Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2022, Volume 10, Issue 08
ISSN: 2321–3647(online)

Neurophysiology and Pathology of Dementia and Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is one of the most devastating brain disorders of elderly humans. It is a decade has witnessed a steadily increasing effort directed at discovering the etiology of the disease and developing pharmacological treatment. Recent developments include improved clinical diagnostic guidelines and improved treatment of both cognitive disturbance and behavioral problems. Symptomatic treatment mainly focusing on cholinergic therapy has been clinically evaluated by randomized, double-blind, placebo-controlled, parallel-group studies measuring performance-based tests of cognitive function, activities of daily living, and behavior. The role of estrogen replacement, anti-inflammatory agents, and antioxidants is controversial and needs further study. Antidepressants, antipsychotics, mood stabilizers, anxiolytics, and hypnotics are used for the treatment of behavioral disturbance. Future directions in the research and treatment of patients with Alzheimer's disease include: applying functional brain imaging techniques in early diagnosis and evaluation of treatment efficacy; development of new classes of medications working on different neurotransmitter systems (cholinergic, glutamatergic, etc.)

Keywords: Dementia, Symptoms and Stages of disease, Etiology, Pathology, Neurophysiology, Risk factors, Causes, Diagnosis, Treatment, Prevalence,

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Received 01 July 2022, Accepted 26 September 2022

Please cite this article as: Malleswari K *et al*., Neurophysiology and Pathology of Dementia and Alzheimer's Disease . American Journal of Pharmacy & Health Research 2022.

INTRODUCTION

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles (Figure 1) as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures[1]. Alois Alzheimer noticed a presence of amyloid plaques and a massive loss of neurons while examining the brain of his first patient that suffered from memory loss and change of personality before dying and described the condition as a serious disease of the cerebral cortex. Emil Kraepelin named this medical condition Alzheimer's disease for the first time in his 8th edition psychiatry handbook [2, 3]. Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease (AD) or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and others [4,5].At present, there are around 50 million AD patients worldwide and this number is projected to double every 5 years and will increase to reach 152 million by 2050. AD burden affects individuals, their families, and the economy, with estimated global costs of US$1 trillion annually. At present, there is no cure for Alzheimer's disease, although there are available treatments that just improve the symptoms[6, 7].

