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A REVIEW PAPER ON ALZHEIMER'S DISEASE: A WAY ON PREVENTION AND ITS TREATMENT

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ABSTRACT
Alzheimer's disease (AD) is the most common cause of dementia associated with a progressive neurodegenerative disorder, with a prevalence of 44 million people throughout the world in 2015, and this figure is estimated to double by 2050. This disease is characterized by blood-brain barrier disruption, oxidative stress, mitochondrial impairment, neuron inflammation, and hypo metabolism; it is related to amyloid-β peptide accumulation and tau hyper phosphorylation as well as a decrease in acetylcholine levels and a reduction of cerebral blood flow. The pharmacological treatments for AD can be divided into two categories: symptomatic treatments such as acetyl cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists and etiology-based treatments such as secretes inhibitors, amyloid binders, and tau therapies. Strategies for prevention of AD through non pharmacological treatments are associated with lifestyle interventions such as exercise, mental challenges, and socialization as well as caloric restriction and a healthy diet. AD is an important health issue on which all people should be informed so that prevention strategies that minimize the risk of its development may be implemented. Increasing epidemiological studies suggest that diet and Nutrition might be important modifiable risk factors for AD. Dietary supplementation of antioxidants, B vitamins, polyphenols, and polyunsaturated fatty acids are beneficial to AD, and consumptions of fish, fruits, vegetables, coffee, and light-to-moderate alcohol reduce the risk of AD

KEYWORDS: Alzheimer's disease (AD), N-methyl-D-aspartate (NMDA).

1. INTRODUCTION[1-3]

In 1907, Alois Alzheimer described the case of a 51-year-old woman with a rapidly degenerating recall who, after a swift decline, died severely uncontrolled 4 years later (Alzheimer, 1907). This condition, which now bears Alzheimer's name, describes a deadly degenerative dementing disorder with initial soft memory destruction that progresses unrelentingly to a total weakening loss of mental and physical faculties. Following symptom onset, the course of the disease varies considerably from a few years to over 20 years, with a mean survival of approximately 8 years.

Alzheimer disease was originally come apart into two clinical conditions depending upon the age of onset. Alzheimer disease, probably due to its initial description in a middle-aged woman (Alzheimer, 1907) , was a term reserved for a type of presenile dementia affecting individuals younger than 65 years of age, whereas a similar dementia in the elderly, i.e., in individuals over 65 years of age, was referred to as senile dementia of the Alzheimer type after the revolutionary studies of Tomlinson, Roth, and Blessed (Roth et al,, 1966, 1967; Tomlinson et al., 1970). Of historical note, Alzheimer himself thought that it was one disease.[3,4,5] Although these age-related classifications are still frequently used, the disease fails to express a bimodal age of onset and is generally recognized as a single unit with a prevalence that increases sharply after age 65.

Alzheimer disease (AD) is neuropathologically characterized by synapse loss, neuritic Ab amyloid plaques, and neuro fibrillary tangles. Making an accurate and reliable diagnosis of AD at the earliest disease stages is challenging and becomes increasingly important as disease-modifying therapies, such as those aimed at lowering Ab amyloid, appear on the horizon. In 2004, Klunk et al. presented a novel method for the in vivo detection of Ab amyloid plaques in the brain using the thioflavin-T analog PET tracer 11C-Pittsburgh compound B (PiB).

As yet, there are no nonessential biochemical markers for the disease, and an ultimate diagnosis can only be made upon histological examination of a cerebral biopsy or, more typically, up on autopsy. Nonetheless, the ability to

clinically identify Alzheimer disease has greatly improved with the use of objective criteria.

2. Clinical Features in Alzheimer Disease[4-6]

Clinical Presentation

The initial clinical manifestations of Alzheimer disease are very difficult to define prospectively. There is a great deal of deviation in the clinical arrangement of the neuropsychological and cognitive abnormalities that, retrospectively, can be correlated to specific regions of degeneration in the brain (Foster et al., 1983). Nonetheless, initial presentation typically involves memory destruction and poor judgment. As the disease progresses, the symptoms become increasingly distressing for the patient and for those who care for him/her. In the latter stages the patient is completely harmed and requires constant regulation.

