IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

ALZHEMIER DISEASE

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Abstract

In a nutshell, Alzheimer's disease (AD) is a condition that results in the brain's cells dying. It is the leading cause of dementia, which is characterised by a loss of mental capacity and independence in daily tasks. The cholinergic and amyloid hypotheses were put up as the disease's two main causes. AD is thought to be a complex illness. Furthermore, the disease is influenced by a number of risk factors, including advancing age, genetic predispositions, head injuries, vascular conditions, infections, and environmental variables. There are currently only two kinds of pharmaceuticals that have been licenced to treat AD, namely cholinesterase enzyme inhibitors and N-methyl d-aspartate (NMDA) antagonists. These medications are only effective in treating the symptoms of AD; they do not treat the underlying cause of the disease. The modern

Keywords: Chaperons, heat shock proteins, -amyloid peptide, tau protein, hazards, and disease-modifying therapies for Alzheimer's disease

Introduction:-

The world’s population is rapidly aging, and the number of people with dementia is expected to grow from 35 million today to 65 million by the year 2030. In the United States alone, 5 million or 1 in 9 people over the age 65 are living with Alzheimer’s disease (AD), the most common cause of dementia. For comparison, accordingtothe Centersfor Disease Control and Prevention (20092012 estimates), about 3 million older adults in the United States have asthma, 10 million have diabetes, 20 million have arthritis, and 25 million have hypertension. Primary care physicians and specialists alike will encounter older adults with dementia atan increasing frequency during their careers. As dementia carries significant implications for patients, their families, and our society, it is imperative for wellrounded

physicians to have a solid understanding of this topic. The purpose of this review article is to provide a brief introduction to AD and the related concept of mild cognitive impairment (MCI). The article emphasizes clinical and neurobiological aspects of AD and MCI with which medical students should be familiar. In addition, the article describes advances in the use of biomarkers for diagnosis of AD and highlights ongoing efforts to develop novel therapies.

