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EMERGING PHARMACOLOGICAL AND NON-PHARMACOLOGICAL THERAPIES IN THE MANAGEMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia worldwide and is characterized by progressive memory loss, cognitive decline, and functional impairment. The disease pathology involves amyloid-β plaque accumulation, tau hyperphosphorylation forming neurofibrillary tangles, neuroinflammation, oxidative stress, and neuronal degeneration. Genetic factors such as the APOE4 allele increase susceptibility to AD.Current treatments, including cholinesterase inhibitors and NMDA receptor antagonists, provide only symptomatic relief without altering disease progression. Recent advances in disease-modifying therapies, particularly monoclonal antibodies targeting amyloid-β, have shown potential in reducing amyloid burden and slowing cognitive decline in early stages, though safety concerns and long-term efficacy remain under evaluation.In addition to pharmacological approaches, lifestyle interventions such as healthy dietary patterns, omega-3 supplementation, cognitive training, regular exercise, and adequate sleep may support brain health and delay disease progression. Overall, a comprehensive and personalized strategy combining early diagnosis, targeted treatment, and preventive measures is essential to reduce the burden of Alzheimer's disease and improve patient outcomes.

KEYWORDS: Alzheimer's disease; Emerging therapies; Amyloid-β; Tau pathology; Neuroinflammation; Disease-modifying therapy.

INTRODUCTION

Alzheimer's disease (AD) was first described over a century ago and is a progressive neurodegenerative disorder that accounts for 60–80% of dementia cases, making it the most common cause of cognitive decline in older adults. Although the risk of dementia increases

with age, it is not a normal part of ageing; rather, it is a pathological condition that significantly impairs memory, language, perception, and thinking, ultimately affecting daily functioning and independence. AD is a major contributor to morbidity and mortality worldwide and adds substantially to the global burden of non-communicable diseases. It is increasingly recognized as a serious public health concern due to its rising prevalence and profound impact on individuals, families, and communities, while often remaining underdiagnosed and underreported. The economic burden of dementia is considerable, with escalating healthcare costs, reduced productivity, and significant out-of-pocket expenses for care, making Alzheimer's disease one of the most important contemporary global health challenges.[1]

Brief overview of Alzheimer's disease (AD)

Incidence and prevalence

Alzheimer's disease (AD) has a substantial global impact and is increasingly prevalent among the ageing population. Approximately 47.5 million people worldwide are affected by dementia, with nearly 62% living in low- and middle-income countries where access to healthcare and social support is limited. The number of dementia cases is expected to nearly double every 20 years as the global population ages. In the United States, about 5.4 million individuals were living with AD in 2016, including both early-onset and late-onset cases. In Africa, over 4 million people are affected, and this number is projected to rise significantly by 2050 due to increasing life expectancy. Although there is no strong gender-specific difference in incidence, dementia is more common in women, largely because of their longer lifespan. In South Africa, epidemiological data are limited, but estimates suggest that over 186,000 individuals were living with dementia in 2015, with numbers expected to increase steadily. Additionally, neurodegenerative conditions such as HIV-associated dementia further contribute to the growing burden of dementia in the region. [1]

Pathophysiology

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the destruction of nerve cells and synaptic connections in the cerebral cortex. Its pathological hallmarks include extracellular deposition of amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. This progressive neuronal damage leads to irreversible decline in memory and cognitive function, eventually resulting in complete dependence on caregivers.Epidemiologically, AD is the leading cause of

dementia and has a complex, multifactorial pathophysiology. Although most early-onset cases do not follow a clear inheritance pattern, rare autosomal dominant forms are caused by mutations in the APP, PSEN1, and PSEN2 genes, accounting for less than 1% of cases. Increased production or reduced clearance of amyloid-β is central to disease development. Late-onset AD, the most common form, has a strong genetic predisposition with heritability estimated at 60–80%. The APOE gene is a major genetic risk factor, and disease expression results from interactions between genetic, environmental, and vascular risk factors such as hypertension and brain injury.[1]

Current global burden (epidemiology, economic impact)

Alzheimer's disease and related dementias (ADRDs) represent a major global health burden, significantly impairing quality of life through progressive memory loss, cognitive decline, reduced mobility, language impairment, and ultimately death. In 2019, ADRDs accounted for 33.1 million disability-adjusted life years (DALYs) worldwide and are projected to rise sharply by 2050 due to population ageing and increasing incidence rates. The economic impact is substantial, as care requires long-term medical treatment, hospice services, and both formal and informal caregiving, with global direct costs expected to reach $2 trillion by 2030 and total costs potentially rising to $9 trillion by 2050. These figures often underestimate the full burden, as intangible losses such as pain, reduced dignity, and productivity decline are difficult to measure. To estimate the broader economic impact, the Value of Statistical Life (VSL) approach is used to assess society's willingness to pay to reduce mortality risk, providing a comprehensive framework for evaluating the present and future financial burden of ADRDs worldwide. [2]

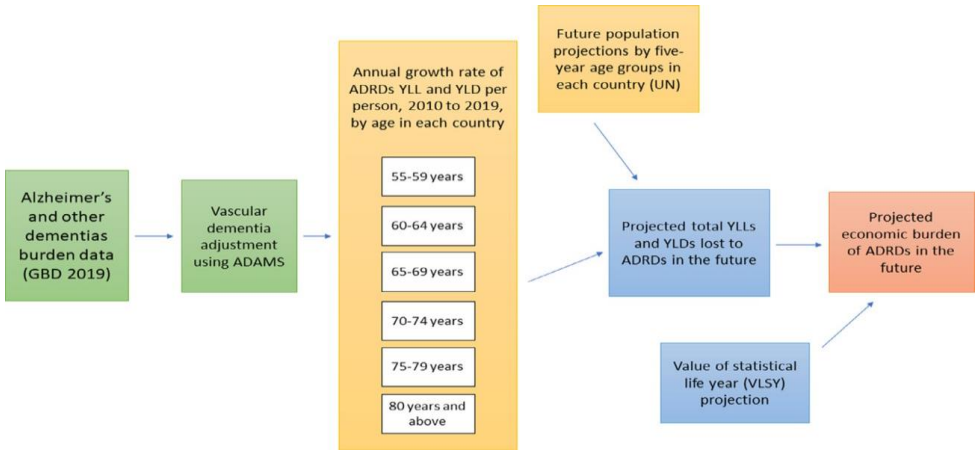

Fig- 1: The future VSL-based economic burden of ADRDs (Model 1) was projected by

estimating age- and country-specific DALYs using past growth trends, applying population forecasts, calculating country-specific VSL values adjusted by GNI per capita (PPP, 2019 US$) with a minimum threshold of 20 times GNI per capita, and classifying countries according to the World Bank's 2020 income group criteria.[2]