A. Epidemiology

Alzheimer disease affects 10-15% of individuals over 65 years and up to 47% of individuals over the age of 80 (Evans et al., 1989). In both clinical and autopsy series in the United States and Europe, Alzheimer disease account for approximately two-thirds of all dementias affecting elderly individuals (Fig. 1). certainly the number of individuals a Micted by this devastating condition will increase as the "baby boom" generation enters senescence and as the clinical management of other life-threatening conditions reduces death by other causes. Definitely, the population of the United States over 65 years of age is expected to rise from the present level of approximately 11% to over 18% by the year 2030, with individuals over the age of 80 years continuing to be the fastest growing segment of the population. Bearing in mind that a significant number of patients are cared for at home, it is shocking that in the United States alone the cost of institutional care for Alzheimer disease patients in 1994 was $1 10 billion. Therefore, Alzheimer disease represents a major public health problem for developed, as well as developing, nations. The most common and distinctive lesions present within the diseased brain are the neurotic senile plaques and neurofibrillary tangles described by Alois Alzheimer (Alzheimer, 1907). Neuronal and dendritic loss, neuropil threads, dystrophic neuritis, granulovacuolar degeneration, Hirano bodies, and cerebrovascular amyloid, as well as generalized misuse of the brain, are also prominent pathological features. Interestingly, a similar pathological presentation is found in cases of Down syndrome, and, of note, most of these pathological features may also be present to a lesser extent in a large proportion of aged non demented controls, raising the possibility.

B. Pathology

The most common and distinctive lesions present within the diseased brain are the neurotic senile plaques and neurofibrillary tangles described by Alois Alzheimer (Alzheimer, 1907). Neuronal and dendritic loss, neuropil threads, dystrophic neuritis, granulovacuolar degeneration, Hirano bodies, and cerebrovascular amyloid, as well as generalized atrophy of the brain, are also prominent pathological features. Interestingly, a similar pathological presentation is found in cases of Down syndrome, and, of note, most of these pathological features may also be present to a lesser extent in a large proportion of aged non demented controls, raising the possibility that such individuals are in an extremely early preclinical stage of Alzheimer disease.

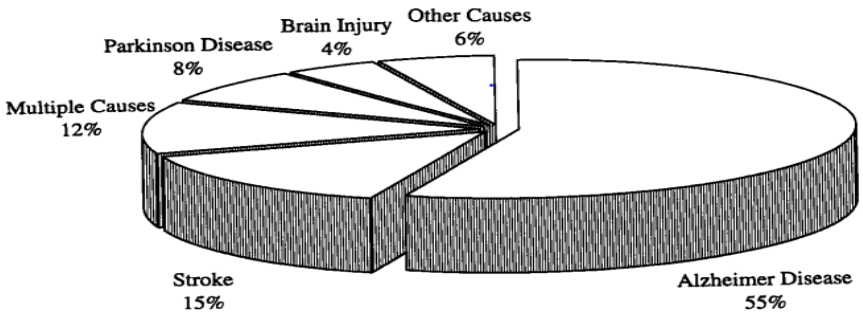

FIG. 1. Alzheimer disease is the leading cause of dementia affecting elderly individuals.

C. Neuron Loss in Alzheimer Disease

Neuron loss is a basic and fundamental feature in the pathogenesis of AD, starting already at preclinical stages when the neuropathological hallmarks are not yet present. A decrease in neuron numbers can be observed in different brain regions in AD patients, culminating in an involvement of the entire brain at late stages. In particular, loss of neurons in the CA1 region of the hippocampus and in the entorhinal cortex seems to correlate with the severity of memory deficits. Even though the exact mechanisms of neuronal death in AD are not yet fully understood, Aβ has been suggested as an initiator by interaction with and disruption of the endoplasmic reticulum (ER) and mitochondrial integrity but also as a potential trigger of apoptosis. In addition to a direct involvement of Aβ in pathways resulting in neurodegeneration and synaptic deficits, the peptide is believed to enhance the phosphorylation of Tau proteins that consequently act as mediators in events contributing to synaptic dysfunction and neuronal death.