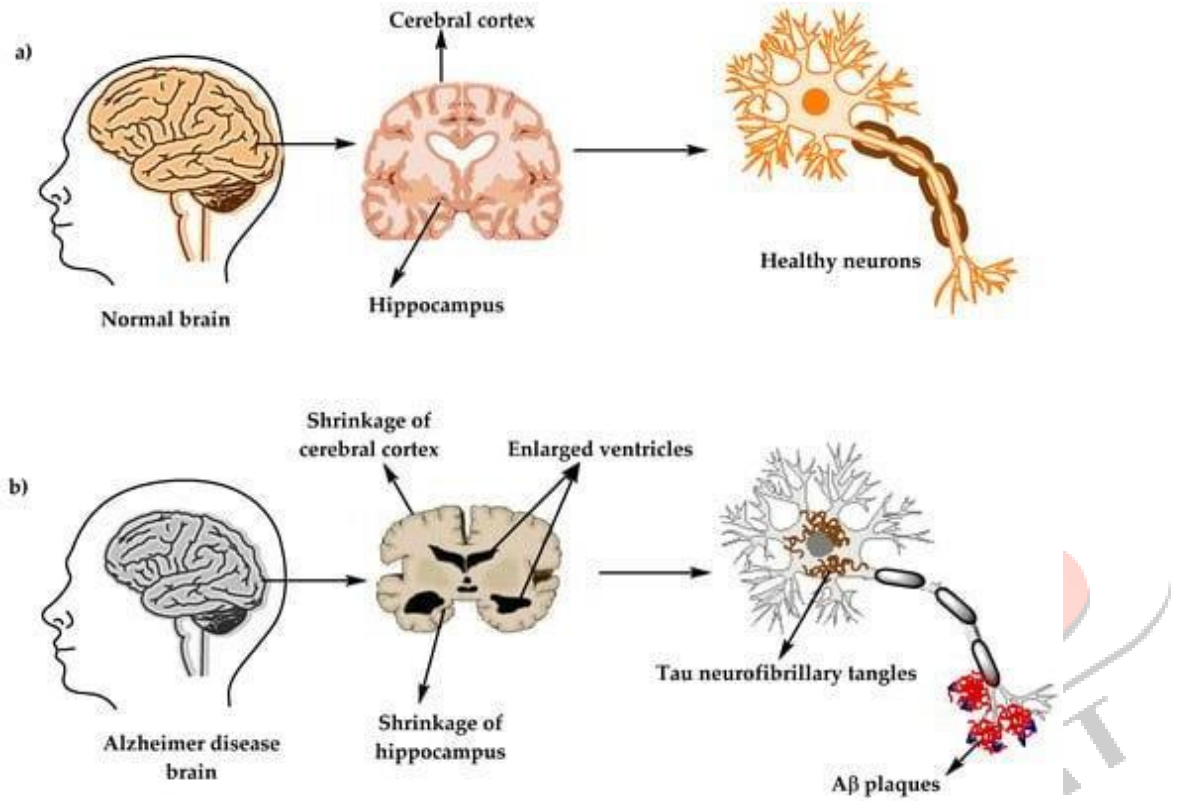

Figure 1. The physiological structure of the brain and neurons in (**a**) healthy brain and (**b**)Alzheimer's disease (AD) brain.

Signs of Mild Alzheimer's disease Memory loss

that disrupts daily life. Poor judgment, leading to

bad decisions.Mood And Personality Changes

Loss of spontaneity and sense of initiative.

Losing track of dates or knowing current location. Taking

longer to complete normal daily tasks.

Repeating questions or forgetting recently learned information.

Historical Information

Alois Alzheimer first described the neurodegenerative disease that would bear his name more than 100 years ago, and today the cardinal features of amyloid plaques and neurofibrillary tangles that he described are still required for its pathological diagnosis [1]. Alzheimer's disease (AD) is a progressive neurodegenerative disease most often characterized by initial memory impairment and cognitive decline that can ultimately affect behavior, speech, visuospatial orientation and the motor system, and it is the most common form of dementia [2]. Variant syndromes with early focal atrophy do not always follow this traditional presentation, and pathological subtypes of AD have been described [3]. Clinical AD dementia cannot be definitively diagnosed until post-mortem neuropathologic evaluation, though research institutes capable of assessing amyloid and tau burden in living patients are challenging this historic paradigm [4]. AD is also characterized by a long asymptomatic preclinical phase, and cognitively normal individuals can also have the disease [5]. Furthermore, AD is rarely found without other neurodegenerative co-pathologies as observed in the Mayo Clinic Brain Bank data in Table 1. It is so tightly associated with old age that there is speculation it is a normal part of aging [6]. Currently, there are no disease modifying therapies for Alzheimer's disease [7]. Table 1 Comorbidities in 1153 Patients with Pathologic Diagnosis of AD. The majority of AD cases were observed to have pathologic comorbidities as observed in the Mayo Clinic Brain Bank 2007–2016. Plus sign (+) in the column on pathological diagnosis of AD indicates additional pathologies beyond the primary and secondary diagnoses listed. Bold indicates significance from the pure AD cases (Student t-Test, $p < 0.01$)

Review of literature

1. Serrano-Pozo [2011]

   There are two types of neuropathological changes in AD which provide evidence about disease progress and symptoms and include: (1) positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients. In addition to (2) negative lesions (due to losses), that are characterized by large atrophy due to a neural, neuropil, and synaptic loss. Besides, other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and injury of cholinergic neurons

2. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH [2011]