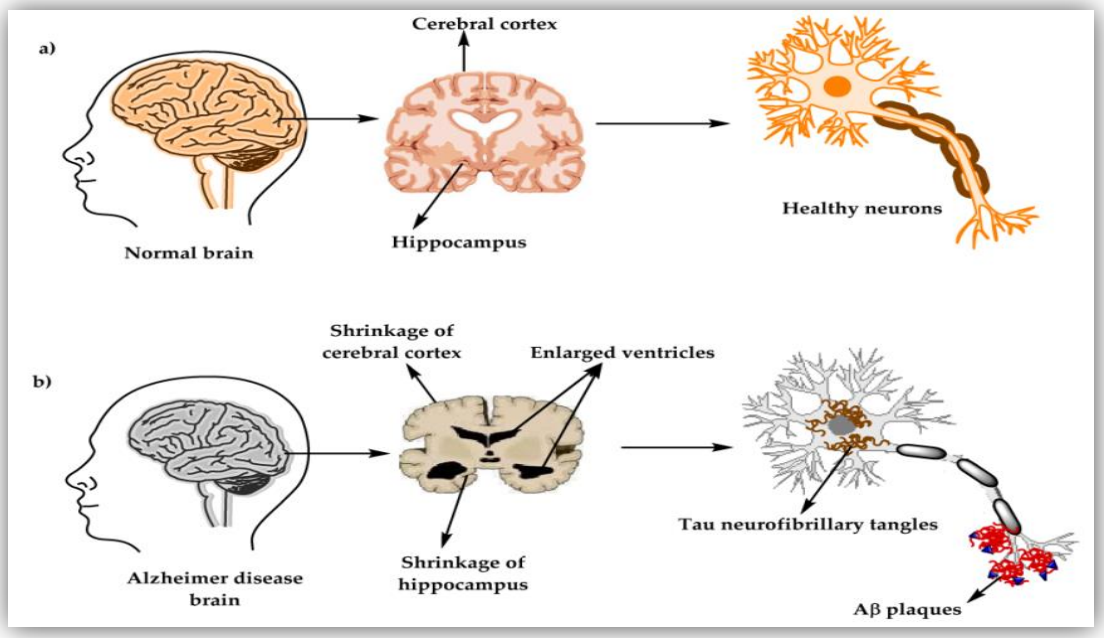

Figure 1: The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease (AD) brain.

Dementia

It is a group of co-occurring signs and symptoms which include memory, language, reasoning, decision making attention. In person it can be recognized by change in personality, emotional regulation and social behavior that occurs which can interfere with social activities and relationships or daily routine activity. There are several causes of dementia such as depression, nutritional deficiency, space occupying lesions and excess addiction of any substance or activities. Certain class of medications is also promoting it in older adult's examples: Anti-cholinergic, analgesic, sedative etc.[8]

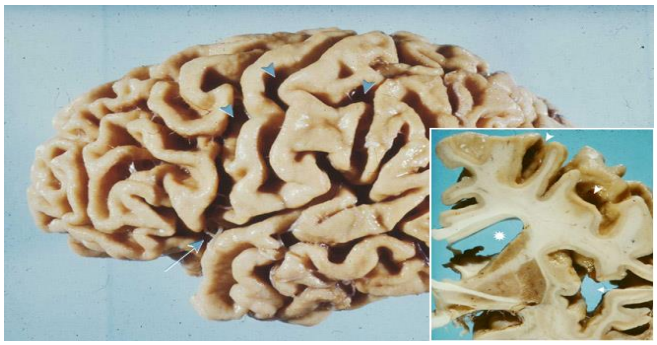

Figure 2: Impact of infection on brain in Alzheimer's disease or Dementia

Symptoms:

Alzheimer's disease is a progressive condition, meaning that the symptoms get worse over time. Memory loss is a key feature, and this tends to be one of the first symptoms to develop. The symptoms appear gradually, over months or years. If they develop over hours or days, a person may require medical attention, as this could indicate a stroke.

Symptoms of Alzheimer's disease include:

Memory loss: A person may have difficulty taking in new information and remembering information. This can lead to:

- repeating questions or conversations
- losing objects
- forgetting about events or appointments
- wandering or getting lost

Cognitive deficits: A person may experience difficulty with reasoning, complex tasks, and judgment. This can lead to:

- a reduced understanding of safety and risks
- difficulty with money or paying bills
- difficulty making decisions
- As getting dressed difficulty completing tasks that have several stages,

Problems with recognition: A person may become less able to recognize faces or objects or less able to use basic tools. These issues are not due to problems with eyesight.

Problems with spatial awareness: A person may have difficulty with their balance, trip over, or spill things more often, or they may have difficulty orienting clothing to their body when getting dressed.

Problems with speaking, reading, or writing: A person may develop difficulties with thinking of common words, or they may make more speech, spelling, or writing errors.

Personality or behavior changes: A person may experience changes in personality and behavior that include:

- becoming upset, angry, or worried more often than before
- a loss of interest in or motivation for activities they usually enjoy[9,10]

Stages of Disease:

Alzheimer's disease can range from mild to severe. The scale ranges from a state of mild impairment, through to moderate impairment, before eventually reaching severe cognitive decline. The sections below will discuss the stages of Alzheimer's trusted source and some of the symptoms that characterize them:

Mild Alzheimer's disease:

People with mild Alzheimer's disease develop memory problems and cognitive difficulties that may include the following:

- taking longer than usual to perform daily tasks
- difficulty handling money or paying the bills
- wandering and getting lost
- confusions in doing regular activities

Moderate Alzheimer's disease:

In moderate Alzheimer's disease, the parts of the brain responsible for language, senses, reasoning, and consciousness are damaged. This can lead to the following symptoms:

- greater memory loss and confusion
- an inability to learn new things
- difficulty performing tasks with several stages, such as getting dressed
- Hallucinations, delusions, or paranoia.

