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Original Article

A Comprehension Review of Alzheimer's Disease ; Epidemiology, Pathophysiology, Diagnosis and Emerging Therapeutic Strategies

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, characterized by gradual deterioration of memory, cognition, behaviour, and functional abilities. The prevalence of AD increases significantly with age, posing a growing global health burden. This review summarizes the epidemiology, classification, pathophysiology, risk factors, diagnostic approaches, and current and emerging therapeutic strategies for Alzheimer's disease. The pathological hallmarks of AD include extracellular amyloid-β plaque deposition, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, and cholinergic neuronal dysfunction, which collectively contribute to neuronal degeneration and cognitive decline. Major risk factors such as hypertension, diabetes mellitus, obesity, and dyslipidaemia are discussed, along with potentially protective factors including vitamin D, oestrogen, and adherence to a Mediterranean-style diet. Diagnostic methods, including cognitive assessment scales, neuroimaging techniques, and laboratory investigations, are reviewed for their roles in early detection and disease monitoring. Current treatment options focus primarily on symptomatic management through cholinesterase inhibitors and supportive non-pharmacological interventions. Furthermore, emerging therapeutic approaches, including immunotherapy, gene therapy, and nanotechnology-based drug delivery systems, show promise in overcoming limitations of conventional treatments and targeting underlying disease mechanisms. Despite advances in understanding AD pathogenesis, effective disease-modifying therapies remain limited. Continued research into novel biomarkers, personalized medicine, and innovative therapeutic technologies is essential to improve clinical outcomes and reduce the global burden of Alzheimer's disease.

Keywords: Alzheimer's disease, dementia, amyloid-β, tau protein, cholinesterase inhibitors, diagnosis, nanotechnology, gene therapy, neurodegeneration.

INTRODUCTION

Alzheimer's disease is a progressive neurological disorder that impacts memory, cognition, and behaviour, resulting in a decline in both cognitive and physical functions.

It is a complex type of dementia with diverse symptoms and currently has no cure, although treatments are available to manage the condition. The disease is marked by changes in the brain, including the buildup of specific proteins, which cause brain shrinkage and cell death.

Aim :

To critically review current knowledge regarding the epidemiology, pathogenesis, diagnosis, and therapeutic management of Alzheimer's disease, while highlighting recent advances and future prospects in disease-modifying therapies.

Objectives :

To summarize the epidemiology and burden of Alzheimer's disease.

To discuss the etiological and pathological mechanisms involved in disease progression.

To evaluate established and emerging diagnostic biomarkers and imaging modalities.

To review available pharmacological and non-pharmacological treatment options.

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To explore novel therapeutic approaches, including immunotherapy, gene therapy, and nanomedicine.

To identify existing research gaps and future opportunities for improving Alzheimer's disease management.

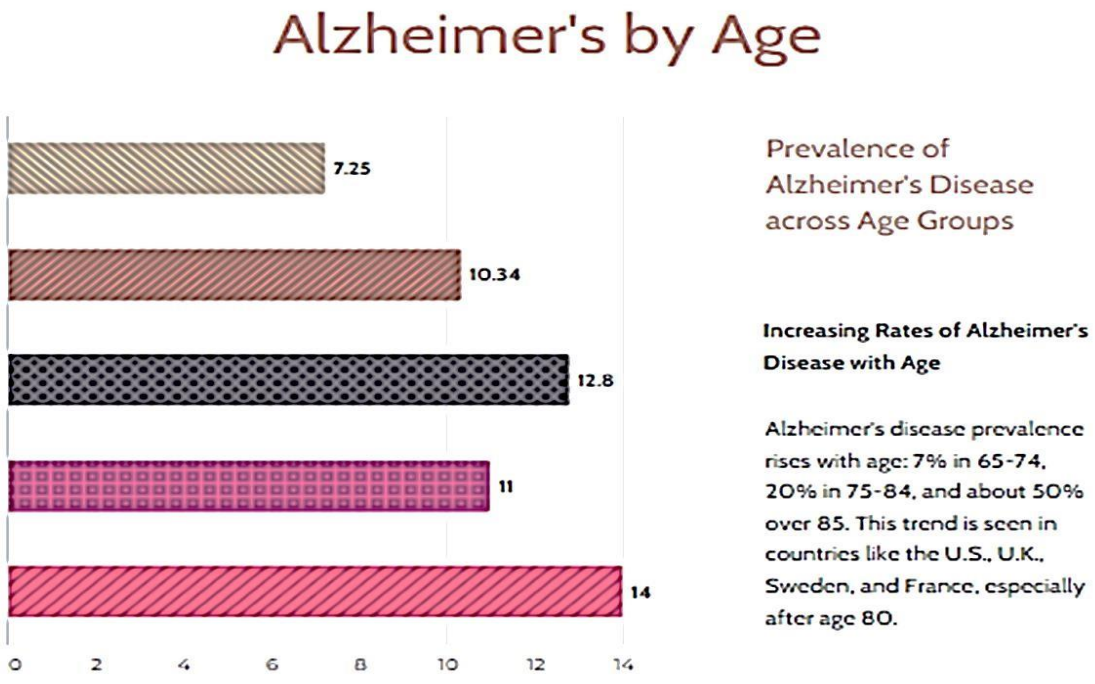
1.3 Literature Review Methodology

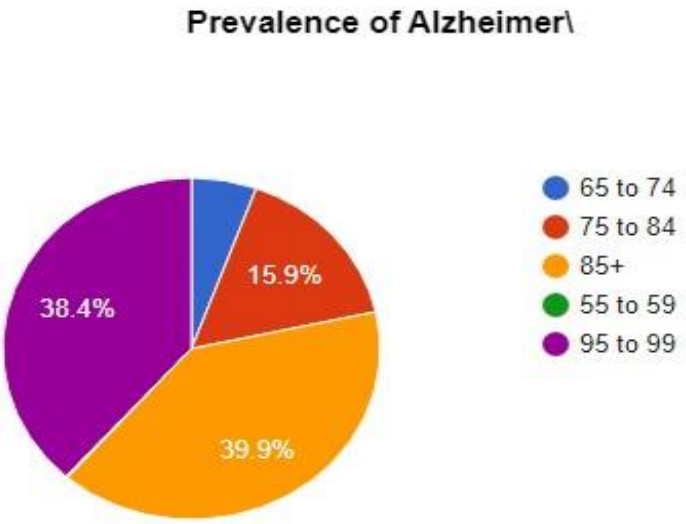
The present review was conducted by collecting and evaluating information from various peer-reviewed journals, review articles, books, and scientific databases related to Alzheimer's disease. Relevant literature was identified through electronic databases such as PubMed, Scopus, Google Scholar, ScienceDirect, and ResearchGate.

The search was performed using keywords including "Alzheimer's disease," "dementia," "amyloid beta," "tau protein," "risk factors," "diagnosis," "pharmacological treatment," "non-pharmacological therapy," "nanotechnology," and "gene therapy." Articles providing information on the epidemiology, classification, pathogenesis, diagnosis, treatment, and recent advances in Alzheimer's disease were selected. Published literature from reputable national and international journals was reviewed and analysed. The collected information was organized systematically to provide a comprehensive overview of the disease, its current management strategies, and emerging therapeutic approaches.

Epidemiology: -French the prevalence of Alzheimer's disease (AD) increases with age, affecting 7% of people aged 65 to 74, 20% of those aged 75 to 84, and about 50% of people over 85 years old. This trend is consistent in countries such as the United States, the United Kingdom, Sweden and France, especially after the age of 80. The overall prevalence of clinically diagnosed AD dementia is significant and is expected to increase as the population ages, with estimates suggesting that 3–4% of adults in their last year of work or retirement are affected.

A systematic review in China showed that the prevalence of AD increases from 0.2% in people aged 55 to 59 years to 48.2% in people aged 95 to 99 years.