E. Symptoms

As the condition develops, memory problems become more severe and further symptoms can develop, such as:

- confusion, disorientation and getting lost in familiar places
- difficulty planning or making decisions
- problems with speech and language
- problems moving around without assistance or performing self-care tasks
- personality changes, such as becoming aggressive, demanding and suspicious of others
- hallucinations (seeing or hearing things that are not there) and delusions (believing things that are untrue)
- low mood or anxiety

3. Prevention and Treatment of Alzheimer's disease[7-8]

3.1.1. As the exact cause of Alzheimer's disease is still unknown, there's no certain way to prevent the condition. But a healthy lifestyle can help reduce your risk.

- stopping smoking
- keeping alcohol to a minimum
- eating a healthy, balanced diet, including at least 5 portions of fruit and vegetables every day
- exercising for at least 150 minutes every week by doing moderate-intensity aerobic activity (such as cycling or fast walking), or as much as you're able to
- making sure your blood pressure is checked and controlled through regular health tests
- if you have diabetes, make sure you keep to the diet and take your medication
- Staying mentally and socially active

3.1.2. It may be possible to reduce your risk of Alzheimer's disease and other types of dementia by.

- reading
- learning foreign languages
- playing musical instruments
- volunteering in your local community
- taking part in group sports, such as bowling
- trying new activities or hobbies
- maintaining an active social life

3.2. FDA-Approved Drugs for Alzheimer's

The U.S. Food and Drug Administration (FDA) has approved medications that fall into two categories: drugs that may delay clinical decline in people living with Alzheimer's, and drugs that may temporarily mitigate some symptoms of Alzheimer's disease.

When considering any treatment, it is important to have a conversation with a health care professional to determine whether it is appropriate. A physician who is experienced in using these types of medications should monitor people who are taking them and ensure that the recommended guidelines are strictly observed.

3.2.1. Drugs that may Delay Clinical Decline

Drugs in this category may delay clinical decline with benefits to both cognition and function in people living with Alzheimer's disease.

Aducanumab (Aduhelm):anti-amyloid antibody intravenous (IV) infusion therapy approved for Alzheimer's disease. An FDA-approved diagnostic test is required; talk with your doctor about options.

Aduhelm works by targeting beta-amyloid, a microscopic protein fragment that forms in the brain and accumulates into plaques. These plaques disrupt communication between nerve cells in the brain and may also activate immune system cells that trigger inflammation and devour disabled nerve cells. While scientists aren't sure what causes cell death and tissue loss during the course of Alzheimer's disease, amyloid plaques are one of the potential contributors. Aduhelm is the first therapy to demonstrate that removing beta-amyloid resulted in better clinical outcomes.

- Aduhelm was shown in clinical trials to delay the clinical decline of people living with early Alzheimer's disease (mild cognitive impairment (MCI) due to Alzheimer's or mild Alzheimer's dementia).
- Some people who received Aduhelm experienced significant benefits on measures of cognition and function. Examples include abilities such as memory, orientation and language.
- Some also experienced benefits on activities of daily living, which refers to the everyday skills we need to take care of ourselves and live well independently. Conducting personal finances, performing household chores (such as cleaning, shopping and doing laundry) and independently traveling out of the home are all examples of activities of daily living.

In clinical trials, the most common side effects were ARIA-E (abnormal brain changes associated with anti-amyloid treatments — most often swelling in the brain — that are spotted with neuro imaging techniques like MRI), headache, ARIA-H (micro haemorrhage /superficial siderosis) and fall.

3.2.2. Drugs that Treat Symptoms

A. Cognitive Symptoms (memory and thinking)

As Alzheimer's progresses, brain cells die and connections among cells are lost, causing cognitive symptoms to worsen. While these medications do not stop the damage Alzheimer's causes to brain cells, they may help lessen or stabilize symptoms for a limited time by affecting certain chemicals involved in carrying messages among and between the brain's nerve cells.