   Clinical features that distinguish AD from other dementias Clinical feature Alzheimer's dementia Vascular dementia Parkinson's dementia Dementia with Lewy bodies Frontotemporal Dementia Patient profile - 65 years old - 40 years old Vascular risk factors 65 years old 75 years old (mean) 50-70 years old 50% autosomal dominant History Gradual onset and deterioration Acute onset, step-wise deterioration Gradual onset and deterioration Gradual onset and deterioration Gradual onset and deterioration Initial symptoms Memory loss Executive dysfunction Visual hallucinations Visual hallucinations Fluctuating attention Memory intact Disinhibition, apathy or aphasia Physical findings No motor impairment (until late stage) Pyramidal (upper motor neuron) signs Parkinsonism (precedes dementia by - 1 year) Parkinsonism (presents within 1 year of dementia) Usually none (rarely associated with motor neuron disease

3. Howard R, McShane R, Lindesay J [2012]
   At present, only two classes of pharmacologic therapy are available for patients with AD. The cholinesterase inhibitors donepezil, rivastigmine, and galantamine are recommended therapy for patients with mild, moderate, or severe AD dementia as well as Parkinson's disease dementia

4. Gupta PP, Pandey RD, Jha D [2015]
   Although many retrospective, observational studies alluded to the role of inflammation in the development of AD by showing a reduced risk of AD with the use of non-steroidal anti-inflammatory drugs, a more-thorough investigation failed to note any significant difference in cognitive performance in patients who took these medications

5. Salomone S. Caraci F. Leggio GMM [2012]
   Much of the research in AD in the last decade has been directed towards disease-modifying therapy that will alter the course of the disease rather than act on symptoms alone, however the lack of effective disease-modifying drugs arising from these studies reflects the challenges involved in developing a therapeutic agent with potential to modify the course of a disease as complex as AD

Methodology:-

Dementia

Dementia is a clinical syndrome (a group of co-occurring signs and symptoms) that involves progressive

deterioration of intellectual function.4Various cogni- tive abilities can be impaired with dementia, including memory, language, reasoning, decision making, visuos-patial function, attention, and orientation. In individualswith dementia, cognitive impairments are often accom-panied by changes in personality, emotional regulation,and social behaviors.
Importantly, the cognitive andbehavioral changes that occur with dementia interferewith work, social activities, and relationships and impair

a person's ability to perform routine daily activities (e.g.,driving, shopping, housekeeping, cooking, managingfinances, and personal care). Table 1 summarizes theclinical criteria for all causes of dementia.4,5There are several reversible and irreversible causesof dementia.4,6
Reversible dementias (also referred toas 'pseudo-dementias') are relatively rare but poten-tiallytreatable and occur secondary to another medicalcondition, including depression, nutritional deficiencies(e.g., vitamin B12), metabolic and endocrine disorders (e.g., hypothyroidism), space occupying lesions (e.g., braintumor), normal pressure hydrocephalus, or substan

Table

1. Progressive impairment in two or more areas of cognition:

a) Memory (ability to learn and remember new information)

b) Language (speaking, reading, writing)

c) Executive function (reasoning, decision making, planning)

d) Visuospatial function (ability to recognize faces and objects)

e) Praxis (ability to perform purposeful movements)

f) Changes in personality, mood, or behavior

2. Cognitive deficits:

a) Interfere with functioning (ability to perform activities of daily living)

b) Represent a decline from previous levels of functioning

c) Are not due to delirium or psychiatric disorder (e.g., depression)

d) Are established using history from patient, corroborated by informant (e.g., family member), and objective cognitive Assessment. Ref No.[05]

abuse. Certain classes of medications also have thepotential to cause cognitive impairment in older adults(e.g., anti-cholinergics, psychotropics, analgesics, seda-tive-hypnotics). Irreversible (primary)dementias involveneurodegenerative and/or vascular processes in the brain.AD is the most common cause of irreversible dementia,accounting for up to 70% of all dementia cases in the United States.7 Other types of primary dementia include vascular dementia (10-20%), dementia associated with

Parkinson's disease, dementia with Lewy bodies, and front temporal dementia.