Types of Alzheimer's disease: -

Scientists have differing opinions on how to categorize Alzheimer's disease. It is most common cause of dementia, not merely "one opinion" along with other forms such as mild cognitive impairment and vascular dementia. Alzheimer's is currently classified into subtypes based on severity, inflammatory response, and the type of onset or trigger.

Alzheimer's disease has subtypes based on symptom severity.

1. **Mild Alzheimer's:** Results in early cognitive problems, such as inability to recall basic activities of daily living like going to work or paying bills. Though it is not an acute attack, these symptoms will make things harder and your task completion speed slower than before.

2. **Moderate Alzheimer's:** At this stage, moderate Alzheimer's causes significant neuronal death for prominent signs like more severe confusion and memory loss. Delusions hinder the performance of routine activities, such that even patient themselves capable physically, but they become dependent on others.

3. **Severe Alzheimer's**: In case of grave Alzheimer's brain cell death is due to plaques and tangles leading to the shrinking of brain tissue. These subtypes correspond to the progressivity of this disease that goes from less severe forms to more grave ones and an early diagnosis enables prompt treatment intervention with better outcomes for prevention.

Alzheimer's is categorized into subtypes based on the inflammatory response:

1.**Inflammatory**: Behavioural, cognitive symptoms in conjunction with the presence of higher serum albumin to globulin ratio and increased C-reactive protein due to inflammation.

2. Non-Inflammatory: This subtype is not associated with up regulation of inflammatory biomarkers but almost always involves some other form of metabolic disturbance. Cortical: This type, which results when zinc-restricted regions of the brain cannot perform their normal functions and leads to Alzheimer's disease, is not inflammatory.

Alzheimer's disease can be classified by the onset type into early-onset and late-onset.

1. **Early-onset** Alzheimer's affects individuals under 65, is rare, and typically manifests in the late 40s or early 50s, often linked to a defect in Chromosome 14.

2. **Late-onset**

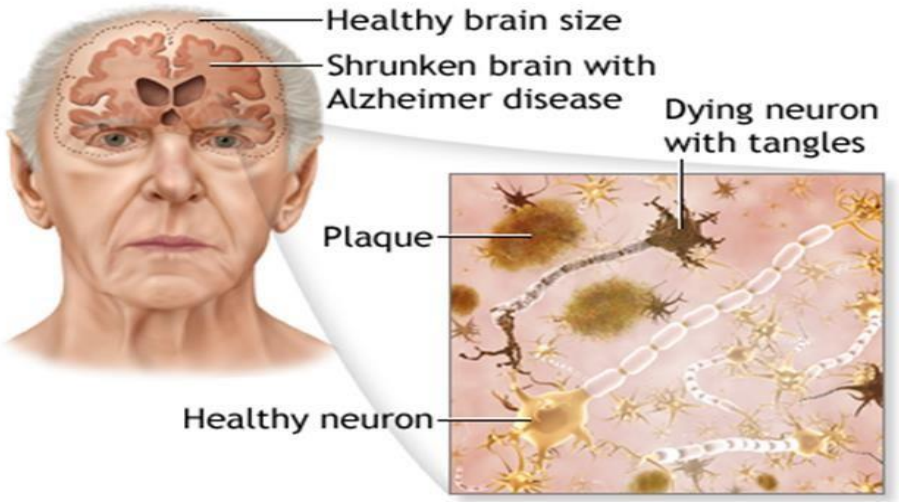
Alzheimer's is more common, impacting those over 65, with ongoing research to identify specific genetic triggers and risk factors.

Familial Alzheimer's disease, another rare form, occurs when a distinct genetic pattern is observed within a family, allowing for predictive diagnosis.

Early detection of Alzheimer's is vital for managing its effects on cognitive, physical, and social abilities.

Alzheimer's disease (AD) primarily affects older adults but can occasionally manifest in individuals aged 50 to 60.

It is a progressive condition with an average life expectancy of 4 to 8 years after diagnosis, though some may live up to 20 years.



The progression of AD involves several stages:

1. Preclinical phase: Pathological changes begin in the entorhinal cortex and hippocampus, where patients experience mild memory loss without significant daily functional impairment.

2. Mild AD: Characterized by cognitive impairment and memory loss, patients forget appointments and often ask repetitive questions, showing confusion, personality changes, and mood swings. This stage typically lasts about two years.

3. Moderate AD: This stage develops over 3 to 5 years, with further memory loss and attention difficulties, behavioral issues, and trouble recognizing family and friends. Patients may exhibit apathy, social withdrawal, and difficulties in language.

4. Severe AD: In advanced stages, patients are completely dependent on caregivers, exhibit incontinence, and may lose the ability to swallow.

Causes and Risk factors: -

People with Alzheimer's disease may be the first to notice difficulties with memory and the organization of thoughts, while some do not understand, despite the obvious changes in others.

The causes of Alzheimer's disease can be explained by three hypotheses.

1. Cholinergic hypothesis: -The cholinergic hypothesis of Alzheimer's disease suggests that memory and learning decline is related to deficits in choline acetyltransferase and acetylcholine due to a reduction in cholinergic neurons and neurotransmission. Although loss of cholinergic function is associated with cognitive decline, a direct causal link has not been established.

In addition, cholinesterase inhibitors are ineffective in more than half of patients, indicating that other factors contribute to disease progression.

2. Amyloid hypothesis: Amyloidosis occurs when abnormal amyloid

proteins accumulate in tissues, leading to the formation of deposits that contain insoluble fibrillar β-sheets. The disease is characterized by a reduction of this cleaning function in tissues and cells. Amyloid-ß membrane protein (APP) is a precursor to Aß, which contributes to the formation of amyloid or neuro plaques in the victims' brains.

3. Tau hypothesis: The Tau hypothesis proposes that neurofibrillary tangles (NFTs) represent an obligatory component of Alzheimer's pathology and develop due to increased phosphorylation of Tau

attached to mt. Such phosphorylation increases the level of free Tau and decreases the number of functional microtubules in the cell. The Tau that is phosphorylated is incorporated into PHFs which coalesce into NFTs. The disturbance of the microtubules leads to a failure in the axonal trafficking of proteins and, eventually, neuronal cell death.

Risk factors such as cerebrovascular disease, diabetes, hypertension, obesity, and dyslipidaemia increase the likelihood of developing Alzheimer's disease. There are causal relationships between Alzheimer's and cerebrovascular illnesses that alter cerebral white matter and blood vessels, leading to dementia.

Hypertension is linked to vascular wall damage, reduced blood flow, and potential effects on the blood-brain barrier, which may hasten Alzheimer's onset.

Type 2 diabetes is particularly connected to Alzheimer's due to insulin resistance and high blood sugar levels, which contribute to the buildup of amyloidal-beta and tau hyperphosphorylation, key elements in neurofibrillary tangles' formation.

The relationship between obesity and Alzheimer's is still not clearly defined; some research suggests a credible connection, while other studies show mixed results regarding dementia risk in older adults.

Additionally, weight loss may increase susceptibility to dementia.

1. Hypertension: -Hypertension has been linked to an increased risk of developing Alzheimer's disease (AD), as highlighted by a longitudinal study. (1996). Subsequent research supports this connection; particularly noting that hypertension during middle age adversely affects cognitive abilities later in life, although this effect tends to diminish with age. The condition can cause changes in vascular walls, leading to reduced blood flow, ischemia, and cerebral hypoxia, which may trigger AD development. Cerebral ischemia has been shown to promote the accumulation of amyloidal precursor protein (APP) and amyloidal-beta (Aβ), and to enhance the expression of presently, which is involved in Aβ production. Additionally, hypertension may impair the blood-brain barrier, further contributing to the onset of AD through these mechanisms.