Severe Alzheimer's disease:

In severe Alzheimer's disease, plaques and tangles are present throughout the brain, causing the brain tissue to shrink substantially. This can lead to:

- An inability to communicate.
- Dependency on others for care.
- Being unable to leave bed all or most of the time.
- Loss of basic brain functionality .[11,12]

Etiology:

The main neuropathological features of AD appear to be senile plaques and neurofibrillary tangles. The senile plaques seem to develop first in brain areas associated with cognition, and spread to other cortical areas as the disease progresses. The senile plaques consist, among other components, of insoluble deposits of amyloid β-peptide (Aβ), a fragment of the amyloid precursor protein (APP). Aβ peptide is generated from APP by two consecutive cleavage events: proteolytic activity by β-secretase generates one end of the Aβ peptide, while γ-secretase generates the other end, also by proteolysis. There appear to be two types of Aβ: a longer species, Aβ42, and a shorter species, Aβ40. Aβ42 seems to be deposited initially and may have a role in initiating the events that ultimately lead to amyloid deposition. It is still not clear if the senile plaques are the cause or a by-product of AD, although there are increasing data that dysfunction in the metabolism of APP with subsequent increase in the insoluble Aβ is responsible for AD.[13, 14]

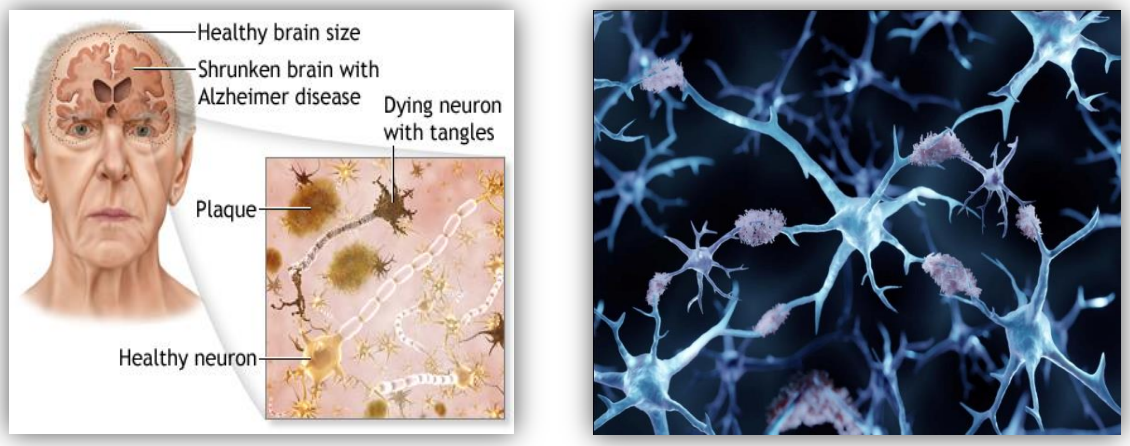

Figure 3: Etiology of Alzheimer's brain (Amyloid plaques and neurofibrillary tangles)

Pathology:

Alzheimer's disease is characterized by an accumulation of abnormal neurotic plaques and neurofibrillary tangles. Plaques are spherical microscopic lesions that have a core of extracellular amyloid beta-peptide surrounded by enlarged axonal endings. Beta-amyloid peptide is derived from a trans-membrane protein known as an amyloid precursor protein (APP). The beta-amyloid peptide is cleaved from APP by the action of proteases named alpha, beta, and gamma-

secretase. Usually, APP is cleaved by either alpha or beta-secretase and the tiny fragments formed by them are not toxic to neurons. However, sequential cleavage by beta and then gamma-secretase results in 42 amino acid peptides (beta-amyloid 42). Elevation in levels of beta-amyloid 42 leads to aggregation of amyloid that causes neuronal toxicity. Beta-amyloid 42 favors the formation of aggregated fibrillary amyloid protein over normal APP degradation. *APP* gene is located on chromosome 21, one of the regions linked to familial Alzheimer's disease.[15]