Limitations of Existing Therapies (Donepezil, Rivastigmine, Memantine)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β plaque deposition, tau hyperphosphorylation, oxidative stress, and neuronal loss. Despite its high global prevalence and increasing burden, there is currently no disease-modifying therapy available. Existing medications—including donepezil and rivastigmine (acetylcholinesterase inhibitors) and memantine (an NMDA receptor antagonist)—provide only symptomatic relief and do not halt or reverse disease progression. Acetylcholinesterase inhibitors temporarily improve cognition by increasing acetylcholine levels but are associated with cholinergic side effects such as nausea, vomiting, diarrhea, and dizziness, which may limit adherence. Memantine, used in moderate-to-severe AD, reduces excitotoxicity by modulating NMDA receptors and offers modest cognitive benefits; however, clinical improvements are generally small and not curative. Although these drugs may slow symptom progression and improve daily functioning to some extent, their overall clinical impact remains limited, highlighting the urgent need for effective disease-modifying therapies targeting the underlying pathology of AD. [3]

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factor, and disease expression results from interactions between genetic, environmental, and vascular risk factors such as hypertension and brain injury.[4]

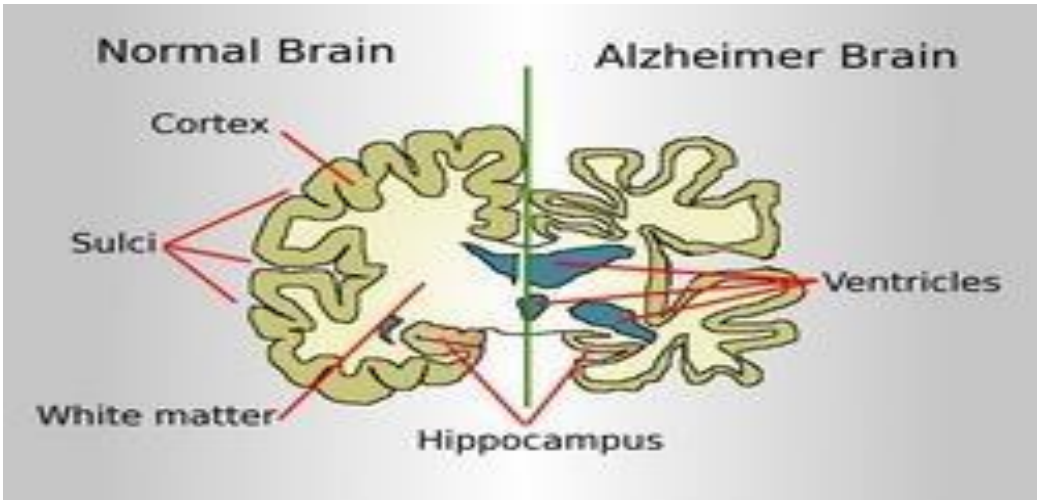

Fig- 2: Diagram of a normal brain compared to the brain of a person with Alzheimer's

Pathophysiology & Targets for New Therapies

Amyloid-β hypothesis

Amyloid-β (Aβ) is the main component of neuritic plaques in Alzheimer's disease (AD) and plays a central role in its pathogenesis. According to the amyloid cascade hypothesis, abnormal production and aggregation of Aβ—generated through sequential cleavage of amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase—lead to the formation of soluble oligomers and insoluble fibrils. Current evidence suggests that soluble Aβ oligomers are particularly neurotoxic and contribute to synaptic dysfunction. Aβ aggregates interact with tau protein and promote oxidative stress, neuroinflammation, mitochondrial dysfunction, and ultimately neuronal death.Although Aβ has been the primary target for AD drug development, many anti-Aβ clinical trials have failed, raising questions about the amyloid hypothesis; however, recent advances have renewed interest in Aβ-targeted therapies. Currently approved drugs—cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine—provide only symptomatic relief and do not modify disease progression, highlighting the urgent need for effective disease-modifying treatments targeting Aβ pathology [4]

Pathology of tau proteins

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder that significantly threatens the health and well-being of older adults worldwide. According to the *World*

Alzheimer Report 2018, approximately 50 million people globally are living with dementia, a number projected to rise to 152 million by 2050, with AD accounting for 60–70% of cases. Tau protein, a microtubule-associated protein primarily located in neuronal axons, plays a crucial role in maintaining microtubule stability, promoting assembly, and regulating axonal transport. In AD, tau undergoes abnormal post-translational modifications (PTMs), including hyperphosphorylation, glycosylation, ubiquitination, acetylation, and methylation. These modifications disrupt tau's normal structure and function, promoting neurofibrillary tangle formation, impairing neuronal signaling, and triggering neuroinflammation, ultimately contributing to disease progression. Understanding the mechanisms of tau toxicity—including its role in mitochondrial dysfunction, synaptic impairment, and glia-mediated inflammation—is essential for improving early diagnosis and identifying potential therapeutic targets for AD.[5]

Neuroinflammation &microglial activation

Neuroinflammation is an immune response in the central nervous system characterized by microglial activation and the release of pro-inflammatory cytokines, and it plays a key role in Alzheimer's disease (AD). In AD, microglia become activated in response to amyloid-β (Aβ) accumulation, changing from a resting, ramified form to an amoeboid, reactive state. While microglia normally help clear Aβ and maintain brain homeostasis, impaired phagocytosis and excessive production of cytokines such as IL-1β and TNF-α contribute to neuronal damage and disease progression. Microglia exhibit diverse phenotypes, including pro-inflammatory (M1), anti-inflammatory (M2), and disease-associated microglia (DAM), each with distinct gene expression patterns and functions. Differences between human and mouse microglial responses, along with aging-related changes, further influence AD pathology, making age the strongest risk factor for disease development.[6]

Oxidative stress and mitochondrial malfunction

Lipid peroxidation is a prominent feature of Alzheimer's disease (AD) and results from free radical attacks on brain membrane phospholipids rich in polyunsaturated fatty acids. The brain is particularly susceptible to oxidative stress due to its high oxygen consumption, elevated energy demand, and intense mitochondrial activity. Neural tissue also contains high levels of lipids and iron, with iron accumulating in amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). Ferrous ions (Fe^{2+}) catalyze the Fenton reaction, in which hydrogen peroxide (H_2O_2) is converted into highly reactive hydroxyl radicals (•OH). These

hydroxyl radicals are potent inducers of oxidative stress, leading to cellular damage and contributing to AD pathology. [7]