2. Diabetes: -Epidemiological studies indicate a strong connection between type

2 diabetes mellitus and a higher risk of Alzheimer's disease. Several mechanisms are suggested to explain this link, including insulin resistance, insufficient insulin, impaired insulin receptors, hyperglycemia toxicity, advanced glycation end products (AGEs), and vascular damage. Animal research shows that insulin deficiency and resistance can activate enzymes that lead to the accumulation of amyloidal-beta in the brain and promote hyperphosphorylation of tau protein, which forms neurofibrillary tangles. Normally, insulin and insulin-like growth factors trigger a process that inhibits the enzyme GSK3β, involved in tau phosphorylation. When insulin signalling fails, GSK3β becomes overactive, enhancing phosphorylated tau formation. Additionally, AGEs can cause neuronal death and increase amyloidal precursor protein processing through elevated expression of specific enzymes, often linked to reactive oxygen species. Glycation of amyloidal-beta may also result in a more harmful neuron toxic form.

3. Obesity: -The relationship between obesity and the risk of Alzheimer's disease (AD) remains unclear, with varying study results. A meta-analysis by Profenno, Porsteinsson, and Faraone in 2010 found a significant association between obesity (BMI ≥30 kg/m2) and AD risk. Conversely, Fitzpatrick et al. in 2009 reported that while obesity in middle age increases dementia risk, it inversely correlates with dementia risk in older age. Additionally, they found that being underweight (BMI <20 kg/m2) also raises dementia risk.

4. Dyslipidaemia:-Elevated cholesterol levels are considered risk factors for Alzheimer's disease (AD) development, with studies indicating that patients with AD have 10% higher cholesterol levels than healthy individuals.

Hypercholesterolemia not only contributes to atherosclerosis but also increases the risk of AD and other neurodegenerative diseases by affecting the blood-brain barrier's integrity. This condition is linked to greater deposition of Aβ peptides, increased

formation of neurofibrillary tangles, cognitive decline,

Neuroinflammation, dysfunction of cholinergic neurons, and cerebral micro hemorrhages. Although observational studies suggest that statins may reduce AD incidence or improve disease progression, clinical studies have not confirmed this benefit against cognitive decline in AD patients. Some research showed a lower risk of developing AD among statin users, while a Cochrane meta-analysis found no significant impact of statins on disease outcomes or mini-mental status examination scores. Questions remain about the effectiveness of statins if treatment begins in middle age or for individuals with a family history of AD compared to those without.

Protective Factors

1. Vitamin D: -Epidemiological studies suggest a link between low serum levels of vitamin D, especially 25-hydroxyvitamin D, and the development of Alzheimer's disease (AD).

Vitamin D plays a crucial role in calcium metabolism, bone regulation, and functions within the central nervous system, including modulation of neurotrophic factors, oxidative stress, immune responses, and inflammation.

Vitamin D deficiency may increase inflammation and enhance the amyloidogenic pathway, contributing to AD pathology. Research has shown that supplementation with vitamin D can lead to reductions in BACE1 and Aβ peptide levels in elderly rats and may help clear Aβ peptide via macrophage action. Furthermore, mutations in the vitamin D receptor gene have been linked to increased AD risk. While larger clinical trials on vitamin D supplementation's effect on AD cognition are lacking, smaller studies report mixed results regarding cognitive improvement from high doses. Therefore, screening for and addressing vitamin D deficiency in the elderly is recommended, though this treatment does not specifically target cognitive enhancement.

2. Estrogen: -

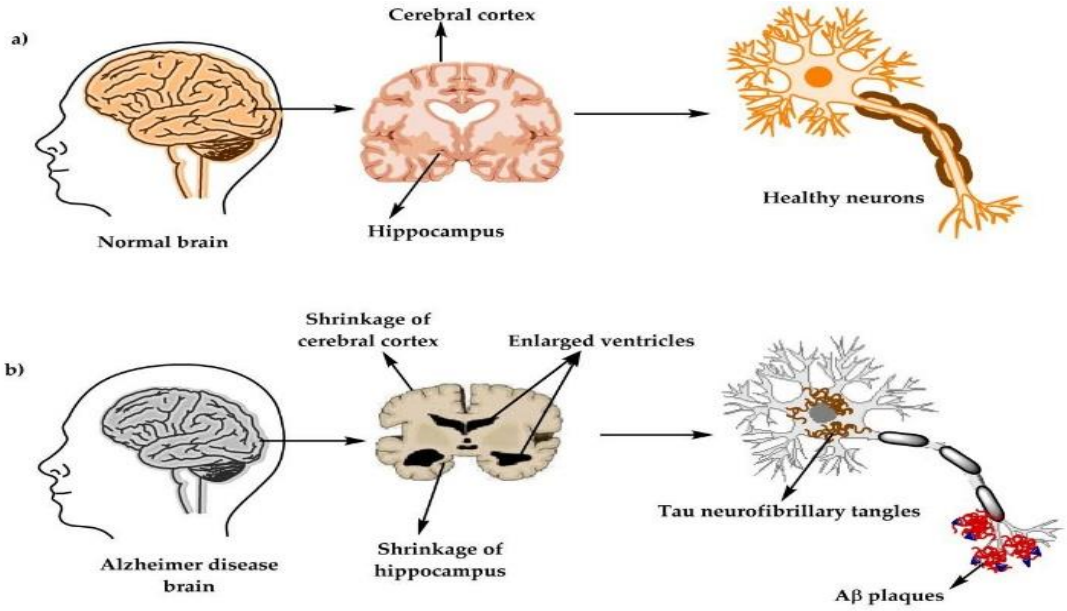
Estrogen, particularly estradiol, is known to have protective roles in sex organs and recently has been recognized for its local production in various tissues, influencing function independently of circulating levels. It provides neuroprotective effects by preventing mitochondrial dysfunction, reducing neuroinflammation, and aiding DNA repair in nerve cells. However, epidemiological studies on hormone replacement therapy yield mixed results. While some indicate no beneficial effects on the risk of Alzheimer's disease, others suggest cognitive protection for women undergoing therapy at different stages post-menopause. Due to inconsistent findings and potential risks like deep venous thrombosis, hormone replacement therapy is generally not recommended for preventing cognitive decline or Alzheimer's development.

3. Diet: -

The article examines the link between diet and the risk of Alzheimer's disease (AD), highlighting that the Mediterranean diet, rich in polyunsaturated fats and antioxidants, is associated with a lower risk of AD, while diets high in saturated and trans fats increase that risk. Key nutrients for brain health include fatty acids such as fish oil, antioxidants (vitamins E and C), fruits, vegetables, some B vitamins, and calorie restriction. Antioxidants combat oxidative damage, and fatty acids like DHA help remove amyloidal beta peptide and support neuronal membrane health. Adequate intake of DHA, EPA, and B vitamins is essential for maintaining synaptic function and preventing neuro degeneration. The Omega AD study suggested that omega-3 supplementation may improve cognitive performance in AD patients.