Epidemiology of AD

AD is a critical public health issue in the United States and many other countries around the world, with a sig-nificant health, social, and financial burden on society. An estimated 5 million Americans have AD, with a new diagnosis being made every 68 sec.8 In the United States, AD is the fifth leading cause of death among olderadults, and about $200 billion are spent annually on direct care of individuals living with dementia. World-wide, it is estimated that 35 million people have AD or other types of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050).9 AD is a multifactorial disease, with no single cause known, and several modifiable and non-modifiable risk factors are associated with its development and progression. Age is the greatest risk

factor for the development of AD. The likelihood of developing AD in-creases exponentially with age, approximately doubling every 5 years after age 65.10,11 The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic'
AD (-95% of all cases).Rare genetic mutations are associated with the devel-opment of AD
before age 65, which is known as 'early-onset' or 'familial' AD (B5% of all cases).12 People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursorprotein (APP) gene located on chromosome 21. In addition, individuals with Down's syndrome (trisomy 21) have an increased risk of developing early-onset AD. The genetics of sporadic AD are more complex andless well understood. It is known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the development of sporadic AD.13 The prevalence of AD is higher among females, reflecting the longer life expectancy ofwomen.14 Lower educational attainment has been asso-ciated with increased risk of AD dementia,10 consistent with the idea that education serves to increase a person's cognitive reserve and resilience to AD pathology.15 A large body of evidence suggests that cerebrovascular risk factors play a significant role in both the develop- ment and progression of AD; people with a history of diabetes, hypertension, obesity, and smoking have a substantially elevated risk of AD.16 Family history of AD in first-degree relatives and a history of head injury with loss of consciousness are also risk factors for the development of AD.4

Diagnosis of AD

The gold standard for the diagnosis of AD is an autopsy-based (post-mortem) pathological evaluation.

The presence and distribution of amyloid plaques and NFT in the brain is used to establish thediagnosis of 'definitive' AD and stage the disease.22 In clinical settings, the diagnosis of AD is largely based on medical history, physical and neurological examinations, and neuropsy- chological evaluation, as well as the exclusion of other etiologies using selective ancillary testing. The clinical diagnosis of AD has an accuracy of 70-

90% relative to the pathological diagnosis, with greater accuracies being achieved in specialty settings such as memory disorder clinics.23 The cornerstone of the clinical diagnosis is a set of consensus criteria first established in 198424 and last updated in 2011 by the National Institute on Aging -Alzheimer's Association (NIA- AA) workgroup.5 The NIA- AA clinical criteria for the
diagnosis of 'probable' AD dementia are summarized in Table 2. When the patient's cognitive impairment has an atypical clini-

cal course or is suspected to be due to other etiologies in addition to AD, the diagnosis of'possible' AD

dementia is recommended. Patients with AD generally have normal findings on physical and neurological examinations.6,25 To help with the differential diagnosis, Table 3 summarizes some of the clinical features that distinguish AD dementia from other causes of irreversible dementia. Laboratory and neuroimaging studies are used only for investigational purposes or asan adjunct to the clinical criteria for AD, particularly to rule out structural brain lesions and
identify 'reversible' causes of dementia. The only laboratory studies that the American Academy of Neurology recommends to be performed on a rou- tine basis as part of dementiawork-up are serum B12, thyroid stimulating hormone (TSH), and free thyroxine

Table 1. Clinical criteria for dementia

1. Progressive impairment in two or more areas of cognition:

a) Memory (ability to learn and remember new information)

b) Language (speaking, reading, writing)

c) Executive function (reasoning, decision making, planning)

d) Visuospatial function (ability to recognize faces and objects)

e) Praxis (ability to perform purposeful movements)

f) Changes in personality, mood, or behavior

2. Cognitive deficits:

a) Interfere with functioning (ability to perform activities of daily living)

b) Represent a decline from previous levels of functioning

c) Are not due to delirium or psychiatric disorder (e.g., depression)

d) Are established using history from patient, corroborated by informant (e.g., family member), and objective cognitive assessment