Amyloid deposition occurs around meningeal and cerebral vessels and gray matter in Alzheimer's disease. Gray matter deposits are multifocal and coalesce to form military structures called plaques. Neurofibrillary tangles are fibrillary intracytoplasmic structures in neurons formed by a protein called tau. They occur first in the hippocampus and then may be seen throughout the cerebral cortex. Tau-aggregates are deposited within the neurons. There is a staging system developed by Braak and Braak based on the topographical staging of neurofibrillary tangles into 6 stages, and this Braak staging is an integral part of the National Institute on Aging and Reagan Institute neuropathological criteria for the diagnosis of Alzheimer disease.[16]

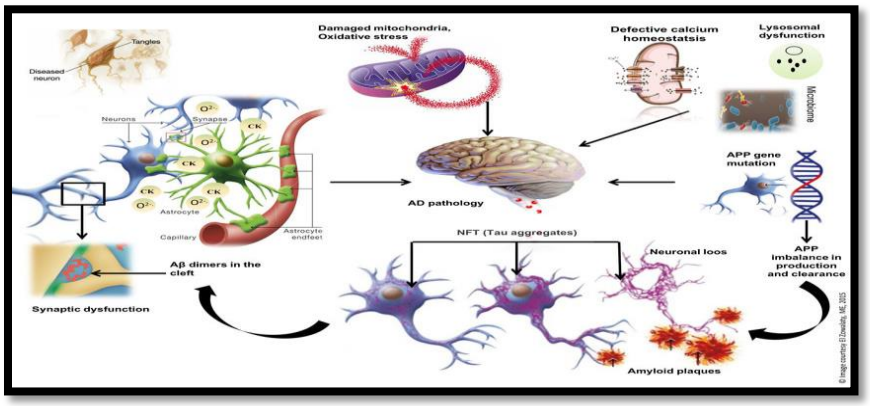

Figure 4: Schematic representation of pathology of Alzheimer's disease

Neurophysiology:

The pathophysiological mechanisms underlying normal aging and neurodegenerative disorders such as Alzheimer's disease (AD) have yet to be fully established. Early recognition of mild cognitive impairment (MCI) and AD requests the identification of biomarkers capable of distinguishing individuals with prodromes from healthy aging adults. Physiological brain aging is characterized by a loss of synaptic contacts and neuronal apoptosis even though neural redundancy as well as functional and structural plastic re-modeling of brain networking promotes maintenance of brain activity in healthy elderly for everyday life. It is, then, important to

implement techniques that are able to measure changes in normal aging brain and to discriminate them from neurodegenerative processes. As oscillatory electromagnetic brain activity is a hallmark of neuronal network function in various brain regions, an integrated approach utilizing modern neurophysiological techniques, including electroencephalography (EEG), event-related potentials (ERPs), and transcranial magnetic stimulation (TMS), [17] This special issue contains a series of cutting-edge articles that provides innovative information and deal with the broad issue of the role of neurophysiology for the assessment of normal aging and dementia. Of necessity, these articles focus on selected topics but the mixture of novel contributions as well as review papers on EEG, TMS and ERP provide an overview and an insight into current areas of debate.

Risk Factors (Protective & Destructive):

Aside from genetic causes of Alzheimer's disease, the exact mechanism of how Alzheimer's develops is still poorly understood, though there are several key risk factors involved.