Disease physiology: -

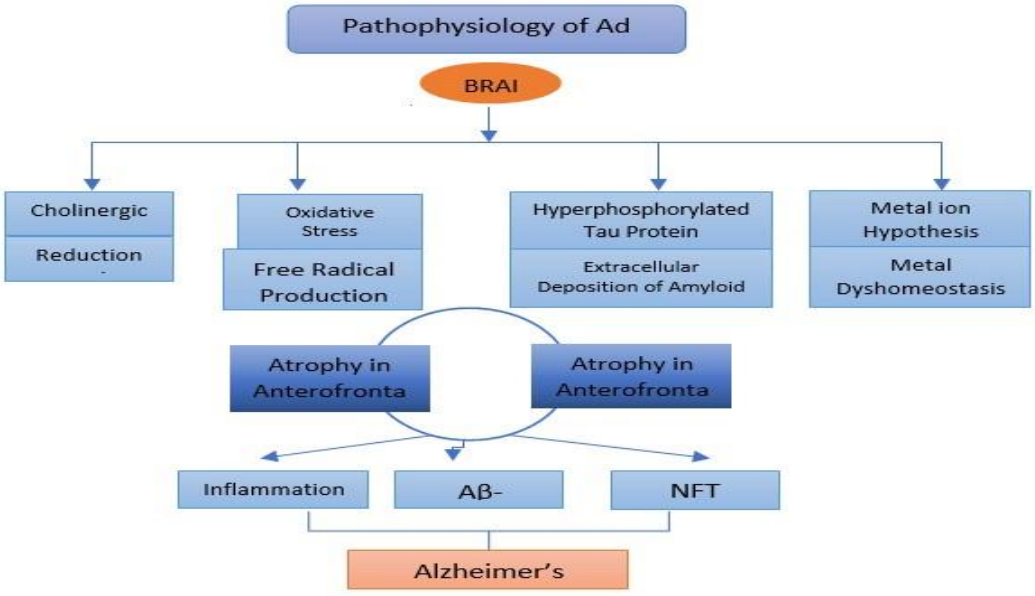
In Alzheimer's disease there are two significant microscopic alterations, which take place: the senile plaques that develop between neurons and the neurofibrillary tangles that develop inside neuron cells. These alterations are believed to be intimately connected to the cause and course of the illness. These beta-amyloidal polypeptide aggregates which are referred to as the plaque, can result from beta amyloid processing and its precursor protein as well. In addition, genetic factors and certain environmental factors like subclinical ischemia or degree of hypertension could increase the risk of developing the disease.



On the other hand, some fragments of neurofibrillary tangles which are partially made of tau protein.

Tangled microtubules are detrimental to normal microtubule functions and thus lead to the degeneration of neurons.

Moreover, cholinergic neuron damage leads to low levels of acetylcholine with the level of acetyl cholinesterase offsetting and but cholinesterase levels increasing with the disease.



Diagnosis:

Diagnosis Criteria: The clinical diagnosis of Alzheimer's disease forms part of a logical sequence that most diseases follow:

clinical history, ideally from an informant i.e. person who knows the patient; mental state assessment validated cognitive function test; and physical examination vascular plus neurological signs supported by investigations and patient history assessment of dementia involves a two-step process in most cases. Firstly, it is important to distinguish dementia syndromes from other conditions that can mimic them, such as depression, delirium, and mild cognitive impairment as is observed in most

Cases, therefore these diseases need to be distinguished first. Secondly, once dementia syndrome is recognized, the diagnosis of a subtype is

important because it may determine the kind of treatment possible. For cognitive screening in general practice, the clock test is popular because of its non-confrontational nature and because the normal drawing of a clock more or less excludes the presence of important cognitive impairment. However, the rules for scoring the tests can be quite complex and using a solitary cognitive test to screen for the presence of a dementia syndrome does not do justice to the wide variety of symptoms and indications that make up the clinical syndrome of dementia. Activities of daily living are assessed alongside cognition, but there is less consistency in the assessment instruments used.

A. Medical History:

When taking a medical history for diagnosing Alzheimer's disease, it is important to consider several key areas.

1. Perceptual symptoms include memory loss, language difficulties, and changes in reasoning

2. Behavioral changes may involve personality shifts, confusion about time or place, and loss of interest in activities.

3. Refusing to work can manifest as difficulty with daily tasks and getting lost in familiar areas.

4. A family history of Alzheimer's or another dementia is significant.

5. Medical conditions like heart disease, diabetes, or neurological issues should be noted.

6. A current list of medications, along with any cognitive side effects, is important.

7. Mental health history, including depression or anxiety, must be considered.

8. Lifestyle factors such as fitness, diet, and substance use are relevant.

9. Changes in sleep patterns, including disturbances like sleep apnea, should be assessed.

10. Lastly, unexplained sensory perception changes, like hearing or vision issues, are relevant. Collecting comprehensive information in these areas' aids in accurate diagnosis.

B. Physical and Neurological Exam:

Physical and neurological examinations are important to diagnose Alzheimer's disease. During the evaluation, a health care professional will check your vital signs and general health for possible problems affecting cognitive function. It will assess neurological aspects such as reflexes, coordination and sensory function to identify deficits. Cognitive tests assess memory, attention, and language skills to detect cognitive impairment. Doctors will also watch for changes in mood, behavior or personality that could indicate dementia.

C. Screening Methods:

1. P.E.T SCAN: Positron emission tomography (PET) is a medical imaging technique that uses radiation signals to create three-dimensional color images of the body. It involves injecting a radiotracer, typically glucose in Alzheimer's studies, which travels to organs that metabolize this molecule. As the radiotracer is broken down, it emits positrons, and the PET scan detects this energy to produce an image indicating the body's functional activity. The varying colors and intensities in the image represent different levels of brain activity. PET scans can identify changes in metabolism, blood flow, and cellular communication in the brain. Research from 1996 showed that PET scans could detect low glucose metabolism rates in the brains of Alzheimer's patients, particularly in the parietal, temporal, and posterior cortices, with more significant decreases in advanced cases. Additionally, PET scans can reveal metabolic changes prior to clinical symptoms and can be used to evaluate treatment effectiveness for Alzheimer's disease.

2. CT SCAN: C T scanning produces detailed cross-sectional images of the body by merging multiple images through computer processing. It assists doctors in evaluating tissue density in various areas, including the brain. Utilizing a contrast agent enhances image clarity by distinguishing similar tissues.

3. Magnetic Resonance Imaging (MRI): first used in 1977, creates detailed images of the body for diagnostic purposes. The heart of the MRI system is a superconducting magnet that generates a stable magnetic field, supplemented by smaller gradient

magnets for area-specific scans. The process mainly involves hydrogen atoms, which align with the magnetic field. A radio frequency pulse changes their spin, and when they return to equilibrium, they release the energy that the system captures to form the image. Fabrics react differently to contrasting colors, producing a unique grayscale look. Research has shown that MRI can identify structural changes in the brains of Alzheimer's patients, particularly hippocampus atrophy, even before clinical symptoms appear. Nunnand's 2002 study found that MRI scans can detect Alzheimer's disease in people with cognitive impairment. Additionally, a 2009 study explored sodium magnetic resonance imaging, which uses sodium ions to detect tumors and track cellular changes in the brain, further improving the ability to diagnose Alzheimer's disease. Research aims to clarify whether the increase in signal intensity is due to changes in ion concentration or changes in volume.

D. Blood Tests: To assess intellectual health a complete blood count (CBC) assesses overall health and checks for abnormalities such as anemia and infections. Thyroid function tests assess hormone levels because thyroid problems can affect cognition. When tested, low vitamin B12 levels can cause memory problems similar to dementia. Electrolyte levels are checked for any imbalances that affect brain function. Liver and kidney function tests help ensure that these organs are working properly. This is because abnormalities in these organs may affect cognitive health. Inflammatory markers, such as C-reactive protein, help identify inflammation associated with cognitive decline. Finally, genetic testing for specific genes can assess the risk of Alzheimer's disease. Especially family history.

Modern Biomarker-Based Diagnosis of Alzheimer's Disease

Alzheimer's disease diagnosis has evolved significantly with the development of biomarkers that detect pathological changes before the appearance of clinical symptoms. Modern diagnostic approaches combine clinical assessment, neuroimaging, cerebrospinal fluid (CSF) biomarkers, and blood-based biomarkers to improve diagnostic accuracy and enable earlier intervention.

1. Cerebrospinal Fluid (CSF) Biomarkers

Analysis of CSF provides important information regarding Alzheimer's pathology.

a) Amyloid-beta 42 (Aβ42)

Decreased CSF Aβ42 levels indicate amyloid plaque accumulation in the brain.