Table 2. Clinical criteria for probable AD dementia

1. Presence of dementia (as per criteria in Table 1)

2. Gradual onset of symptoms over months to years

3. History of progressive cognitive decline

4. Initial presentation may be amnestic (typical) or non-amnestic (atypical)

5. No evidence for another cause of cognitive impairment:cerebrovascular disease, other dementia syndromes, or neurological/medical disease

Table 3. Clinical features that distinguish AD from other dementias Clinical feature Alzheimer's dementia Vascular dementia Parkinson's dementia Dementia with Lewy bodies Frontotemporal

Dementia Patient profile - 65 years old - 40 years old Vascular risk factors 65 years old 75 years old (mean) 50- 70 years old 50% autosomal dominant History Gradual onset and deterioration Acute onset, step- wise deterioration Gradual onset and deterioration Gradual onset and deterioration Gradual onset

and deterioration Initial symptoms Memory loss Executive dysfunction Visual hallucinations Visual hallucinations Fluctuating attention Memory intact Disinhibition, apathy or aphasia Physical findings No motor impairment (until late stage) Pyramidal (upper motor neuron) signs Parkinsonism (precedes dementia by - 1 year) Parkinsonism (presents within 1 year of dementia) Usually none (rarely associated with motor neuron disease [Ref. No.**04 & 05**]

Alzheimer's Disease's Neuropathology

There are two types of neuropathological changes in AD which provide evidence about disease progress and symptoms and include: (1) positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients. In addition to
(2) negative lesions (due to losses), that are characterized by large atrophy due to a neural,neuropil, and synaptic loss. Besides, other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and injury of cholinergic neurons [**1, 2, 3**]

A] Senile Plaques (SP)

The senile plaques are extracellular deposits of beta-amyloid protein (Aβ) with different morphological forms, including neuritic, diffuse, dense-cored, or classic and compact type
plaques. Proteolytic cleavage enzymes such as β-secretase and γ-secretase are responsible for the biosynthesis of Aβ deposits from the transmembrane amyloid precursor protein (APP) [**6, 7, 8**]. These enzymes cleave APP into several amino acid fragments: 43, 45, 46, 48, 49, and 51 amino acids, which reach the final forms Aβ40 and Aβ42. There are several types of Aβ monomers, including large and insoluble amyloid fibrils which can accumulate to form amyloid plaques and soluble oligomers that can spread throughout the brain. Aβ plays a major role in neurotoxicity and neural function, therefore, accumulation of denser plaques in the hippocampus, amygdala, and cerebral cortex can cause stimulation of astrocytes and microglia, damage to axons, dendrites, and loss of synapses, in addition to cognitive impairments [**8, 9, 10**].

B] Neurofibrillary Tangles (NFTs)

NFT are abnormal filaments of the hyperphosphorylated tau protein that in some stages can be twisted around each other to form paired helical filament (PHF) and accumulate in neuralperikaryal cytoplasm, axons, and dendrites, which cause a loss of cytoskeletal microtubules and tubulin-associated proteins. The hyperphosphorylated tau protein is the major constituent of NFTs in the brains of AD patients, and its evolution can reflect NFTs morphological stages, which include: (1) pre-tangle phase, one type of NFT, where phosphorylated tau proteins are accumulated in the somatodendritic compartment without the formation of PHF, (2) mature NFTs, which are characterized by filament aggregation of tau protein with the displacement of the nucleus to the periphery part of the soma, and (3) the extracellular tangles, or the ghost NFTs stage, that results from a neuronal loss due to large amounts of filamentous tau protein with partial resistance to proteolysis [**11, 12**].