The following medications are prescribed to treat symptoms related to memory and thinking.

a. Cholinesterase inhibitors (Aricept, Exelon, Razadyne)

Cholinesterase (KOH-luh-NES-ter-ays) inhibitors are prescribed to treat symptoms related to memory, thinking, language, judgment and other thought processes. These medications prevent the breakdown of acetylcholine (a-SEA-til-KOH lean), a chemical messenger important for memory and learning. These drugs support communication between nerve cells.

The cholinesterase inhibitors most commonly prescribed are.

- **Donepezil (Aricept):** approved to treat all stages of Alzheimer's disease.
- **Rivastigmine (Exelon):** approved for mild-to-moderate Alzheimer's as well as mild-to-moderate dementia associated with Parkinson's disease.
- **Galantamine (Razadyne):** approved for mild-to-moderate stages of Alzheimer's disease.

Though generally well-tolerated, if side effects occur, they commonly include nausea, vomiting, loss of appetite and increased frequency of bowel movements.

b. Glutamate regulators (Namenda)

Glutamate regulators are prescribed to improve memory, attention, reason, language and the ability to perform simple tasks. This type of drug works by regulating the activity of glutamate, a different chemical messenger that helps the brain process information. This drug is known as.

- Memantine (Namenda): approved for moderate-to-severe Alzheimer's disease.

Can cause side effects, including headache, constipation, confusion and dizziness.

c. Cholinesterase inhibitor + glutamate regulator (Namzeric)

This type of drug is a combination of a cholinesterase inhibitor and a glutamate regulator.

- **Donepezil and memantine (Namzaric):** approved for moderate-to-severe Alzheimer's disease.

Possible side effects include nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness.

B. Non-cognitive symptoms (behavioural and psychological symptoms)

Alzheimer's affects more than just memory and thinking. A person's quality of life may be impacted by a variety of behavioural and psychological symptoms that accompany dementia, such as sleep disturbances, agitation, hallucinations and delusions. Some medications focus on treating these non-cognitive symptoms for a time, though it is important to try non-drug strategies to manage behaviours before adding medications.

At this time, the FDA has approved one drug to address insomnia in people living with dementia, but trials into drugs that address other non-cognitive symptoms are underway.

a. Orexin receptor antagonist (Belsomra)

Prescribed to treat insomnia for individuals living with dementia, this drug is thought to inhibit the activity of orexin, a type of neurotransmitter involved in the sleep-wake cycle.

- **Suvorexant (Belsomra):** approved for mild-to-moderate Alzheimer's disease.

Possible side effects include, but are not limited to: risk of impaired alertness and motor coordination (including impaired driving), worsening of depression or suicidal thinking, complex sleep behaviours (such as sleep-walking and sleep-driving), sleep paralysis and compromised respiratory function.

4. Pharmacological Treatment[9]

Alzheimer's disease requires precise diagnosis, early if possible, and adequate etiological treatment, and, as an incurable age-related neurodegenerative disorder, its particular pathophysiology needs to be considered. The therapeutic options have focused on ameliorating the symptoms as well as reducing the rate of progression of damage, although this has not significantly reversed the disease, so prevention is a better solution for this public health problem.

The toxic conformations of Aβ or tau in the brain are thought to spread the disease, and blocking the generation of these peptides may be part of useful treatments.

4.1. Symptomatic Treatment

4.1.1. Acetylcholine Sterase Inhibitors

It is well known that acetylcholine (ACh) plays a crucial role in mediating learning and memory.

On this basis, effective treatment for AD is achieved with cholinesterase inhibitors, which corresponds well to Davies and Maloney's early cholinergic deficit hypothesis (1976) explaining AD pathophysiology.

Tacrine, donepezil, rivastigmine, galantamine, xanthostigmine, para-aminobenzoic acid, coumarin, flavonoid, and pyrroloisoxazole analogs have been developed and studied for the treatment of AD. Rivastigmine, donepezil, and galantamine are the approved drugs that promote higher ACh levels and improve the brain's cholinergic function by inhibiting the enzyme acetyl cholinesterase which degrades the neurotransmitter.