Considered an early biomarker of Alzheimer's disease.

b) Total Tau (t-tau)

Elevated CSF total tau reflects neuronal injury and neurodegeneration.

c) Phosphorylated Tau (p-tau181 and p-tau217)

Highly specific biomarkers for Alzheimer's disease.

Increased levels correlate with neurofibrillary tangle formation and disease progression.

2. Blood-Based Biomarkers

Recent advances have enabled the detection of Alzheimer's pathology through simple blood tests.

a) Plasma p-tau217

One of the most accurate blood biomarkers currently available.

Demonstrates high sensitivity and specificity for Alzheimer's disease.

b) Plasma p-tau181

Useful for differentiating Alzheimer's disease from other neurodegenerative disorders.

c) Neurofilament Light Chain (NfL)

Marker of neuronal damage and neurodegeneration.

Elevated levels are associated with disease severity.

d) Plasma Aβ42/Aβ40 Ratio

Lower ratios indicate amyloid plaque deposition in the brain.

3. Neuroimaging Biomarkers

a) Amyloid PET Imaging

Visualizes amyloid-beta plaque accumulation in vivo.

Useful in early and atypical presentations of Alzheimer's disease.

b) Tau PET Imaging

Detects tau protein deposition in the brain.

Correlates strongly with cognitive decline.

c) Magnetic Resonance Imaging (MRI)

Demonstrates hippocampal atrophy and cortical volume loss.

Useful for monitoring disease progression.

Detects reduced glucose metabolism in temporoparietal and posterior cingulate regions.

Indicates neuronal dysfunction before structural changes become apparent.

4. AT(N) Biomarker Framework

The National Institute on Aging and Alzheimer's Association (NIA-AA) proposed the AT(N) classification system:

Biomarker Category

Interpretation

A (Amyloid)

Amyloid PET or CSF Aβ42

T (Tau)

CSF p-tau or Tau PET

N (Neurodegeneration)

MRI atrophy, FDG-PET, or NfL

Scales used in Alzheimer's disease:

Scale	Purpose	Description	Completion time	Comments
Mini-Mental State Examination	Measures cognition	Assesses orientation, registration, attention, recall, and language on a 30-point scale	5 to 10 minutes	Score decreases about 2 to 3 points per year in patients with Alzheimer's disease. Requires minimal training to administer; useful in clinical practice
Alzheimer's Disease Assessment Scale, Cognitive Section	Measures cognition	Assesses cognitive domains with an 11-item, 70-point scale	20 to 45 minutes	Score decreases by 6 to 12 points per year in patients with Alzheimer's disease. Requires significant training to administer; a research instrument
Global Impressions	Quantifies an overall perception of change	Assesses cognitive domains, behavior, and self care on a scale of 1 (marked improvement) to 7 (very much worse); often used with caregiver input	10 to 30 minutes	Requires a consistent and systematic interview at each visit Requires moderate training to administer; most useful in research
Neuropsychiatric Inventory	Measures disturbed behaviors	Assesses severity and frequency of 12 symptoms (e.g., agitation, irritability, depression, hallucinations); also measures caregiver distress	10 to 20 minutes	Useful in research; in clinical practice, it may be more useful to use a "global" approach to assess disturbed behaviors.
Functional Activities Questionnaire's	Quantifies disability	Scores functional capacity on a scale of 1 (normal) to 7 (severely incapacitated)	5 to 10 minutes	Easy to complete
Physical Self-Maintenance Scale and instrumental Activities of Daily Living	Measures ability to accomplish basic and instrumental tasks	Assesses six basic tasks and eight areas of higher functioning on a scale of 1 to 5	10 minutes	Requires minimal training to administer; useful in clinical practice

The Mini Mental Status Examination (MMSE) is a general test that assesses cognitive functioning such as memory and attention. With a maximum score of 30, the Montreal Cognitive Assessment (MoCA) provides a comprehensive assessment of cognitive skills. Including the work of executives The Clinical Dementia Rating (CDR) scale determines the severity of dementia by classifying stages and evaluating performance in six domains. The Alzheimer's disease AssessmentCognitive Subscale (ADAS-Cog)

measures cognitive performance. It focuses specifically on memory, language, and behavior. The Activities of Daily Living (ADL) scale assesses a person's ability to perform daily tasks. It emphasizes the impact of cognitive decline.

TREATMENT:

Early treatment enhances patients' quality of life by utilizing pharmacological approaches that help manage cognitive disorders, slow the progression of deficits, and reduce psychiatric symptoms like agitation, depression, and psychosis. Additionally, non-pharmacological treatment focuses on psychotherapeutic methods and engaging with patients' families and caregivers. Psycho-education plays a key role in fostering behavioral changes, minimizing reliance on symptomatic treatment, establishing structured routines, preventing isolation, and providing cognitive stimulation and emotional support.

A. Non pharmacological Treatment:

Drug-free treatments for Alzheimer's disease focus on enhancing quality of life and cognitive function without medication. These approaches include cognitive stimulation therapy to engage patients in mentally stimulating activities, regular exercise to boost overall health and mood, and a structured daily routine to minimize confusion and anxiety. Reminiscence therapy encourages discussions about past experiences to enhance emotional well-being, while music and art therapy facilitate emotional expression and communication.

B. Pharmacological Treatment:

A) Neurotransmission dysfunction treatment.

B) Neuronal metabolism disorder treatment.

C) Compounds under research.

A) Neurotransmission dysfunction treatment.

CHOLINESTERASE INHIBITORS are the most researched medications for treating Alzheimer's disease (AD). These drugs enhance cholinergic transmission by inhibiting the enzyme in various ways, resulting in moderate benefits for patients in the early stages of the disease and helping to slow down cognitive decline over time. Predictors of a favorable response include having a slight to moderate disease stage, late onset, and the absence of the Apo E, allele 4. The main cholinesterase inhibitors include Tacrine, rivastigmine, Donepezil, and Galantamine.

Which should be used cautiously in patients with specific health issues additionally, there is evidence suggesting that these inhibitors may alleviate psychiatric symptoms associated with AD by regulating cholinergic transmission in key brain areas, linking emotional and cognitive functions.

1. Tacrine: tetra-hydro-amino acridine (THA), is a reversible cholinesterase inhibitor with proven effectiveness in eight placebo-controlled studies since 1981, some showing significant improvements. It is metabolized in the liver and has a half-life of 2-4 hours. Key side effects include nausea, vomiting, stomach pain, anorexia, bradycardia, muscle pain, ataxia, and elevated hepatic enzymes, particularly in 40% of cases. Tacrine is contraindicated in patients with liver impairment. Elevated liver enzymes typically occur within the first 12 weeks of treatment, more commonly in women, and return to normal levels within 4 to 6 weeks after stopping the drug. Regular monitoring of liver enzymes is recommended, with specific follow-up intervals. Dosage increases should be limited to 40 mg every 6 weeks. Several derivatives of tacrine are under investigation, and approximately 90% of patients tolerate the medication well

2. Rivastigmine: Rivastigmineis a carbamate acetyl cholinesterase inhibitor that selectively targets the brain. Its action is pseudo-reversible, which means that it can continue to inhibit acetyl cholinesterase even after the drug has been removed from the body. The drug has a half-life of one hour and its effects last up to 10 hours. The interaction of acetylcholine with enzymes at the acetate site occurs rapidly, while dissociation from the carbamate region is slower. Rivastigmine is eliminated by the kidneys and is mainly absorbed orally, reaching peak levels within one hour. It is weakly protein bound and effectively crosses the blood-brain barrier. The drug undergoes hydrolysis and is eliminated 90% in 24 hours, indicating a low degree of pharmacological interaction due to minimal hepatic metabolism. It is commonly used to treat Alzheimer's disease in some

countries, with clinical studies of about 3000 patients showing an improved quality of life in those who received higher doses of rivastigmine (6 to 12 mg) per day compared to placebo. Side effects are usually mild and include nausea, vomiting and diarrhea.