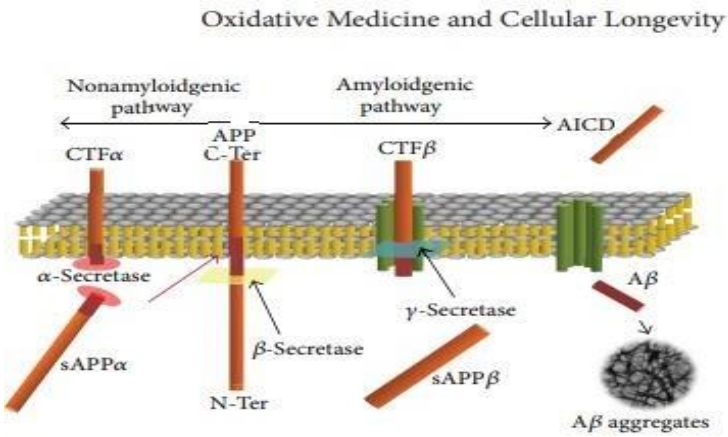

Fig:3- Oxidative Medicine and Cellular Longevity.[7]

Neurotransmitter imbalance

Glutamate, the primary excitatory neurotransmitter in the central nervous system, plays a crucial role in learning and memory through its metabotropic (mGluRs) and ionotropic receptors (NMDA, AMPA, and kainate receptors). In Alzheimer's disease (AD), abnormal interaction between amyloid-β (Aβ) and NMDA receptors promotes excitotoxicity, synaptic dysfunction, and neuronal death, while impaired astrocytic glutamate clearance and microglial activation further elevate extracellular glutamate levels, amplifying inflammation and tau hyperphosphorylation. Mitochondrial dysfunction also contributes to AD pathology by increasing reactive oxygen species (ROS) production, oxidative stress, and energy failure, particularly in memory-related brain regions such as the hippocampus and cortex. Monoamine neurotransmitters are similarly disrupted: dopamine levels and D1/D2 receptor expression are reduced in AD, contributing to cognitive decline, motivational deficits, and impaired synaptic plasticity, with monoamine oxidase activity further increasing oxidative stress. Degeneration of dopaminergic neurons in the ventral tegmental area and substantia nigra exacerbates memory dysfunction. Norepinephrine, produced mainly in the locus coeruleus, is also significantly affected in AD, as early loss of noradrenergic neurons worsens cognitive deficits. Adrenergic receptors (α and β subtypes) regulate memory, synaptic plasticity, and amyloid precursor protein processing, and their dysfunction contributes to disease progression. Altogether, disturbances in glutamatergic, dopaminergic, and noradrenergic systems, combined with mitochondrial impairment and oxidative stress, play a central role in the neurodegenerative processes underlying AD.[8]

Genetic factors (APOE4, etc.)

APOE plays a central role in Alzheimer's disease (AD), with its three isoforms—APOE2, APOE3, and APOE4—differentially influencing disease risk. APOE4 is the strongest genetic risk factor for late-onset AD, associated with earlier cognitive decline, increased amyloid-β (Aβ) aggregation and deposition, impaired Aβ clearance, altered lipid metabolism, inflammation, and reduced synaptic plasticity, whereas APOE2 appears relatively protective and is linked to longevity and reduced neurodegeneration. APOE4 is also implicated in other neurological disorders such as cerebral amyloid angiopathy, dementia with Lewy bodies, and vascular dementia, though paradoxically it may be protective in age-related macular degeneration due to its effects on angiogenesis. Mechanistically, apoE4 contributes to AD through Aβ metabolism, defective lipidation, impaired neuronal repair, and possibly through nuclear translocation where it may act as a transcription factor regulating genes involved in growth and autophagy. These findings suggest that targeting apoE4-specific pathways, enhancing apoE2-like effects, or modifying apoE lipidation and nuclear activity could represent potential therapeutic strategies for AD.[9]

Emerging Therapies

Alzheimer's disease treatment is rapidly changing as disease-modifying medications become available. Recent research focuses on the underlying pathogenic mechanisms, such as amyloid-beta buildup, tau protein aggregation, and neuroinflammation. Novel techniques such as monoclonal antibodies, gene therapy, and stem cell therapy have shown promising outcomes. These emerging treatments aim not only to treat symptoms but also to slow the disease's progression.[10]

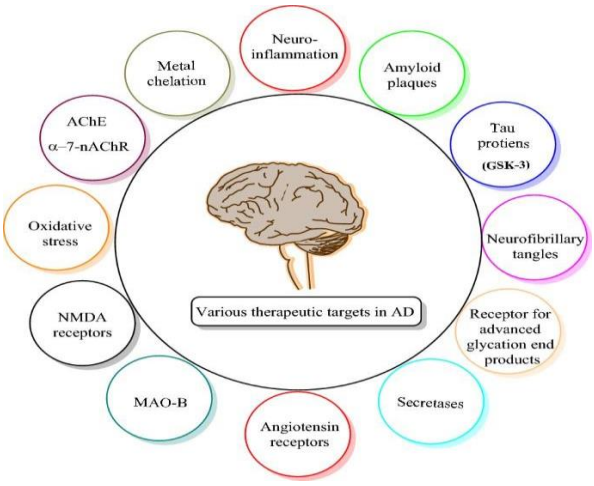

Fig-4:Various Therapeutic Targets In AD.

A.Anti-Amyloid Therapies

In a healthy brain, α-secretase and γ-secretase enzymes break down amyloid precursor protein (APP) into harmless soluble protein fragments that the cell can easily degrade. Alzheimer's disease disrupts the normal process by causing β-secretase and γ-secretase to produce amyloid-beta (Aβ) peptides from APP. These peptides are sticky and tend to clump, resulting in amyloid-beta plaques (ABPs) within brain tissue.

The buildup of these plaques disrupts normal neural communication by preventing neurotransmitter passage across synapses, resulting in poor memory and cognitive function. Furthermore, the immune system responds to these plaques, causing local inflammation and additional harm to the surrounding neurons. The accumulation of amyloid plaques on the walls of cerebral blood arteries, known as cerebral amyloid angiopathy, can weaken them and cause bleeding or rupture. Collectively, these pathogenic alterations contribute to neuronal death, brain tissue loss, and the gradual decline observed in Alzheimer's disease.[11]