4.1.2. N-Methyl-D-aspartate Receptor (NMDA) Antagonist

Glutamate-mediated excite toxicity is known to result in calcium excess and mitochondrial dysfunction, with increased nitric oxide generation, which can be detrimental to cells, forming high levels of oxidants and eliciting neuronal apoptosis. This overstimulation can be

blocked by NMDA receptor antagonists such as memantine.

Memantine can protect neurons by attenuating tau phosphorylation through a decrease in glycogen syntheses kinas' activity.

4.1.3. Other Neurotransmitter Systems

Muscarinic and nicotinic ACh receptors are also considered targets for AD treatment, although selectivity of the agonists has been a problem outcome in clinical trials.

Histamine receptors, particularly H_3 receptors, are also present in large amounts in memory- and cognition-related structures in the brain. It seems that H_3 receptor antagonists may improve cholinergic neurotransmission. Phase I and II studies with H_3 antagonists are currently being conducted.

4.2. Etiology-Based Treatment

As indicated above, the major genetic risk factor for irregular AD (the major risk factor is age), although, for disease-modifying treatment based on the amyloid cascade hypothesis, efforts are targeting secretase modulation and amyloid binders, as well as targeting kinas involved in the hyper phosphorylation of tau protein.

4.2.1. Secretase Inhibitors

APP is first cleaved either by α-secretase or by β-secretase enzymes, and the resulting fragments are processed by γ-secretase. The proposal of the "over activation" of β- and γ-secretases, or age-related decreased α-secretase processing, has led to the use of inhibitors for this amyloidogenic pathway.

4.2.2. Amyloid Binders

The deposition of Aβ in AD is concentration-dependent; increased amyloidogenic processing of APP and inefficient removal of peptides may be involved in the pathology. There is reduced activity of Aβ-degrading enzymes, such as neprilysin, an insulin-degrading enzyme, as well as the ApoE determinant, which correlates well with the proposal of AD as a metabolic disorder.

Preventing the formation of Aβ extracellular neurotic (senile) plaques is one of the targets for disease-modifying treatment in AD, although there is evidence of correlation with Aβ biomarkers and cognitive deficits, previous to senile plaques.

4.2.3. Anti-Aβ Aggregation Compounds

In recent decades, research has focused on developing therapies in which the Aβ peptide formation or its aggregation is prevented. Among the small molecule inhibitors of Aβ aggregation in clinical trials are tramiprosate (phase III), clioquinol (phase II), scylloinositol (phase II), and epigallocatechin-3-gallate (phase II/III); although these drugs have achieved stabilization of the Aβ monomers, they have important side effects.

4.2.4. Tau Therapies

Prevention of aggregates of paired, helically twisted filaments of hyper phosphorylated tau in neuro fibrillary tangles is one of the targets of this therapy. Immunotherapy has been developed; AADvac1 was the first vaccine in clinical trials, and ACI-35 (another liposomal-based vaccine) trials have begun.

4.2.5. Other Therapies

As an age-related pathology, AD is correlated with other chronic-degenerative disorders, and coordinated therapies are needed. A type 3 diabetes hypothesis of AD has been developed, and intranasal insulin is included as a possible treatment for the disease, due to its ability to penetrate the brain-blood barrier.

