown that having a rigid blood sugar control has minimal impact on the life expectancy of patients with Alzheimer's disease as many patients begin to lose weight in the middle or later stages of the disease as a result of insufficient nutrition (Dementia Education & Training Program, n.d.).

Biopsychosocial Approach to Alzheimer's Disease

The effective management of Alzheimer's disease requires a biopsychosocial approve that include the involvement of the patient and the caregiver (Dementia Education & Training Program, n.d.). In this approach, a person's social context and psychological well-being are recognized as the key factors to the illness and potential recovery, if applicable, along with their thoughts, beliefs, and emotions. The theory of the biopsychosocial approach is to not only treat the disease but also the patient as the psychological and social factors related to Alzheimer's disease can be neglected (White, 2010). It is imperative that clinicians attend to the neuropsychiatric complications of Alzheimer's disease as well as the psychological complications (not only with the patients but also the caregivers) and the social support needs to the Alzheimer's patient. When it comes to the neuropsychiatric complications clinicians ensure that these are not ignored but are appropriately managed either the use of non-pharmacological or pharmacological interventions, or a combination of both therapies. The same process for managing neuropsychiatric complications should also be applied to the psychological complications in order to for the patient to achieve optimal care and with social support needs to emotional and human needs of the patient should be addressed in order for them to maintain some level of functionality with the progressive disease.

Pharmacological Management of Alzheimer's disease

There are many up-to-date treatment approaches, particularly the use of pharmacological agents, that are currently on the market for the symptoms of Alzheimer's disease that are designed to target the cognitive decline, behavioral and neuropsychiatric disturbances. The slowing of the cognitive decline associated with Alzheimer's disease is usually accomplished through the use of a class of drugs called cholinesterase inhibitors or cognitive enhancers that include donepezil (Aricept®), rivastigmine(Exelon®), galantamine (Razadyne®, Razadyne ER®) formerly Reminyl, and tacrine (Cognex®). The cholinesterase inhibitors work by inhibiting acetylcholinesterase (enzyme responsible for the hydrolysis of acetylcholine) thereby this leads to an increase in the central nervous system level of acetylcholine (Hahn, Albers, & Reist, 2008). The purpose of using the cholinesterase inhibitors is to temporarily stabilize cognition and reduce the rate of cognitive decline in patients with mild to moderate Alzheimer's disease (Cummings et al., 2002). When treated with a cholinesterase inhibitors about 20-35% of patients display a seven-point improvement on neuropsychologic tests but prior to the initiation of therapy patients and caregivers must be informed of the fact that only modest benefits can be achieved with these agents. Tacrine was the first cholinesterase inhibitor to be approved for the treatment of mild to moderate dementia of Alzheimer's type in 1993. The use of tacrine has fallen out of favor and is rarely used due to the potential risk for hepatotoxicity which requires the performance of liver tests every other week for 16 weeks and then every 3 months thereafter (Delagarza, 2003). The second cholinesterase inhibitor that was approved was donepezil for the treatment of all stages of Alzheimer's disease in 1997. Donepezil has no reported hepatotoxicity and no significant drug interactions but the most common side effect which is observed with all of the cholinesterase inhibitors is gastrointestinal upset, nausea, diarrhea (Hahn, Albers, & Reist, 2008). The next cholinesterase inhibitor that was released after donepezil was rivastigmine in 2000 for mild to moderate stages of Alzheimer's disease as well as use in Parkinson's disease. Rivastigmine is currently the only cholinesterase inhibitor that is available as a transdermal patch (4.6mg/24 hours and 9.5mg/24hours). Following rivastigmine was galantamine which is approved for mild to moderate Alzheimer's disease and unlike the other cholinesterase inhibitors it also acts on nicotinic receptors (Cummings, 2000). A 2-year placebo-controlled trial conducted in more than 2000 patients with mild cognitive impairments found that galantamine may increase the risk of cardiovascular death because thirteen deaths (MI, stroke) resulted from patients taking

galantamine. Memantine (Namenda®) belongs in a class of its own and works by binding to N-methyl-D-asparate (NMDA) receptors to block the action of glutamine It is used in the treatment of symptoms associated with moderate to severe Alzheimer's disease (Gauthier, Herrman, & Agbokou,2006). It can be used in conjunction with an acetylcholinesterase inhibitor but because of the risk of discontinuation syndrome (or withdrawal reaction) when a cholinesterase inhibitor is stopped it is suggested that there should be a one month overlap between these two drug classes.