Synaptic Loss

A synaptic damage in the neocortex and limbic system causes memory impairment and generally is observed at the early stages of AD. Synaptic loss mechanisms involve defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that can contribute to small fractions, like the accumulation of Aβ and tau at the synaptic sites. These processes eventually lead to a loss of dendritic spines, pre-synaptic terminals, and axonal dystrophy [**13**]. Synaptic proteins serve as biomarkers for the detection of synapses loss, and
severity, such as neurogranin, a postsynaptic neuronal protein, visinin-like protein-1 (VILIP-1), and synaptotagmin-1 [**14,15**].

Treatment-

Current treatment

At present, only two classes of pharmacologic therapy are available for patients with AD. The cholinesterase inhibitors donepezil, rivastigmine, and galantamine are recommended therapy for patients with mild, moderate, or severe AD dementia as well as Parkinson's disease dementia [**16**]. Memantine, which has activity as both a non-competitive N-methyl-D-aspartate receptor antagonist and a dopamine agonist, is approved for use in patients with moderate-to- severe AD (mini-mental state examination [MMSE] <15) who show difficulty with attention andalertness [**17**]. For patients who choose alternative therapy, the nutraceutical huperzine A has shown benefit in both memory function and activities of daily living [**18**]. However, while huperzine A is a government-approved medication outside of the US, it is not regulated by the US Food and Drug Administration and may be subject to fluctuations in potency and purity.

Vitamin D deficiency was also identified as an independent risk factor for the development of dementia of any cause, and supplementation is recommended for patients in whom deficiencyis diagnosed [**19**]. Although many retrospective, observational studies alluded to the role of inflammation in the development of AD by showing a reduced risk of AD with the use of non- steroidal anti-inflammatory drugs, a more-thorough investigation failed to note any significant difference in cognitive performance in patients who took these medications [**20**]. In the past decade, omega-3 fatty acid supplements including fish oil have received much attention owing to their cardiovascular benefits. Two recent randomized, controlled, double-blinded studies showed improvement in thinking and memory in patients with MCI who took fish oil supplements, though these studies were limited by small sample size [**21,22**].

Finally, the management of cardiovascular risk factors contributes to overall brain health in both cerebrovascular disease and neurodegenerative disease[**23**]. Recent systematic reviews found that people who adhere to the Mediterranean diet (meals consisting of fresh produce, wholegrains, olive oil, legumes, and seafood while limiting dairy and poultry products and avoiding red meat, sweets, and processed foods) have reduced risk of developing cognitive decline and AD[**24,25**]. Regular aerobic exercise, long known to prevent metabolic conditions such as diabetes mellitus and coronary artery disease, also shows preservation of function and reduces caregiver burden in patients with AD[**26**]. Not only does physical exercise prevent loss of strength and agility as patients age but it also reduces neuropsychiatric symptoms and the increased care requirements associated with these issues. Recreational physical activity increases cognitive function later in life, with benefit noted regardless of age at the initiation of exercise[**27**]. Less atrophy was observed in the brains of patients with genetic risk factors for ADwho exercised regularly compared with those who did not, suggesting that aerobic activity prevents neurodegeneration[**28**]. Although larger controlled studies are still needed to examinethe long-term effects of physical activity in patients with biomarker-proven AD pathology, the inherent systemic benefits and lack of health risks should lead all healthcare providers to recommend regular exercise for their patients, regardless of cognitive function.