BACE1 Enzyme and Its Inhibitors in Alzheimer’s Therapy

Alzheimer's disease research focuses on developing BACE1 inhibitors, which target the β-secretase enzyme that cleaves amyloid precursor protein (APP). This cleavage causes the synthesis of amyloid-beta (Aβ) peptides, resulting in amyloid plaque buildup. Experiments with transgenic mice models that overexpress human APP with familial Alzheimer's mutations and lack the BACE1 gene showed that deleting BACE1 successfully reduces amyloid-beta plaque development. These data demonstrate that BACE1 is directly involved in amyloid plaque formation. A rare human mutation that reduces BACE1 activity reduces Aβ formation by nearly 40%, significantly lowering the risk of developing Alzheimer's disease.Limiting BACE1-containing vesicles at neural synapses has also been proven to enhance synaptic function and communication. Furthermore, gene deletion of BACE1 in animal models protects memory impairments and neuronal degeneration, indicating therapeutical potential. Inhibiting γ-secretase is not a realistic method as it performs critical physiological activities beyond amyloid processing. Current data strongly supports the continued development and testing of BACE1 inhibitors as possible treatments for reducing amyloid- beta plaque (ABP) production in the brain. BACE1 has a variety of physiological effects, including cleaving and activating Neuregulin-1, which is required for myelination and normal peripheral nervous system development. Because of these crucial roles, total inhibition of BACE1 may result in unexpected consequences, stressing the importance of selective targeting. BACE1 activity is also regulated by multiple post-translational

mechanisms, including 5′UTR control, microRNA interaction, and non-coding RNA regulation. Modern research is exploring the use of monoclonal antibodies and small-molecule inhibitors that can pass the blood-brain barrier to modify BACE1 activity efficiently. However, attaining high potency and specificity remains a significant issue. The long-running controversy over the amyloid hypothesis continues, with some researchers seeing amyloid accumulation as a primary driver of Alzheimer's pathogenesis, while others believe it is only a side effect.Recent evidence suggests that Aβ oligomers are the true hazardous species. With amyloid- clearing medications now in clinical usage, the focus has turned from laboratory research to real-world clinical evaluation.[11]

Lecanemab (approved 2023, Japan/US)

Lecanemab (Leqembi) is a humanized monoclonal antibody used to treat Alzheimer's disease by removing amyloid-beta plaques in the brain. When given intravenously every two weeks, it has shown limited benefit in delaying cognitive decline. In a Phase III clinical trial with 1,795 patients aged 50 to 90 years, lecanemab reduced clinical decline by about 27% over 18 months compared to placebo. It is recommended for people with mild cognitive impairment or mild dementia, but not for those in moderate or severe stages. However, its use is linked to amyloid- related imaging abnormalities (ARIA), which can cause brain swelling or hemorrhage, especially in people who inherit the ApoE4 genetic variation. The United States FDA granted accelerated approval in January 2023 and full approval in July 2023. The European Medicines Agency (EMA) refused permission in July 2024, citing safety and efficacy concerns. Despite these concerns, lecanemab remains a promising disease-modifying medication that may halt the progression of Alzheimer's disease.[12,3]

Mechanism of action of lecanemab: Lecanemab is a humanized IgG1 monoclonal antibody produced from mAb158 that preferentially targets soluble amyloid-beta (Aβ) protofibrils. These toxic aggregates affect memory-related neuronal function. It significantly decreases pathogenic Aβ levels, stops plaque deposition, and removes protofibrils from brain tissue and cerebrospinal fluid. Compared to aducanumab, lecanemab has up to 100-fold higher affinity for tiny protofibrils and much reduced binding to monomers, making it a powerful second-generation anti-amyloid antibody. Although various clinical trials have shown potential efficacy and safety, more systematic testing is required to validate its long-term advantages in Alzheimer's disease.[12]

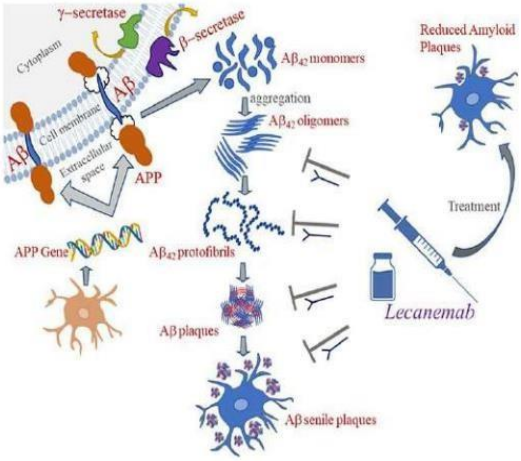

Fig-5:Anti-Tau Therapies.

Tau aggregation inhibitors

Tau aggregation inhibitors are novel therapeutic medicines that prevent aberrant clumping of tau proteins inside neurons, a critical mechanism in Alzheimer's disease and other tauopathies. Tau stabilizes microtubules in healthy neurons, but when hyperphosphorylated, it creates toxic clumps known as neurofibrillary tangles, which impede neuronal transport and function. These inhibitors are designed to prevent tau-tau interactions, dissolve existing clumps, and restore normal neuronal activity. Compounds such as methylene blue derivatives and TRx0237 (LMTX) are now being researched for their ability to delay disease progression and improve cognitive function in Alzheimer's sufferers.Tau aggregation inhibitors (TAIs), specifically methylene blue (MB) and its derivative methylthioninium chloride (MTC), are the most advanced treatment possibilities for Alzheimer's disease. These compounds have non-covalent interactions with tau proteins, preventing tau-tau binding and fibril formation. MTC, a tricyclic phenothiazine derivative, can pass through the blood-brain barrier and prevent tau aggregation at micromolar levels. MTC has been proven in experimental investigations on tau-transgenic mice to lower soluble tau levels and enhance behavioral outcomes, although the results are inconsistent. Beyond tau inhibition, MTC has a variety of biochemical effects, including monoamine oxidase inhibition, increased mitochondrial oxidation, and antioxidant activity, though their clinical relevance is unknown. Despite inconsistent findings, MTC and similar compounds remain important options in the ongoing hunt for disease-modifying Alzheimer's treatments. A double-blind, placebo-controlled research of 321 mild-to-moderate Alzheimer's disease patients used methylthioninium chloride (MTC) at doses of 69 mg, 138 mg, and 228 mg/day for 24 weeks. Compared to placebo, the 138 mg/day dose significantly improved ADAS-Cog scores in moderately

impaired patients. However, mild cases showed no significant advantage. Side effects of the medication included gastrointestinal and urinary issues, as well as dose-dependent reductions in red blood cell count and hemoglobin. MTC (Rember™) for Alzheimer's treatment was discontinued due to formulation and safety concerns, despite promising cognitive outcomes.[4] TRx0237 (LMTX™) is a stabilized reduced version of methylthioninium chloride (MTC). TauRx Therapeutics is developing a tau aggregation inhibitor (TAI) to treat Alzheimer's disease. Preclinical research demonstrated that TRx0237 efficiently disrupted tau aggregates and enhanced learning and behavior in mouse models at lower dosages than MTC. Several Phase III clinical trials are being conducted to assess its efficacy in mild-to- moderate Alzheimer's disease and frontotemporal dementia, employing cognitive and clinical scales such as ADAS-Cog and ADCS-CGIC. TRx0237 reportedly has better pharmacokinetics and tolerability than MTC, but human data on safety, CSF levels, and efficacy are limited. The ultimate results of these trials are likely to shed light on TAIs' clinical potential for treating neurodegenerative tauopathies.[13]