Factors associated with increased Alzheimer's risk:

- **Advancing age** –1 in 6 people over the age of 80 has dementia, and the risk of developing Alzheimer's doubles every 5 years after 65.
- **Head injuries** –There is an association with severe head injuries and the development of Alzheimer's. Furthermore, having head injuries when dementia is present can actually worsen the symptoms and prognosis.
- **Cardiovascular disease** –Lifestyle factors that are associated with heart disease such as diabetes, high blood pressure, high blood cholesterol levels, smoking and obesity.
- **Down's syndrome** –The genetic basis for Down's syndrome (trisomy 21) which has a 3rd copy of chromosome 21, also carries an extra copy of the APP gene which produces beta-amyloid. Having an extra copy of the APP gene leads to a 50% increase in amyloid is production over normal levels. Therefore, persons with Down's syndrome are at higher risk of developing Alzheimer's.
- **Coexisting Health Problems** -It is observed that there is a strong link between cardiovascular health and brain health of an Alzheimer's patient. Having heart disease, high blood pressure or high cholesterol can increase the risk of developing Alzheimer's disease to a greater extent. [18]

Protective factors

Alzheimer's disease is not a preventable condition. However, a number of lifestyle risk factors for Alzheimer's can be modified. Evidence suggests that changes in diet, exercise and habits - steps to reduce the risk of cardiovascular disease - may also lower your risk of developing

Alzheimer's disease and other disorders that cause dementia. Heart-healthy lifestyle choices that may reduce the risk of Alzheimer's include the following:

- Exercising regularly
- Eating a diet of fresh produce, healthy oils and foods low in saturated fat such as a Mediterranean diet
- Following treatment guidelines to manage high blood pressure, diabetes and high cholesterol
- Asking your doctor for help to quit smoking if you smoke.

Causes of Alzheimer's disease:

The exact causes of Alzheimer's disease aren't fully understood. But at a basic level, brain proteins fail to function normally, which disrupts the work of brain cells (neurons) and triggers a series of toxic events. Neurons are damaged, lose connections to each other and eventually die. Scientists believe that for most people, Alzheimer's disease is caused by a combination of genetic, lifestyle and environmental factors that affect the brain over time. Less than 1% of the time, Alzheimer's is caused by specific genetic changes that virtually guarantee a person will develop the disease. These rare occurrences usually result in disease onset in middle age. The loss of neurons spreads in a somewhat predictable pattern to other regions of the brains. By the late stage of the disease, the brain has shrunk significantly.

Researchers trying to understand the cause of Alzheimer's disease are focused on the role of two proteins:

- **Plaques-**Beta-amyloid is a fragment of a larger protein. When these fragments cluster together, they appear to have a toxic effect on neurons and to disrupt cell-to-cell communication. These clusters form larger deposits called amyloid plaques, which also include other cellular debris.
- **Tangles-** Tau proteins play a part in a neuron's internal support and transport system to carry nutrients and other essential materials. In Alzheimer's disease, tau proteins change shape and organize themselves into structures called neurofibrillary tangles. The tangles disrupt the transport system and are toxic to cells.[19]

Diagnosis Criteria:

The clinical diagnosis of Alzheimer's disease follows a logical sequence as is observed in many diseases: the history should include information from information. Neuroimaging is a promising and widely expanding area of research for detecting Alzheimer's disease. There are multiple brain imaging procedures that can be used to identify abnormalities in the brain, including PET,

MRI, and CT scans which are considered to be preliminary tests for the detection of disease. Each scan involves a unique technique and detects specific structures and abnormalities in the brain and associated parts. Brain imaging is not currently a standard part of Alzheimer's disease testing, however current clinical studies have shown promising results that may change the procedure used by physicians to diagnose the disease.[20]