Future treatment

Research into future treatments of AD involve targeting of the etiologic pathologies: neurofibrillary tangles (composed of p-tau) and senile plaques (Aβ). However, there remains debate as to which abnormality is the best target to slow or halt neurologic decline as well as how soon treatment should be initiated[**29,30**]. Another approach aims to fortify transcorticalnetworks and enhance inter-neuronal connections in order to enhance cognitive function[**31**]. From previous studies, we learned that early identification of an at-risk population and subsequent treatment in the pre-clinical stage is the approach most likely to slow or halt the progression of AD[**32**]. Clinical trials are underway that aim to recruit asymptomatic patients with a genetic predisposition or biomarkers suggestive of higher risk of developing Alzheimer's dementia, with results expected early in the next decade. The EU/US/Clinical Trials in AD Task Force in 2016 examined many of these trials in an attempt to identify the most effective measures of patient recruitment and retention, infrastructure development, and patient assessment including biomarkers and objective testing for clinical outcomes[**32**]. Some of the persistent challenges identified include the timeline of recruitment and recruitment failures, difficulty in predicting success based upon prior studies for certain drugs, and the overall costs for such large-scale clinical trials. With a more cooperative effort between researchers, private and public funding, and screening of at-risk populations, a better predictor of successful clinicaltrials can be created.

Drug therapy

Much of the research in AD in the last decade has been directed towards disease-modifying therapy that will alter the course of the disease rather than act on symptoms alone, however the lack of effective disease-modifying drugs arising from these studies reflects the challenges involved in developing a therapeutic agent with potential to modify the course of a disease ascomplex as AD.[**33**]

Approved drug treatments

Cholinesterase inhibitors

Tacrine was the first-generation cholinesterase inhibitor but was limited by hepatotoxic side effects[**34**] Donepezil, rivastigmine and galantamine then followed, with the former probablythe most widely used agent.

Efficacy appears similar between these different agents so choice should be based on cost, individual patient tolerance and physician experience.

Donepezil is prescribed at an initial dose of 5 mg in the evening, increased to 10 mg after one month if appropriate[**35**] Response is gauged by a rating of better memory, function or behaviour by the patient or carer: there is no point in trying to measure change with brief mental status schedules such as the mini mental state examination, as these are not designed to detect clinically relevant change. If there is no response after three months of treatment it isreasonable to consider stopping the medicine at that stage although opinions around this can differ. Common side effects are gastrointestinal, fatigue and muscle cramps, and all patients should have an electrocardiogram prior to commencing a cholinesterase inhibitor because of the risk of sick sinus syndrome and other conduction abnormalities. Care should be taken if considering commencing a cholinesterase inhibitor in a person with a history of peptic or duodenal ulcer disease. Small numbers of patients may exhibit an acute worsening of cognition or agitation on starting; in which case, the medicine should be stopped immediately.

Average effects on cognition and function are generally modest[**36**] and response rates are variable, with around one-third of patients showing no benefit and a smaller proportion (around one-fifth) showing larger benefit. It is expected that about one-third of patients may not tolerate a cholinesterase inhibitor because of side effects

Risk Factors for LOAD (Late Onset Alzheimer disease)

To minimize the possibility of a future with a high percentage of people with AD, it is necessary to determine which are the factors that influence this disease. In recent years, a significant number of epidemiological studies related to the definition of risk factors for AD have been published. Risk factors for LOAD are classified as susceptibility genes and environmental factors [**37**]. LOAD has a strong genetic component, namely, apolipoprotein E (ApoE), the most widely studied genetic risk factor for AD. ApoE is produced by the liver, macrophages, and the central nervous system (CNS) [**38**]. In the CNS, it is produced by astrocytes and microglia; however, neuronal expression of ApoE can be induced in response to stress or neuronal damage under certain pathological conditions (stressors and injurious agents) [**39.**].

The main metabolic and nongenetic risk factors include hypercholesterolemia [**40,41**], obesity [**42,43**], hyperhomocysteinemia, hypertension [**44**], and type 2 diabetes mellitus (T2DM) [**45,46**].

Conclusion

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.

Activities of daily living are disrupted in those with dementia. As the dementia gets worse, family members and caregivers must step in an assist with personal care and household management. Individual and group activities can provide a sense of accomplishment and well-being.

After the Age of 40, The Person Should take his Physical Responsibility As well as the Mental Health. From such way, exercise, Yoga, Diet, Meditation Etc.

This activities will help the person after the age of 40 too fight with the dicious like Alzheimer

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