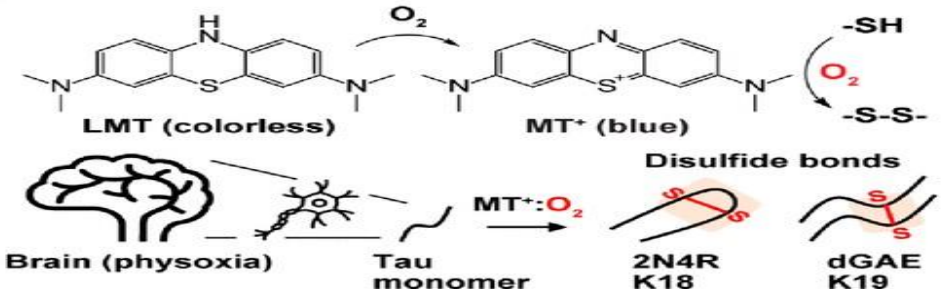

Fig-:6 (LMT-Leucomrthylthioninium , MT-Methylthioninium)

Anti-tau monoclonal antibodies

Anti-tau monoclonal antibodies are a type of medicine that targets and neutralizes aberrant tau proteins that collect and create neurofibrillary tangles in the brains of Alzheimer's patients. These antibodies are designed to block the spread of harmful tau aggregates across neurons, thereby delaying neurodegeneration and cognitive decline. By binding to extracellular tau, they help reduce tau pathology and preserve neuronal function, indicating a potential but still experimental approach in Alzheimer's therapy.

Gosuranemab: A humanized IgG4 monoclonal antibody called gosuranemab (BIIB092) targets the extracellular N-terminal region of tau (residues 15–22). Preclinical research revealed that it could bind firmly to several tau types and reduce Aβ generation and tau-related toxicity. At first, it showed promise in treating tauopathies such as **Alzheimer's

disease (AD) and progressive supranuclear palsy (PSP). Later Phase 2 studies (PASSPORT, TANGO) did not demonstrate cognitive or functional improvement in AD and PSP patients, despite early trials showing high safety and tolerability. The development of gosuranemab for AD and other tauopathies was discontinued due to lack of efficacy. **Semorinemab :** Semorinemab (RO705705) is a humanized IgG4 antibody that binds to all six human tau isoforms and targets extracellular tau. It protects neurons from tau oligomer-induced neurotoxicity and demonstrated encouraging preclinical results, lowering tau accumulation in cell and animal models. Additional trials in early Alzheimer's disease followed the confirmation of its safety and dose-dependent target engagement in a phase 1 trial. The challenge of developing tau-based therapies is highlighted by the fact that differences in tau species, epitope targeting, and tau- spreading mechanisms in humans have made it difficult to translate preclinical success into clinical benefit.[14]

Neuroprotective & Anti-Inflammatory Agents

Drugs that target microglial activation are currently being developed for the treatment of neurodegenerative illnesses such as Alzheimer's and Parkinson's, although none have yet been approved for clinical use. Several pharmaceutical companies are developing medicines such as AL002 (Alector), DNL919 (Denali), and VGL101 (Vigil Neuroscience) that target the TREM2 receptor to boost microglial activation and promote phagocytosis of amyloid-beta (Aβ), decreasing Alzheimer's progression. AL014 targets MS4A4A, while Roche's Gantenerumab binds aggregated Aβ and activates microglia to remove plaques, obtaining FDA breakthrough therapy classification. Small-molecule inhibitors such as DNL201 and DNL151 decrease LRRK2 activity in Parkinson's, with DNL151 demonstrating improved pharmacokinetics and progressing to Phase III studies. Despite breakthroughs, some anti-tau monoclonal antibodies, including ABBV-8E12 and Gosuranemab, have failed clinical trials, highlighting the complexities of tau- targeted therapy. Microglia-targeting drugs are classified into five types: those that suppress overactive microglia to reduce neuroinflammation; agents that shift microglia from pro-inflammatory to anti-inflammatory phenotypes; drugs that improve phagocytic clearance of toxic proteins; therapies that target specific microglial subtypes identified through single-cell sequencing; and strategies that involve microglial depletion and regeneration. Although existing evidence is scant and numerous ideas need to be validated, microglia remain a highly promising therapeutic target due to their critical involvement in neuroinflammation, amyloid clearance, and neuronal survival, making them important to future neuroprotective medication development.[15]

novel anti-inflammatory pathways

Anti-inflammatory treatments in AD : Several research have looked into the potential function of nonsteroidal anti- inflammatory drugs (NSAIDs) in delaying or lowering the risk of Alzheimer's disease. Retrospective studies analyzing historical patient data have revealed that the use of NSAIDs may provide therapeutic benefits by delaying the onset of Alzheimer's disease. This is most likely owing to its anti-inflammatory characteristics, which are thought to contribute to Alzheimer's disease progression. Furthermore, a one-year follow-up study discovered that AD patients who used NSAIDs had a slower deterioration in cognitive abilities such as verbal fluency, spatial recognition, and orientation than those who did not take them. The Rotterdam Study looked into this further and discovered that people who used NSAIDs for at least six months and were under the age of 85 had a lower risk of acquiring Alzheimer's disease. However, when looking at the entire population, there was no statistically significant link between NSAID use and a lower risk of Alzheimer's disease. Thus, while some findings point to potential benefits of NSAIDs, the overall evidence is ambiguous.The first generation of anti-inflammatory drugs for Alzheimer’s disease (AD) mainly includes nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit both COX-1 and COX-2 enzymes, thereby reducing prostaglandin-mediated neuroinflammation implicated in AD progression, particularly as COX-2 is overexpressed in affected regions like the hippocampus; clinical trials with drugs such as indomethacin showed slower cognitive decline in mild to moderate AD, and NSAIDs may exert neuroprotective effects by decreasing prostaglandin production, limiting glutamate-mediated excitotoxicity, and reducing microglial activation, although their use is limited by gastrointestinal adverse effects due to COX-1 inhibition, sometimes managed with protective agents like misoprostol. The second generation comprises selective COX-2 inhibitors developed to preserve anti-inflammatory and potential neuroprotective benefits while minimizing gastric and renal toxicity associated with COX-1 inhibition; since COX-2 is inducible during inflammation and overexpressed in pathological states, selective inhibition aims to suppress disease-related prostaglandin synthesis without affecting protective physiological functions, and these agents are also being explored for roles in cancer and neurodegenerative disorders, though long-term safety and efficacy in AD require further well-designed clinical trials. [16]