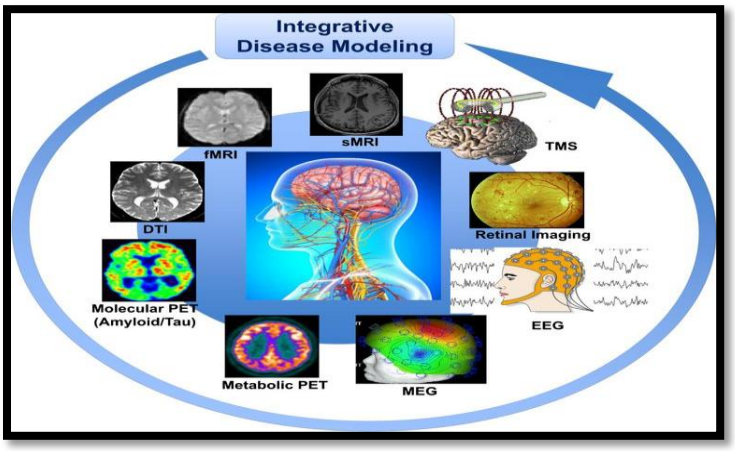

Figure 5: Integrative disease modelling

PET:

Positron emission tomography (PET) uses radiation signals to create a three-dimensional color image of the human body. The patient is injected with a radiotracer, composed of a radioactive medicine bound to a naturally occurring chemical. For the study of the Alzheimer's disease chemical is usually glucose and is used widely. The radiotracer travels to the organs that use that specific molecule for energy. As the compound is metabolized, positrons are emitted. The energy from these positrons is detected by the PET scan broken down. The amount of positron energy emitted creates a variety of colors and intensities, which reflects the extent of brain activity. A PET scan has the capacity to detect changes in metabolism, blood flow, and cellular communication processes in the brain and other activities taking place inside the brain.

Figure 6: PET scan image for Alzheimer's disease diagnosis

PET imaging may include the following:

- Fluorodeoxyglucosem (FDG) PET

- Amyloid PET imaging
- Tau PET imaging

CT:

A computed tomography (CT) scan takes a series of cross-sectional images of the body. With the help of a computer, the individual scans are integrated and incorporated into one detailed image. The CT scan provides the physician with information about the density of tissues in the body and in various parts of the brain. For improved clarity, a contrast dye may be injected to provide a distinction between similar tissues.

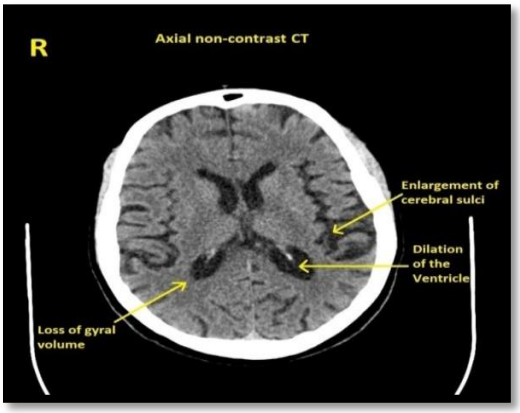

Figure 7: CT scan image for diagnosis of Alzheimer's disease

MRI:

Magnetic resonance imaging (MRI) techniques, first used in 1977, create two or three-dimensional images of the body that can be used to diagnose injury and illness. The essential component of the MRI system is the super conducting magnet, which produces a large and stable magnetic field. There are smaller gradient magnets that create weaker magnetic fields. These magnets allow for different parts of the body to be scanned. However, it is the hydrogen atoms that are altered by the magnetic field. Hydrogen atoms are each randomly spinning around an axis, but inside the magnetic field of the MRI, the molecules are lined up with the direction of the field.

TREATMENT

Drug Therapy:

There are two types of medication used to treat Alzheimer's disease: acetyl cholinesterase inhibitors and N-methyl D-aspartate antagonists. The two types work in different ways:

Cholinesterase Inhibitors:

There are lower levels of a chemical called acetylcholine in the brain of a person with Alzheimer's disease. Acetylcholine performs the function of sending messages between nerve

cells. Cholinesterase inhibitors (CI) aim to increase acetylcholine availability in synaptic neurotransmission in order to treat memory disturbances. Currently, three CIs are being used as the first-line treatment in mild to moderate Alzheimer's disease: donepezil, rivastigmine and galantin While donepezil and rivastigmine are both selective inhibitors, galantamine inhibits both ACh and butyrylcholinesterase. A meta-analysis collaborating 13 randomized, double bind trials that were designed to evaluate the effectiveness and safety of CIs showed no improvement in ADL and behavior. In addition, donepezil and rivastigmine showed no significant difference in their impact on cognitive functions, ADLs and behavior. Overall, similar benefits were observed across all three drugs.