5. Non-pharmacological Treatment[10-12]

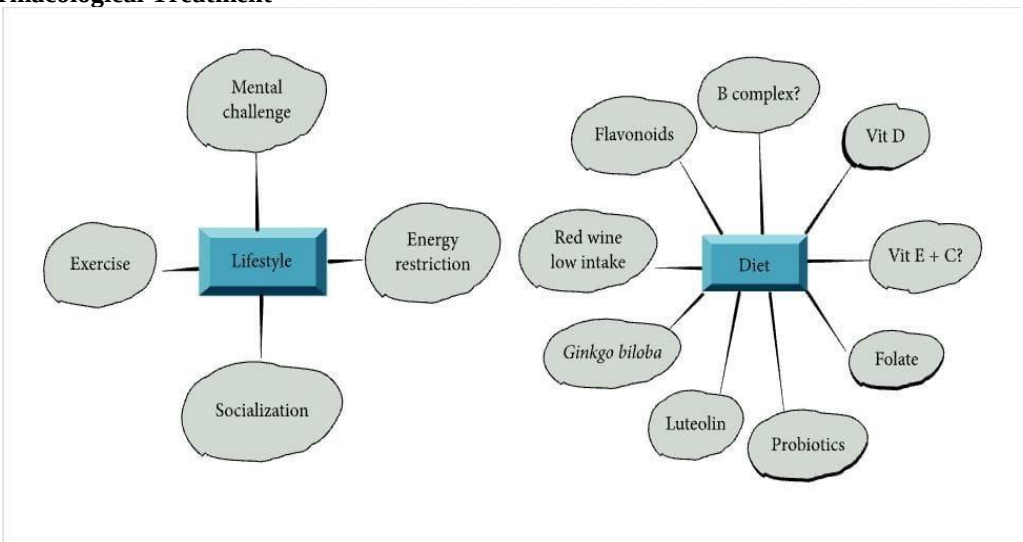

Fig_-Non-Pharmacological Treatments

Non-pharmacological treatments are important for the prevention of AD or as adjuvant in other treatments. AD prevention strategies can be divided into two groups, the first associated with lifestyle and the second with diet and chemical compounds.

5.1. Lifestyle

Lifestyle strategies include physical activity, mental challenges, energy restriction, and socialization as preventive factors in AD. Physical activity such as aerobic exercise was associated with the reduction of AD deficits in a group study. This was not consistent with studies that considered a small number of cases.

Exercise was reported to enhance hippocampal neurogenesis and learning in aging rodents Computer courses and psycho education have moderate beneficial effects.

The relation between caloric restriction and brain motivation is important since many years ago humans needed to obtain their food by killing wild animals and often vigorous exercise was required. In different AD mouse models treated with food and caloric restriction, a decrease in phosphorylated tau and amyloid-β was observed in the brain.

Socialization is important to mental and physical human development and a lack thereof induces loneliness, which has been associated with various diseases such as depression, alcohol abuse, obesity, diabetes, hypertension, AD, and cancer.

5.2. Diet and Chemical Substances

Dietary supplements for prevention of AD were studied with vitamins such as B6, B12, and E, C, and D vitamins. Vitamin B studies produced mixed results; on one hand, a two-year treatment with homo cysteine and vitamin B in patients indicated a vital difference compared to placebo in whole brain atrophy additionally, vitamin D supplementation improves cognitive performance.

Other studies of chemical substances related to possible protection against neuropsychiatric disorders such as AD were those related to the intake of plants and their secondary metabolites: flavonoids, alkaloids, or terpenoids. Flavonoids are considered safe and their neuro protection was confirmed in people treated with flavanol Flavonoids also inhibit acetyl cholinesterase and improve memory in addition to inhibiting glutamate release.

The Mediterranean diet may improve neuro protection because it is based on low intake of saturated fatty acids, but high consumption of unsaturated fatty acids, as well as vegetables, legumes, fruits, fish, and olive oil, along with poly phenols such as oleuropein aglycone (OLE), which interfere with amyloid aggregation, and reduced the LDL cholesterol levels.

OLE is an important compound with neuroprotective effects because it interferes with amylin, tau, and Aβ peptide aggregation and toxicity *in vitro*, studied by behavioral, biological, biophysical, biochemical, and electrophysiological techniques.

6. CONCLUSION

In this paper, we searched Research paper, Research articles published , using the search terms “Alzheimer's disease,” “nutrition,” “nutrients,” “food,” “diet,” “dietary patterns,” which are the way of prevention and treatment of the Alzheimer disease.

Dementia is a degenerative disease that eventually affects a person’s ability to live independently. There are many types of dementia, although Alzheimer’s disease is the most common type. Delirium and depression can be confused with dementia and a thorough evaluation should rule out other causes of cognitive loss prior to making a diagnosis of dementia.

People with dementia need to be treated with kindness and with the knowledge that they can still enjoy life. Physical and chemical restraints should be used only as a last resort. There are many proven alternatives to physical and chemical restraints that are the mainstays of individualized care.

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