Neurotransmitter Modulators

Early development of muscarinic acetylcholine receptor (mAChR) agonists for Alzheimer’s disease (AD) focused on selective activation of the M1 subtype, which is highly expressed in

the hippocampus and neocortex and plays a key role in memory and learning. The first M1 allosteric agonists, AC-42 and 77-LH-28-1, demonstrated selective receptor activation, while brucine was identified as the first positive allosteric modulator (PAM); however, AC-42 lacked in vivo efficacy. Xanomeline showed cognitive improvement in AD patients but failed clinically due to poor selectivity and gastrointestinal side effects. Subsequent compounds such as TBPB, 77-LH-28-1, AC-260584, AF267B, VU0364572, and BQCA demonstrated greater M1 selectivity, improved brain penetration, enhanced NMDA receptor-mediated signaling, promoted non-amyloidogenic APP processing, reduced β-amyloid deposition, limited tau hyperphosphorylation, and improved memory in animal models, suggesting potential disease-modifying effects. In contrast, nonselective agonists like talsaclidine and milameline failed due to systemic adverse effects. Additionally, nicotinic receptors (α7 and α4β2) have been explored, with agents such as AZD0328 and encenicline showing cognitive benefits but limited by safety concerns. Overall, while selective M1 agonists and PAMs offer promising dual benefits—symptomatic cognitive enhancement and possible slowing of AD pathology—their clinical success depends on improved selectivity, safety, pharmacokinetics, and intact presynaptic cholinergic function.[17]

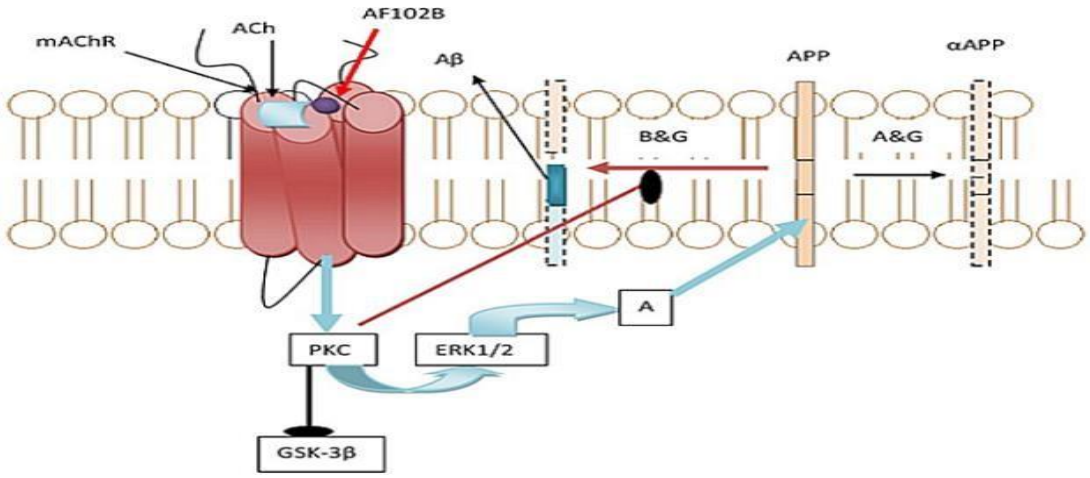

Fig:7-Activation O f muscarinic acetylcholine receptor by agonist AF102B stimulates PKC-mediated ERK1/2 signaling, promoting α- and γ-secretase activity while inhibiting β-secretase, thereby enhancing non- amyloidogenic APP processing and reducing β-amyloid formation.[17]

Novel & Future Approaches

Immunotherapy & Vaccines for AD

Immunotherapy is a promising treatment for Alzheimer's disease, targeting aberrant proteins

such as β-amyloid (Aβ) and tau, which cause neurodegeneration and cognitive loss. The primary goal is to either avoid or improve their removal from the brain.

Types of Immunotherapy

Active immunotherapy:AN1792 was the first clinically tested anti-Aβ vaccination. It contained synthetic full-length Aβ42 and the QS-21 adjuvant. In a phase IIa trial (NCT00021723), 19.7% of treated patients achieved high anti-AN1792 IgG titers and were categorized as antibody responders. In these responders, AN1792 reduced Aβ deposition and improved neuropsychological test battery (NTB) scores and CSF tau levels. However, the study was halted after 6% of the individuals contracted T cell-mediated meningoencephalitis. Long- term follow-up revealed that antibody responders had low but detectable anti-AN1792 titers, which were associated with continued functional advantages and slower cognitive decline.[18,9]**Amilomotide** (CAD106) is a vaccine that uses the N-terminal Aβ1-6 sequence as a B-cell epitope to produce anti-Aβ antibodies without eliciting T-cell response. Phase I trials (NCT00411580) demonstrated an acceptable safety profile and sufficient antibody production. Subsequent phase II trials (IIa: NCT00733863, NCT00795418, NCT00956410, NCT01023685; IIb: NCT01097096) showed a balance of immunogenicity and tolerance. However, unanticipated alterations in cognitive function, brain capacity, and body weight caused the phase II/III trial (NCT02565511) to be terminated early.**UB-311** is a combination of two synthetic Aβ1-14 peptides conjugated to helper T-cell epitopes using the Th2-biased UBITh® delivery technology. The goal is to maximize immunogenicity while limiting T-cell inflammation. A phase II experiment (NCT02551809) found a 100% response rate, high on-target immunogenicity, and potential cognitive improvements in early- to-mild Alzheimer's disease patients. This experiment compared ADAS-Cog score changes between mild (MMSE≥20) and moderate AD subgroups, but did not include a placebo. Another phase II trial (NCT03531710) was discontinued due to treatment assignment issues.[18]

Passive immunotherapy

Semorinemab (RO705705) is a humanized IgG4 anti-tau monoclonal antibody that targets extracellular tau and can bind all six human tau isoforms, thereby protecting neurons. While its safety profile has been established, clinical trials have revealed no substantial efficacy in Alzheimer's disease, indicating the need for more well-designed investigations. A study in moderate Alzheimer's disease is ongoing until October 2023 (NCT03828747), while a 2021 report revealed that a phase II trial (NCT02754830) failed to improve symptoms.Biogen