Rivastigmine is marketed in tablet form under the names Exelon, Rivasmine, and Zimina. A transdermal patch for rivastigmine has been approved for treating mildto-moderate Alzheimer's disease (AD) in the USA and Europe. This patch offers a better pharmacokinetic profile by delivering the drug continuously into the bloodstream, reducing fluctuations seen with oral administration. Studies show that a 10 cm2 patch (9.5 mg/day) is as effective as a 12 mg/day capsule while also significantly reducing nausea and vomiting. Comparisons from several randomized controlled trials indicate that rivastigmine patches have better safety and tolerability than capsules, with less risk of skin reactions by rotating patch locations. A recent study reported cognitive and functional improvements in AD patients using the patch, which is generally well tolerated with only mild side effects like erythematic and pruritus noted. The marketed rivastigmine patch is known as the Exelon patch.

3. Donepezil: Donepezilis a reversible cholinesterase inhibitor that is more effective than tacrine. In two double-blind studies with 900 patients aged 50 to 90 who had mild to moderate dementia, cognitive improvement or preservation of function was noted over 15and 30-weeks using doses of 5 to 10 mg daily. It is nearly completely absorbed orally, reaches peak levels in 3 to 4 hours, and binds to plasma proteins at a rate of 96% without displacing other medications. Metabolism occurs in the liver via cytochrome P450 enzymes 2D6 and 3A4 in a slow, nonsaturable manner, with some elimination through the kidneys. Its average half-life is 70 hours, allowing for once-daily dosing. Common side effects include nausea, vomiting, diarrhea, anorexia, insomnia, fatigue, and cramps, while less frequently, bradycardia, syncope, increased gastric heartburn, bronchospasm, and convulsions may occur.

ORAL DONEPEZIL THERAPY IMMEDIATE-RELEASE TABLETS:

Donepezil immediate-release tablets (5 or 10 mg) were approved in the US in November 1996 for treating Alzheimer's dementia. It functions as a reversible, non-competitive, and selective acetyl cholinesterase inhibitor (ChEI), effectively inhibiting brain AChE while having minimal impact on peripheral AChE. Its low hepatotoxicity, strong selectivity for AChE, and long half-life (90 hours) enable convenient once-daily dosing, making it popular among Alzheimer's patients globally.

4. Lecanemab:

Lecanemab is a humanized monoclonal antibody that selectively binds to soluble amyloid-beta protofibrils and facilitates their clearance from the brain. It is one of the first therapies shown to slow the progression of early Alzheimer's disease by targeting an underlying pathological mechanism rather than merely treating symptoms.

Mechanism of Action:

Binds to amyloid-beta protofibrils.Promotes immune-mediated clearance of amyloid plaques.Reduces amyloid burden in the brain.

Indications:Early Alzheimer's disease.Mild cognitive impairment (MCI) due to Alzheimer's disease.Mild Alzheimer's dementia with confirmed amyloid pathology.

Administration:Intravenous infusion every two weeks.

Clinical Benefits:Slows cognitive and functional decline.Reduces amyloid plaque accumulation demonstrated by PET imaging.

Improves disease management when initiated early.

Adverse Effects:

Amyloid-related imaging abnormalities (ARIA), including cerebral edema (ARIA-E) and microhemorrhages (ARIA-H).

Infusion-related reactions.

Headache and dizziness.

5. Donanemab

Donanemab is a monoclonal antibody directed against a modified form of amyloid-beta found in established amyloid plaques. It promotes plaque removal and has

demonstrated significant reduction of amyloid burden in patients with early symptomatic Alzheimer's disease.

Mechanism of Action:

Targets deposited amyloid plaques in the brain.

Activates immune-mediated plaque clearance.

Reduces amyloid accumulation associated with disease progression.

Indications:

Early symptomatic Alzheimer's disease.

Mild cognitive impairment due to Alzheimer's disease.

Mild Alzheimer's dementia with confirmed amyloid pathology.

Administration:Intravenous infusion every four weeks.

Clinical Benefits:Slows clinical progression of Alzheimer's disease.Produces substantial amyloid plaque reduction.May delay worsening of cognitive and functional impairment.Adverse Effects:ARIA (brain edema and microhemorrhages).Infusion-related reactions.Nausea, headache, and confusion.

SUSTAINED-RELEASE TABLETS:

In 2010, the FDA approved sustained-release tablets of 23 mg donepezil, designed to provide a higher daily dose without a sharp peak in concentration. The tablets contain several inactive ingredients and a film coating with specific compounds. These SR tablets were tested against the 10 mg immediate-release (IR) tablets in patients with moderate to severe Alzheimer's disease (AD) who had been stable on 10 mg/day for at least three months. A total of 1500 patients participated, receiving either the 10 mg IR with placebo or the 23 mg SR with its corresponding placebo. The 23 mg SR tablets showed significant cognitive and global functioning improvements, but the long-term safety and efficacy are still being investigated.

ORALLY DISINTEGRATING TABLETS:

Donepezil (Aricept) is available as an orally disintegrating tablet (ODT), approved in the US in 2004. This form is beneficial for patients who struggle to swallow tablets and is administered once daily. The tablets come in dosages of 5 or 10 mg of donepezil hydrochloride, along with other ingredients like carrageenan, mannitol, colloidal silicon dioxide, and polyvinyl alcohol. The 10 mg tablets also include a yellow coloring agent, ferric oxide**.**

TRANSDERMAL DONEPEZIL THERAPY:

The fluctuations in plasma levels after oral donepezil administration are linked to various gastrointestinal issues such as diarrhea, nausea, and abdominal pain. A transdermal drug delivery system may provide significant benefits for patients who struggle to swallow. This method could reduce adverse effects by avoiding first pass effects, minimizing plasma level fluctuations, and simplifying dosing. Additionally, if side effects arise, the drug delivery can be quickly stopped by removing the patch. These improvements in tolerability and compliance could lead to better treatment adherence, making the patch a preferred option for many caregivers in the future.

4. Galantamine: Galantamine is a tertiary alkaloid found in plants such as narcissus and the Caucasian snowdrop, and it is approved for treating Alzheimer's disease (AD). It has good oral bioavailability, with lower protein binding and a shorter time to peak concentration and half-life compared to donepezil.

Metabolized by the liver and mainly excreted by the kidneys, galantamine can interact with drugs that affect the CYP3A4 and CYP2D6 enzymes

It shares similar neuroprotective properties with donepezil by activating certain pathways to reduce neuronal death. Research by Tariot et al. evaluated the efficacy and tolerability of various doses of galantamine in a 5-month clinical trial with participants having mild to moderate AD.

B) Neuro protectors/Neuronal Metabolism treatment:

B1) Estrogen: Women are more prone to Alzheimer's disease (AD) and suffer from greater cognitive deficits. Research shows that postmenopausal women

who take estrogen have a lower risk or delayed onset of AD compared to those who do not. Estrogens are thought to protect against AD through various mechanisms, including activation of cholinergic neurons, providing antioxidant effects, reducing APOE levels, improving neuronal glucose utilization, promoting neuronal survival, and degrading the amyloid precursor protein (APP) into less harmful fragments. However, the use of oestrogen is controversial. Some studies show that they can be effective, alone or with cholinesterase inhibitors, while others show no benefit and an increased risk of deep vein thrombosis. It is therefore essential to weigh the risks, which include breast and endometrial cancer, as well as deep vein thrombosis, against the benefits associated with improved memory and cardiovascular health.

B2) Vitamin E: Vitamin E acts as a potent antioxidant by blocking lipid per oxidation. It has been investigated as a neuroprotective antioxidant, cognitive impairment is not considered its typical therapeutical effect. It is generally well tolerated, with rare side effects including cataracts, increased haemorrhage risk in vitamin K deficient patients, and syncope.