Other agents that are used for the cognitive symptoms of Alzheimer's disease include selegiline (Eldepryl®), anti-inflammatory agents, estrogen, and gingko biloba. Some studies have shown that selegiline may lead to improvement in cognition, behavior, and mood but there is little evidence to support a global benefit in cognition, functional ability, and behavior so there is currently not enough evidence to support the use of selegiline for Alzheimer's disease. On the other hand, one well-constructed study, The Alzheimer's Disease Cooperative Study) by Ano and colleagues(1997) showed that the daily administration of 2000iu of vitamin E or 10mg of selegiline may slow the progression of the functional symptoms in patients with Alzheimer's disease and the current expert consensus recommends the use of vitamin E (Cummings et al., 2002). Another class of agents that have been suggested for use in Alzheimer's disease is anti-inflammatory agents with some observational studies indicating that regular use of non-steroidal anti-inflammatory drugs can decrease the incidence of Alzheimer's disease along with having neuroprotective effects but these agents currently have not demonstrated any benefit related to treating Alzheimer's disease. The use of estrogen for Alzheimer's disease has described in descriptive studies of postmenopausal women having a lower risk of Alzheimer's disease.

While estrogen was suggested to be neuroprotective it was shown to improve cognition or function. Lastly, the use of gingko biloba has shown to have modest therapeutic benefit in four trials but several reports of side effects (e.g coma, bleeding, and seizures) have limited its use but alternatively a systematic review showed that it was superior over placebo in improving function (Cummings et al., 2002). With all of the agents that are currently use for the cognitive decline of Alzheimer's disease clinicians must keep in mind and inform patients and caregivers that they only provide symptomatic relief of symptoms and maintain cognitive function for a limited time period.

Non-pharmacological Management of Alzheimer's Disease

The use of non-pharmacological interventions for the behavioral, psychological, and neuropsychiatric disturbances of Alzheimer's disease have been considered to first line for symptoms. The use of non-pharmacological measures has to be exhausted before resorting to the use of pharmacotherapy (Cummings et al., 2002). Some of the non-pharmacological interventions include the use of individualized music therapy, redirecting, and one-on-one contact which have the potential to calm the patients and decrease verbal agitation, aggression, and disruptive behaviors (Cohen-Mansfield, 2001). Also, the use of music and pet therapy has been shown decrease agitation/aggression, and the use of light therapy can aid with sleep disturbances and lessen the severity of sundowning effect.

Behavioral and Neuropsychiatric Treatment of Alzheimer's Disease

There are wide array of pharmacotherapies that are available for the management of the behavior, psychological, and neuropsychiatric disturbances of Alzheimer's disease. The first generation typical antipsychotics (conventional antipsychotic) exert their antipsychotic effects by blocking dopamine receptors (D1 and D2 receptors in the brain) with the D2 blockade being responsible for their therapeutic effect. The typical antipsychotic, haloperidol (Haldol®) has been generally used to control the psychotic and behavioral disturbances in the elderly Alzheimer's patients but troubling side effects