produced BIIB076 and Gosuranemab, both of which target tau. BIIB076 (NI-105), a mid-domain IgG1 antibody, has completed a phase I trial and is now in early clinical trials (NCT03056729). Gosuranemab (BIIB092) targets extracellular N-terminal tau, and although it reduced unbound tau in CSF by 98% in progressive supranuclear palsy, it lacked clinical effectiveness. A phase II research in early Alzheimer's disease was halted due to a lack of cognitive and functional improvement (NCT03068468).**Tilavonemab (ABBV-8E12**) binds to aggregated extracellular tau at the N-terminus and shown safety in phase I (NCT02880956). Howeveits phase II experiment failed to reach the desired efficacy and was halted. Bepranemab (UCB0107) is an IgG4 antibody that targets the tau mid- region (aa 235-250), and it may be more effective in preventing tau propagation. A phase II study in mild Alzheimer's disease is running until November 2025 (NCT04867616). Zagotenemab (LY3303560), derived from MCI-1, completed phase I and II trials but failed to meet the primary goal and was discontinued. **Donanemab (LY3002813)** is a humanized IgG1 antibody that targets the N-terminal pyroglutamate Aβ epitope in accumulated amyloid. In the phase II TRAILBLAZER-ALZ trial (NCT03367403), donanemab reduced cognitive and functional decline in early AD, dramatically removed amyloid plaques on 18F-florbetapir PET, and decreased plasma P-tau217 levels. ARIA-E incidence was greater in the donanemab group (26.7% vs. 0.8% placebo), emphasizing the importance of larger and longer studies. TRAILBLAZER-EXT, TRAILBLAZER-ALZ 2, and TRAILBLAZER-ALZ 3 are follow-up studies designed to investigate efficacy in early and preclinical AD populations.[18,9] **Lecanemab (BAN2401)** targets soluble aggregated Aβ, specifically oligomers and protofibrils. The phase II data (BAN2401-G000-201, NCT01767311) demonstrated dose-dependent decreases in amyloid PET SUVR, ADCOMS, and ADAS-Cog14 scores, with conflicting results for CDR-SB decline. CSF biomarker analysis revealed elevated Aβ42 levels and decreased p- tau levels. ARIA-E incidence was 9.9% overall and 14.3% in APOE4 carriers. Clarity AD and AHEAD 3-45 are currently undergoing phase III trials to assess long-term safety and efficacy.**Solanezumab (LY2062430)** targets the mid-domain of Aβ (Aβ13-28), improving clearance. The Phase III trials EXPEDITION 1, 2, and EXPEDITION EXT failed to show cognitive improvements in mild-to-moderate AD, and additional trials (Expedition 3, ExpeditionPRO) were canceled. Current trials, such as A4 (NCT02008357), are looking at the impact on asymptomatic or very early Alzheimer's patients.[18,9]**Crenezumab (RG7412)** binds numerous Aβ types with a tenfold greater affinity for oligomers. The phase III studies CREAD and CREAD2 were halted because interim

analysis revealed that the primary endpoints were unlikely to be met. Ongoing phase II trials (NCT01998841) are evaluating efficacy in preclinical AD patients with PSEN1 mutations.**Gantenerumab (RO4909832)** binds to aggregated Aβ and increases clearance through Fcreceptor-mediated phagocytosis. The Phase II DIAN-TU trials demonstrated significant decreases in Aβ plaques, CSF total tau, and phospho-tau181, but no cognitive improvement. ARIA-E occurred in 19.2% of subjects. Phase III GRADUATE 1 and 2 trials, as well as open- label rollover studies (NCT04339413, NCT04374253), are underway to assess long-term efficacy and safety in larger AD populations.[18]

Immunotherapies based on tau protein

Neurofibrillary tangles, composed of abnormally phosphorylated tau (p-tau), are another major hallmark of Alzheimer's disease (AD). Tau is a cytoplasmic protein that normally stabilizes microtubules by binding to tubulin, but hyperphosphorylation in AD reduces its microtubule- binding ability, leading to the formation of tangles and intracellular aggregates. Notably, tau pathology correlates more closely with cognitive decline than amyloid-β, making tau a promising therapeutic target. Current anti-tau strategies focus on preventing abnormal phosphorylation, inhibiting aggregation, and promoting clearance of tau aggregates. Most agents under clinical investigation are immunotherapies. Since 2007, when tau immunotherapy was first effective in JNPL3 mice, several active vaccines (e.g., AADvac1, ACI-35) and passive antibodies (e.g., semorinemab, gosuranemab, BIIB076) have shown significant benefits in preclinical models. Active vaccines work by stimulating the patient's immune system to generate antibodies against tau, aiming to reduce both intracellular tau and extracellular spread. Achieving this balance is challenging, as excessive immune activation can cause inflammatory side effects. Nevertheless, given tau's central role in AD progression, tau-targeted immunotherapy remains a highly promising approach.[18]

Active Immunotherapy AADvac1 :

Axon Neuroscience created AADvac1, a first-generation active immunotherapy vaccine, which targets a 12-amino-acid sequence (KDNIKHVPGGGS) in tau protein's microtubule-binding region. Phase I trials (NCT02031198) showed that AADvac1 is safe, with few adverse events, and provides benefits such as reduced brain atrophy, slower cognitive decline, and significant decreases in CSF biomarkers p-tau181 and p-tau217. Although a phase II trial ended on November 14, 2019, the results were not released. A second phase II research found that while AADvac1 was safe and well tolerated in 196 patients, it did not

significantly improve cognitive function. Despite this, AADvac1 represents substantial advances in tau-targeted active immunotherapy, and bigger stratified studies are needed to assess its therapeutic efficacy.[18]

AC Immune developed ACI-35, an active vaccination that targets pathogenic conformers of hyperphosphorylated tau. It contains 16 copies of a synthetic tau peptide that recognizes the phosphorylation sites S396 and S404. ACI-35 is now being studied in a multicenter, double-blind, randomized phase I/II clinical trial in Finland to determine its safety and efficacy in individuals with mild-to-moderate AD. The trial is planned to be completed before October 31, 2023 (NCT04445831).[18,9]

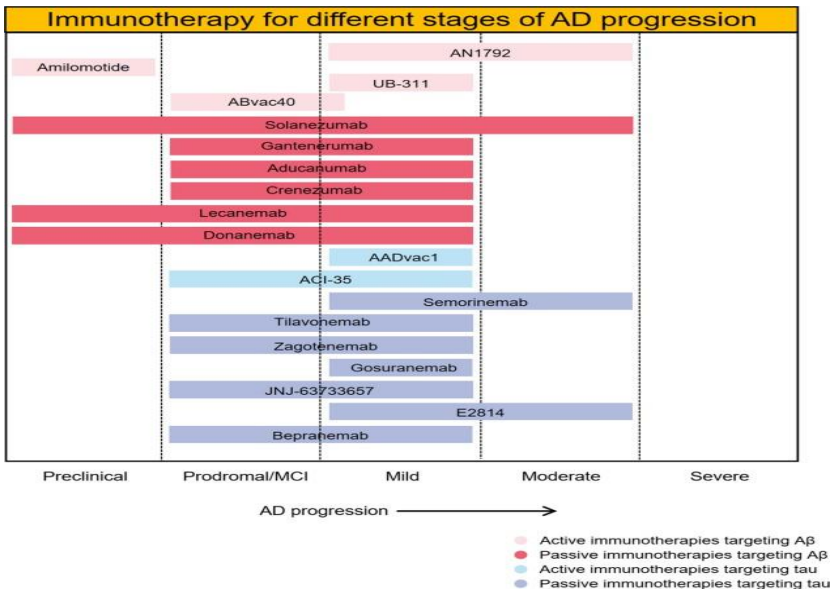

Fig-8:Immunotherapies for AD in ongoing clinical trials. Immunotherapies for different stages of AD progression are shown. Most of the current immunization therapies target the early phase of AD[18]

Stem cell therapy for neuronal regeneration

Stem cells have emerged as attractive options for Alzheimer's therapy due to their ability to replace damaged neurons, control inflammation, and produce neurotrophic substances. Their taxonomy and roles in AD can be summarized according to cell origin and cell type.