NMDA Receptor Antagonists:

Memantine is a non-competitive NMDA receptor antagonist effective in the treatment of moderate-to-severe Alzheimer's disease. The modulation of NMDA receptors results in reduced glutamate-induced excitotoxicity. Its benefits were proven in a 28-week, double blind, parallel-group study, which showed that treatment significantly, reduced deterioration in patients. Most adverse reactions to the drug were not severe and were considered to be unrelated to the drug. The positive effect on cognitive function translates to behavioral improvements: patients were less agitated and required less assistance from caregivers Improvement of the behavioral and psychological symptoms related to dementia (BPSD) was also highlighted by a meta-analysis of 6 studies involving memantine treatment.[21]

Antidepressants and Antipsychotics:

BPSD is a common occurrence in Alzheimer's disease and a major source of burden on caregivers. CIs and memantine help to control these symptoms to a certain extent, but as patients continue to deteriorate, control by these drugs becomes insufficient. Depression is very common, especially in the early and late courses of the disease. Antidepressants such as: selective serotonin reuptake inhibitors (SSRI: citalopram, fluoxetine, paroxetine, sertraline, trazodone), tricyclic agents and combined serotonergic and noradrenergic inhibitors may be used to counter this. Discontinuation of antidepressants in demented patients in a double blinded, randomized, parallel-group place of controlled trial showed significant increases in depression when compared to those who continued treatment.

Anti-inflammatory agents:

The hypothesis that anti-inflammatory therapy can slow the progression of AD has gained support from some retrospective epidemiologic studies; there are very few prospective double-blind clinical trials of non-steroidal anti-inflammatory drugs (NSAIDS) in AD. Nonrandomized

studies with NSAIDS (indomethacin, ibuprofen, diclofenac, naproxen), steroids (low-dose prednisone), and other anti-inflammatory agents (hydroxychloroquine, colchicine) showed promising results in modulating the course of the disease. Unfortunately, these studies included small sample sizes. Recent studies have not replicated the previous positive results. A 16-month, double-blind, placebo-controlled, low-dose study in 138 patients with AD receiving prednisone showed that there was no slowing of the rate of cognitive decline compared with placebo.

Antioxidant agents: Selegiline and vitamin E

Current theories suggest that an increase in free-radical formation may occur in AD and have a direct toxic effect. The brain may be vulnerable to the damaging effects of oxidative stress because of an abundance of catecholamines and a relatively low concentration of antioxidative enzymes (superoxide dismutase, catalyses, glutathione peroxides, and glutathionereeducates). Furthermore, Aβ has been implicated in increased free-radical formation. Vitamin E in doses of 1000 IU orally twice daily and selegiline (a monoamine oxidase B inhibitor) in doses of 5 to 10 mg orally every morning seem to minimize free-radical damage by acting as free-radical scavengers. A recent major double-blind study comparing the effect of selegiline alone, vitamin E alone, selegiline and vitamin E with placebo in patient with AD showed that both delayed nursing home placement and the loss of activities of daily living.