(extrapyramidal side effects, stiffness, immobility, and the increased risk of mortality and cerebrovascular events (CVE) lead the Food and Drug Administration to issue a public warning followed by a black box warming against the use of conventional antipsychotics and second-generation antipsychotics in elderly patients with dementia (Sink et al., 2005). The second generation antipsychotics (e.g. clozapine, risperidone, quetiapine, aripiprazole, olanzapine, ziprasidone, paliperidone, etc.,) work by not only binding to dopamine receptors (D_2) but also serotonin ($5HT_2$) receptors (Davis, Chen, & Glick, 2003). The second-generation antipsychotics were the first to receive the black box warning against use their in the elderly population with dementia for psychosis due to increased mortality, and then the first-generation antipsychotics received the labeling as well when it was determined that they were associated with similar or even higher mortality rates when compared to atypical antipsychotics in elderly patients with and without dementia (Livingston et al., (2007). The results from the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) showed the some of the atypical antipsychotics provide modest benefits on behaviors, psychosis, agitation, and aggression but this was offset by their adverse effects such as anticholinergic effects, hematological effects, weight gain, hyperlipidemia, and sedation (Ücok,2008). Even the adverse effects associate with atypical antipsychotics they are known for producing lower incidences compared to typical antipsychotics and despite the safety concerns these agents have been proven to be effective for the behavioral, psychological, and neuropsychiatric symptoms of Alzheimer's disease. Besides the use of antipsychotics there are other psychotropic medications that can be used to alleviate the behavioral and neuropsychiatric disturbances associated with Alzheimer's disease First of all, mood stabilizers are also used in Alzheimer's disease and while their mechanism of action is unclear it is hypothesized that the range of neurotransmitters affected by these medications and their disparate modes of actions suggest that mania can be controlled at altering the function of the different neurotransmitters. Agitation has been shown to be reduced by the use of mood stabilizer. In a randomized controlled trials conducted for 6 weeks by Tariot and colleagues (1998) consisting of 51 participants the use of carbamazepine was examined with participants receiving a mean dose of 304 mg/day. The results of the trials showed an improvement of agitation in carbamazepine versus placebo on all measures including the Brief Psychiatric Rating Scale. Another mod stabilizer that is one of the most studied is valproic acid is the most studied agent for the behavioral neuropsychiatric disturbances associated with Alzheimer's disease with case reports indicating effectiveness in the treatment of agitation, physical aggression, and disinhibition (Blaszczyk & Mathys, 2007). The use of divalproex sodium (mean dose of 216mg/day) was examined by Porsteinsson and colleagues (2001) during a 6 week study that consisted of 56 participants and the outcome of the study results showed no difference in the total scores between drug and placebo on the Brief Psychiatric Rating Scale. On the other hand, there is no clear benefit with the recommended use of carbamazepine in light of the black box warning for the potential development of hematological toxicity and potential drug-drug interactions (Herrmann et al., 2007). Furthermore, the use of antidepressants, specifically, selective serotonin reuptake inhibitors have been outranked the use of tricyclic antidepressant for the depressive symptoms of Alzheimer's disease given their favorable side effect profile but as a class antidepressants have not demonstrated significant benefits on neuropsychiatric symptoms based on reports from controlled studies but they have been shown to aid with aggressive behavior (Finkel et al., 2004). One study that does stand out in terms of yielding positive outcomes for the use of antidepressants for neuropsychiatric symptoms was conducted by Pollok and colleagues (2002) which consisted of 52 patients on citalopram 20mg/day over 17 days. The study was able to identify that the changes in the Neurobehavioral rating scale for participants on

citalopram was significantly greater than placebo (10 vs. 2.03, $p<0.001$) with agitation and lability improving with citalopram compared to placebo. Lastly, while the exact mechanism of benzodiazepines is unknown it is believe that they exert their therapeutic effect by enhancing the activity of gamma-aminobutyric acid (GABA). Benzodiazepines have been used for agitation management in some patients but have only provided modest response in Alzheimer's disease. Lorazepam has shown significant improvement over placebo in agitation scales two hours when compared to olanzapine but olanzapine and other benzodiazepines are not recommended for long-term management of behavioral and neuropsychiatric disturbances in Alzheimer's disease especially in the elderly population (Meehan et al., 2002).

Current Management and Future Directions

In conclusion, Alzheimer's disease still continues to be a perplexing disease with no clear explanation as to its origin but the scientific/medical community making attempts to understand the pathophysiology of this disease, and agents that can be used to treat the core features of the disease, cognitive decline, behavioral, psychological, and neuropsychiatric disturbances. Based on recommended guidelines, non-pharmacological strategies still remain the cornerstone for the management of Alzheimer's disease-related behavioral symptoms while cognitive enhancers can be used for cognitive decline (Livingston et al., 2007). Pharmacological interventions should only be utilized when deemed to be necessary for problem behaviors. Besides being utilized as first-line agents for cognitive decline with Alzheimer's disease, cholinesterase inhibitors and memantine have been proven to have modest effect for the management of not only cognitive decline but also can be useful for the management and treatment of the agitation, aggression, irritability, and behavioral dysregulation associated with Alzheimer's disease (Borson, 2002). In terms of the future directions, more research is required into the pathophysiology of symptoms of Alzheimer's disease as well as other types of dementia. More quality trials that focus on the use of non-pharmacological interventions in combinations with drug therapy for Alzheimer's disease need to be conducted as multiple interventions are likely to replace single treatment approaches as it relates to the future treatment of Alzheimer's disease. It is hope that future exploration into the complexity of Alzheimer's disease through research will lead to a better understanding and shed some light on some of the unanswered questions that still exist with the disease state and open the door for innovative treatment approaches to combat the disease.

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