Vitamin E has protective effects on the immune response and heart diseases. In a two-year study involving 341 patients, those taking 2,000 IU of vitamin E and 10 mg of selegiline daily showed better results in delaying deterioration and institutionalization compared to combination therapy.

Animal studies also indicated that it helps delay neuronal degeneration, but it is contraindicated for patients taking warfarin.

B3) Anti-inflammatory Drugs:

Anti-inflammatory Drugs in Alzheimer's Disease

Neuroinflammation plays an important role in the pathogenesis of Alzheimer's disease. Activated microglia and astrocytes release inflammatory mediators that contribute to neuronal damage and disease progression. Epidemiological studies initially suggested that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) might reduce the risk of developing Alzheimer's disease. However, most randomized clinical trials have failed to demonstrate significant clinical benefits in patients with established Alzheimer's disease.Several anti-inflammatory agents, including aspirin, ibuprofen, naproxen, and corticosteroids, have been investigated. While some observational studies reported potential protective effects, clinical trials generally showed limited efficacy in slowing cognitive decline. Therefore, anti-inflammatory drugs are not currently recommended as a primary treatment for Alzheimer's disease. Ongoing research is focused on developing targeted therapies that modulate neuroinflammation without causing systemic adverse effects.

B4) Other Antioxidants: Selegiline enhances cognition and slows cognitive decline due to its antioxidant effects and support for aminergic transmission.

In Alzheimer's disease and other dementias, elevated levels of MAO-A and MAOB result in monoamine deamination, free radical release, and reduced nor epinephrine, do all of which contribute to cognitive deficits. Research indicates that selegiline is as effective as vitamin E in decelerating Alzheimer's progression. Typical daily doses range from 5 to 10 mg, with orthostatic hypotension being the most frequent side effect. Ginkgo biloba is suggested to halt cognitive decline in mild Alzheimer's, but results are varied, and a double-blind study found it ineffective over 24 weeks for dementia patients. Side effects of ginkgo biloba are rare and include rash, nausea, and gastrointestinal issues.

C) Compounds in Research:

Contrary to what turned into believed a few years ago, neurons can regenerate with inside the mind from the mom cells gift in the ventricles and the hippocampus. The signs and symptoms of AD grow to be greater glaring after the lack of 50 % of the neurotrophic elements with inside the Nucleus Basalis [102-105], consequently it is able to be feasible to put off demise or to manage to pay for regeneration as a healing approach.

NGF is the nice known, even though there are numerous different neurotrophic elements.

There is tons revel in in its management in animals, however very negative revel in humans when you consider that toxicity has been located aside from

anoxia, dizziness and lack of weight. Synthetic molecules are being advanced much like NGF and different neuro trephines that are smaller molecules, that could attain the Nucleus Basalis to have its atrophic movements believed a few years ago, neuron scan regenerate with inside the mind from the mom cells gift in the ventricles and the hippocampus. The signs and symptoms of AD grow to be greater glaring after the lack of 50 % of the neurotrophic elements with inside the Nucleus Basalis [102-105], consequently it is able to be feasible to put off demise or to manage to pay for regeneration as a healing approach.

NGF is the nice known, even though there are numerous different neurotrophic elements.

Vaccine:

Vaccines and Immunotherapy in Alzheimer's Disease

Immunotherapy has emerged as a promising strategy for targeting the underlying pathology of Alzheimer's disease. Vaccine approaches aim to stimulate the immune system to remove amyloid-beta plaques and tau protein aggregates from the brain.

Early active immunization studies, such as the AN1792 vaccine, demonstrated plaque reduction but were discontinued because some participants developed meningoencephalitis. These findings led to the development of safer vaccine candidates and passive immunotherapies.

Current research focuses on:Amyloid-beta vaccines: Designed to stimulate antibody production against amyloid-beta deposits.Tau vaccines: Intended to reduce tau aggregation and neurofibrillary tangle formation.Passive immunotherapy: Administration of monoclonal antibodies target amyloid-beta.Recent advances include monoclonal antibodies such as Lecanemab and Donanemab, which have demonstrated the ability to reduce amyloid plaque burden and modestly slow cognitive decline in patients with early Alzheimer's disease. Although these therapies represent significant progress, concerns regarding cost, accessibility, and adverse effects such as amyloid-related imaging abnormalities (ARIA) remain important considerations.

Future research is focused on developing safer and more effective vaccines and immunotherapies capable of preventing or delaying disease progression.

NANOTECHNOLOGY IN ALZHEIMERS DISEASE:-

Nanotechnology ambitions to design, produce, and use nano materials-substances with as a minimum one size falling among 1 and a hundred nm. At this scale, substances often showcase bulk-independent homes which might be taken into consideration exciting to the clinical community, inclusive of super Para magnetism or floor plasmon resonance (Khan et al., 2019). Additionally, due to the fact proteins and nucleic acids are within side the identical length variety as nano materials, specially nano particles, they're well-perfect for interacting with the ones bimolecular and, as a result, with cells. Likewise, a huge floor-quantity ratio related to nano metric length gives blessings in programs of organic recognition, especially in sensing. Therapeutic makes use of of those compounds have gone through sizeable testing

Applications of nano materials have additionally been studied within side the subject of precision medication for the beyond few years

Because of the drug's incapability to bypass the BBB, the most effective remedy for AD presently available in the marketplace specializes in symptomatic relief. Due to its many blessings, nanotechnology-primarily based totally remedy might also additionally triumph over this restriction (Ling et al., 2021).

The FDA has given its blessing for the usage of commercially to be had medicines to a huge form of nano carriers that variety in length from very tiny to very huge. These nano carriers are used within side the remedy of neurological situations together with AD and mind cancer (Association, 2013; Patra et al., 2018). Nan medicines are made out of diverse nanocarriers containing distinct drugs. The ability for nanomaterials to manipulate the pathologies of AD is receiving sizeable investigation. The remedy of AD presently makes use of nanostructure-primarily based totally shipping systems that allows you to be mentioned within side the following sections. Most of them are categorized as both metal NPs, natural nanostructures.

Liposome's: The phospholipids belayed of leptosomes is the maximum possibly approach to the hassle of transporting medicinal drugs throughout the BBB. However, it's far forbidden to move the BBB. Numerous floor adjustments were carried out to reinforce liposomal provider shipping throughout the BBB numerous proteins, peptides, antibodies, and different ligand receptors can be gift at the floor of the BBB. Transcytosis may be facilitated with the aid of using making use of floor-lively ligands, which includes the ones discovered in those compounds. Transcytosis and cationic liposome absorption into the BBB take region simultaneously. Liposomes are usually covered with vitamins like glucose to make it simpler for them to transport thru the body. Once the liposomes have entered the mind, the passive diffusion mechanism can proceed. This procedure is prompted with the aid of using the mind's passive efflux (Noble et al., 2014).

Through related receptors on BBB cells, curcumin loaded liposome can considerably enhance drug shipping to the CNS (Lajme and Shusta, 2015), The liposome provider device that has been changed with a floor with mannose ligand and cell-penetrating peptides (CPPs) has been hired to supply lipoprotein E (ApoE2) with inside the mind injured with the aid of using AD.