Treatment of behavioral disturbance:

A wide range of dementia-associated behavioral disturbances afflict the majority of patients with AD, with depression and psychosis being the most commonly studied from the point of view of treatment. Depression in patients with AD should be treated aggressively, with careful monitoring of cognitive function. With limited clinical trial data, the treatment of depression in AD remains empirical and consists in starting an antidepressant at a low dose and increasing it slowly. Sufficient dosage and duration of treatment arc needed for clinical response in depressed patients without dementia. All newer antidepressants, including fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, Nefazodone, bupropion, mirtazapine, and venlafaxine appear to have beneficial effects in depression in AD patients.[22]

Psychosocial treatment:

Environmental manipulation, family support and prevention of other medical comorbidities can improve functioning of AD patients. In attempting to maintain patients with AD in their homes for as long as possible, some adjustment of a patient's environment is important. Written daily reminders can be helpful in the performance of daily activities. Prominent clocks, calendars, and windows are important. Patient activities should have minimal changes. Maintaining adequate

hydration, nutrition, exercise and cleanliness, is important. Family support is essential, since members are at risk for depression, anxiety syndromes, and insomnia.[23]

PREVALENCE:

In 2021, an estimated number of 6.2 million Americans 65 years and older are living with Alzheimer's disease 75% of this population are 75 years and above. About 8 million are affected around the world. It is expected that by 2050 that number will have increased almost three-fold around 115.4 million. The known prevalence is 6% in people over the age of 65, 20% in people over the age of 80, and more than 95% in those 95 years of age. Alzheimer's disease is the sixth leading cause of death in adults. The period from onset to death is usually seven to 11 years. While death from other top 10 diseases has been observed to decline, from 2000-2014 AD as the primary cause of death has increased by 89%.A retrospective cohort study found cardiovascular diseases (CVD) as a significant cause of death in older people who have dementia with a relatively shorter survival approximately 4 years after the diagnosis of dementia. Early-onset AD manifests between the ages of 30 and 60 years. This occurs in 1-6%of all cases. Late-onset AD manifests after the age of 60 years and accounts for around 90% of cases.[24]

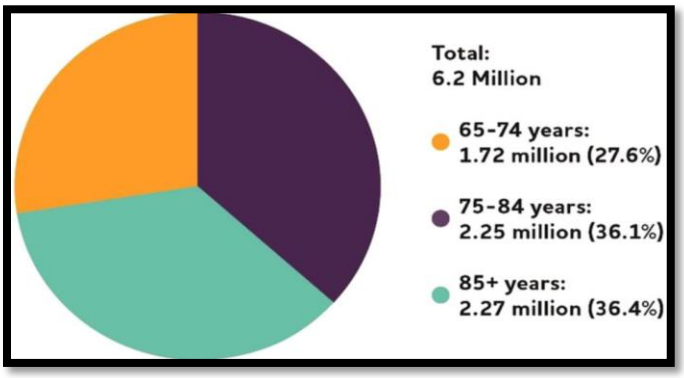

Figure 8: Number and ages of people 65 or older with Alzheimer's disease, 2021

(Created from data from Rajan et al.[1216] percentages do not total 100 due to rounding)

CONCLUSION:

The main pathophysiological mechanisms of AD are amyloidosis and tau-related neurodegeneration, and have specific topographical and chronological pathways. For instance, brain amyloidosis starts in neocortical regions and then affects sub cortical structures. On the other hand, neurodegeneration first appear on locus coeruleus and then spreads through transentorrinal area and neocortical regions. Cognitive and behavioral features of AD are significantly correlated to the topographical distribution of neurofibrillary tangles. There is great variability in topographical patterns of pathological findings in AD, causing great phenotypical

variability, with atypical presentations of the disease. It is not clear how risk and beneficial factors may modulate the topographical progression of amyloidosis and neurodegeneration. The effects of modifiable risk factors on cross-sectional cognition have been the target of multiple WRAP (The Wisconsin Registry for Alzheimer's Prevention) investigations. This study has investigated risk factors for AD in middle age, since this phase of life is less studied in relation to the later stages of aging. However, this is a critical time because it is when the Alzheimer's pathology begins and thus, when its trajectory can be modified through pharmacological approaches and / or lifestyle changes. Within this context, the WRAP study, reported by Johnson et al. (2018).

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