Polymeric biodegradable nano particles:

Recent studies have proven that polymeric biodegradable nano particles functionalized with antibodies and polyethylene glycol can efficiently deal with reminiscence deficits and decrease degrees of soluble amyloidal-beta peptides in transgenic Alzheimer's sickness mice. Specifically, meantime-loaded nanoparticles have verified enormous discounts in amyloidal plaques and irritation related to Alzheimer's while examined on mind tissue. Additionally, polymeric nanoparticles focused on the mind have the ability to lower the dimensions of amyloidal plaques and mitigate neuronal deficiencies. Huperzine A, an acetyl cholinesterase inhibitor, is added the usage of changed mucoadhesive poly lactic-co-glycolic acid nanoparticles, displaying promising sustained-launch and focused on talents in addressing Alzheimer's pathology. Thymoquinone, a bioactive compound from Nigella sativa, has proven ability as an Alzheimer's treatment, despite the fact that greater studies are wanted to verify its effectiveness in neurological conditions. Nanoparticles containing thymoquinone, lined with polysorbate 80, may also provide a dependable approach for transporting pills throughout the blood-mind barrier. Polymeric biodegradable substances like PLGA are applied however may be liable to fast removal with the aid of using the body. Coating nanoparticles with surfactants can guard them from this process, bearing in mind sustained drug launch via the breakdown of PLGA into non-poisonous metabolites. The autocatalytic degradation of the polymer performs a enormous position within side the drug launch mechanism. The aim is to gain a aggregate of excessive porosity and powerful drug diffusion.

Nanogels: nanogels are proven to be extra powerful for pharmaceutical transport than unfastened tablets because of improved cell absorption, decreased toxicity, better drug loading, and managed launch at focused sites. They can bind diverse energetic compounds and were used to cope with problems associated with extraordinary pathologies, consisting of Alzheimer's disease (AD). Recent researches recommend the usage of nanogels to supply deferoxamine, using chitosan and tripolyphosphate, as an powerful AD treatment. Additionally, changed polysaccharide pullulan backbones act as synthetic chaperones to relieve AD pathology through stopping Ap amyloidal formation. Preclinical exams on mice imply that the usage of nanogels can beautify the nose-to-mind transport of insulin, a candidate drug for AD. Nanogels have several benefits while blended with polysaccharides, consisting of non-toxicity, stability, hydrophilicity, and biodegradability.

Research on Micelle Formulations Utilized in Alzheimer's Disease (AD) Treatment: Double transgenic AD mice had been given a micelle system of coenzyme Q10, which advanced long-time period reminiscences and decreased Aß plaque levels. The aggregate of Tween-eighty with curcumin led to stronger effectiveness for treating AD symptoms. Research on PEG ceramide nanomicelles discovered their capability in disrupting tau proteins and selling autophagy in cells. Additionally, curcumin-loaded polymeric nanomicelles drastically inhibited the amyloidogenesis manner in AD mice. Lastly, an synthetic chaperone crafted from mixed-shell polymeric micelles turned into proven to assist hold

amyloidal homeostasis and suppress AD development thru diverse mechanisms

Antibody-primarily Based Totally Nanoparticles (NPs):

provide a promising opportunity to conventional immunotherapy for Alzheimer's Disease (AD) via way of means of concentrated on and breaking down protein aggregates in mind cells, which could assist keep away from headaches like meningo encephalitis. Researchers use secondary ion mass spectrometry with steel oxide-covered antibodies to visualise AD-associated proteins within side the mind. Additionally, nanoparticles covered with chitosan and amyloidal beta (Aβ) fragments had been evolved to in particular goal amyloidal-wealthy cells in AD. Incorporating evaluation dealers like fluorescein isothiocyanate and Alexa Fluor complements the absorption of those NPs throughout the blood-mind barrier. Moreover, remedies are being explored the use of receptor activators which includes XD4 mixed with unique Aβ oligomer-concentrated on strategies.

GENE Therapy:

Gene remedy for Alzheimer's disorder (AD) has lately received huge attention. This technique entails introducing a gene that produces an enzyme or boom issue to make certain long-time period healing expression of decided on genes. The purpose is to alter or spark off unique proteins concerned in neurodegenerative disorder methods to obtain neuro protection and neuro restoration simultaneously. Gene remedy is complex, requiring cautious attention of different factors like timing, location, gene regulation, and shipping methods. The desire among integrating or non-integrating gene transfer, and administering remedy in vivo or ex vivo, relies upon at the goal disorder. Techniques used encompass gene enhancement, inhibition, and genome editing, in addition to the usage of small antisense oligo nucleotides, which intrude with messenger RNA to save you gene translation. IONIS MAPTR, an antisense oligo nucleotide focused on tau synthesis with inside the brain, is present process medical research as a capacity approach to lessen tau production.

Clinical Significance:

Alzheimer's disease is a major public health challenge that significantly affects patients, caregivers, and healthcare systems worldwide. Early recognition of cognitive decline and the use of advanced diagnostic tools, including neuroimaging and biomarker-based testing, can facilitate timely intervention and improved patient management. Understanding modifiable risk factors such as hypertension, diabetes mellitus, obesity, and dyslipidaemia provides opportunities for preventive strategies. Current pharmacological therapies offer symptomatic benefits, while emerging disease-modifying treatments, including monoclonal antibodies such as Lecanemab and Donanemab, demonstrate potential to slow disease progression in selected patients. Furthermore, advances in nanotechnology, gene therapy, and personalized medicine may improve drug delivery and therapeutic outcomes in the future. Therefore, continued research, early diagnosis, multidisciplinary care, and caregiver support are essential for reducing the clinical and societal burden of Alzheimer's disease.

Critical Analysis

Alzheimer's disease remains one of the most challenging neurodegenerative disorders due to its complex and multifactorial pathogenesis. Although significant advances have been made in understanding the disease mechanisms, the exact cause of Alzheimer's disease is still not fully understood. Current evidence suggests that amyloid-beta deposition, tau protein hyperphosphorylation, neuroinflammation, oxidative stress, genetic susceptibility, and environmental factors all contribute to disease progression.

Current pharmacological therapies, including cholinesterase inhibitors and NMDA receptor antagonists, provide symptomatic relief and modest improvements in cognitive function; however, they do not halt or reverse disease progression. The effectiveness of these treatments varies among individuals, highlighting the need for personalized therapeutic approaches.

Recent developments in disease-modifying therapies, immunotherapy, gene therapy, and nanotechnology-based drug delivery systems have shown promising

results. However, many of these approaches remain in preclinical or early clinical stages, and their long-term safety, efficacy, and accessibility require further investigation. Additionally, challenges such as blood-brain barrier penetration, treatment-related adverse effects, and high treatment costs continue to limit clinical application.

Although advances in neuroimaging and biomarker research have improved early diagnosis, definitive diagnosis remains challenging, particularly during the preclinical stages of the disease. Further research is needed to identify reliable biomarkers that can facilitate early detection and therapeutic intervention.

Overall, current evidence highlights the need for continued research focusing on disease-modifying therapies, early diagnostic tools, and individualized treatment strategies to improve clinical outcomes and reduce the global burden of Alzheimer's disease.

CONCLUSION

Alzheimer's disease is a progressive neurodegenerative disorder and the leading cause of dementia worldwide, posing significant challenges to patients, caregivers, and healthcare systems. The disease is characterized by complex pathological mechanisms involving amyloid-β plaque accumulation, tau protein hyperphosphorylation, neuroinflammation, oxidative stress, and neuronal loss, resulting in progressive cognitive and functional decline.Advances in diagnostic technologies, including neuroimaging techniques and biomarker-based approaches such as cerebrospinal fluid and blood biomarkers, have improved the accuracy of early diagnosis and disease monitoring. Current pharmacological therapies, including cholinesterase inhibitors and NMDA receptor antagonists, provide symptomatic benefits but are unable to stop disease progression. Recently approved disease-modifying therapies targeting amyloid pathology, along with emerging approaches such as immunotherapy, gene therapy, and nanotechnology-based drug delivery systems, offer promising directions for future treatment.Despite substantial progress in understanding the disease, significant challenges remain regarding early detection, treatment accessibility, long-term therapeutic efficacy, and prevention strategies. Continued research focused on biomarker discovery, personalized medicine, and novel therapeutic interventions is essential to improve patient outcomes and reduce the global burden of Alzheimer's disease. A multidisciplinary approach integrating early diagnosis, effective treatment, caregiver support, and public health awareness remains crucial for the comprehensive management of Alzheimer's disease.

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