Classification based on cell origin.

embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent cells produced from the inner cell mass of blastocysts with the ability to differentiate into neurons, astrocytes, and oligodendrocytes,

including basal forebrain cholinergic neurons (BFCNs) and GABA neurons. In Alzheimer's disease (AD) rat models, ESC-derived neurons were found to improve spatial learning and memory. However, their clinical use is limited due to the possibility of teratoma formation, immunological rejection, and ethical problems. Current research focuses on transforming ESCs into neural progenitor cells (NPCs) before transplantation in order to improve safety and therapeutic potential. Mouse ESCs (mESCs) and human ESCs (hESCs) have been effectively employed to generate cholinergic neurons, and their transplantation into AD models has resulted in better cognitive performance and integration into existing neural networks. Differentiation into medial ganglion protrusion (MGE)-like progenitor cells has also showed promise, as these cells can give rise to basal forebrain neurons, adding to the potential of ESCs in AD therapy.[18]

Mesenchymal stem cells (MSCs) are pluripotent cells produced from various sources, including umbilical cord blood, Wharton's jelly, bone marrow, and adipose tissue. MSCs have shown promising therapeutic effects in AD models, including immunomodulation, decrease of Aβ plaques, suppression of tau hyperphosphorylation, and stimulation of neuroregeneration. They secrete extracellular vesicles and microvesicles that aid in neuronal growth and repair, and they can be genetically manipulated to overexpress cytokines or vascular endothelial growth factor, which improves regenerative benefits. Umbilical cord blood-derived MSCs are especially favorable due to their accessibility, ethical acceptability, and ease of use. Preclinical research in AD animal models have repeatedly showed benefits in spatial learning, memory, and neuronal protection after MSC transplantation.[18]

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) are created by transforming mature somatic cells into pluripotent states utilizing transcription factors or small chemicals. They can differentiate into neurons, glial cells, and macrophage-like cells that can degrade Aβ, making them ideal tools for simulating familial Alzheimer's disease (fAD) mutations in APP, PSEN1, and PSEN2. iPSC-derived neurons show disease-specific characteristics, such as increased Aβ42:40 ratios, facilitating research into pathogenic processes and potential treatments. Despite their potential, difficulties including as genetic instability, teratoma formation risk, and differentiation variability limit their clinical applicability. Advanced genome-editing tools, such as CRISPR/Cas9, may help create healthy neurons for transplantation, increasing the viability of iPSC-based therapies.

Classification based on cell type.

Neural Stem Cells

Both developing and adult brains include neural stem cells (NSCs), which are concentrated in the subgranular zone of the hippocampus dentate gyrus and the subventricular zone of the lateral ventricles. They are pluripotent, able to produce neurons, astrocytes, and oligodendrocytes. NSCs secrete neurotrophic substances such BDNF and NGF, reducing tau and Aβ levels, improving synapse development, and cognitive performance. Transplantation studies in animal AD models have shown that NSCs can move, develop into neurons and glial cells, reduce neuroinflammation, restore synaptic density, and improve spatial memory. NSCs genetically modified to overexpress neurotrophic factors improve cognitive recovery and neural regeneration, indicating its potential for Alzheimer's disease therapy.

STEM CELLS AND AD.

Preclinical experiments using stem cells in Alzheimer's disease models have yielded promising results. Transplanting ESCs, NSCs, and iPSCs into mouse brains improves memory and reduces disease markers like tau and Aβ. MSCs can lower Aβ plaque size, alter immunological responses, and promote neuronal development through Wnt signaling. iPSC-derived cells can also be utilized to model familial Alzheimer's disease and investigate gene-specific pathogenic processes and potential treatment approaches. Despite promising preclinical results, translating into human clinical trials has proven difficult. Small phase 1 trials involving human umbilical cord blood-derived MSCs injected into Although the hippocampus of individuals with mild-to-moderate AD was safe and viable, there were no substantial cognitive gains or decreases in Aβ pathology detected. The clinical problems include determining the best cell source, stage, dose, method of administration, and therapy duration, as well as creating sensitive metrics for detecting minor neuroprotective benefits. Overall, stem cell therapy has tremendous potential for treating Alzheimer's disease, but more study is needed to optimize methods, assure safety, and produce consistent clinical success.[18]

Non-Pharmacological & Adjunct Therapies

Role of diet (Mediterranean diet, omega-3, antioxidants)

Dietary interventions are important for maintaining brain health and lowering the risk of neurodegenerative diseases (NDs) like Alzheimer's disease (AD). Research indicates that diets that improve blood sugar regulation, insulin sensitivity, and weight control also improve

memory, learning, mood, and general cognitive function. The Mediterranean diet, which is high in olive oil, fruits, vegetables, whole grains, legumes, green tea, walnuts, and polyphenols, is linked to decreased oxidative stress, inflammation, brain atrophy, and cognitive decline; however, cultural, economic, and allergenic factors may limit adherence. Similarly, the ketogenic diet, which is low in carbohydrates and high in fat, improves mitochondrial function, reduces neuroinflammation, AD, Parkinson's disease, and other neurological disorders, though long-term sustainability and micronutrient deficiencies are still a concern Specific nutrients also contribute substantially: omega-3 fatty acids (DHA and EPA) from seafood reduce dementia and AD risk; vitamins C and E provide antioxidant neuroprotection and may delay disease progression; polyphenols and flavonoids exert anti-inflammatory and antioxidant effects that protect against AD, PD, and stroke; and saffron and its bioactive compounds such as safranal and crocin demonstrate antioxidant, anti-inflammatory, stress-modulating, and neuroprotective properties in experimental models. Overall, while these dietary strategies and nutrients show promising mechanisms—including reduced oxidative stress, improved synaptic function, modulation of neuroinflammation, enhanced mitochondrial activity, and decreased amyloid pathology—further well-designed human trials are necessary to confirm their long-term efficacy and safety in preventing or managing neurodegenerative diseases.[19]

Cognitive training, lifestyle modifications

Cognitive training and mental stimulation are important non-pharmacological strategies for improving working memory, executive function, attention, and problem-solving, particularly in neurodegenerative diseases (NDs). Approaches include computerized cognitive training (CCT) programs such as Lumosity and Cogmed, cognitive stimulation therapy (CST), mindfulness-based training, resistance and multimodal exercise, and brain stimulation techniques like transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), deep brain stimulation (DBS), vagus nerve stimulation (VNS), and transcranial direct current stimulation (tDCS). These interventions act through mechanisms such as modulation of the default mode and frontoparietal networks, increased neural activity in regions like the hippocampus and prefrontal cortex, enhanced synaptic plasticity, and elevated brain-derived neurotrophic factor (BDNF) levels, leading to improved cognition in conditions such as Alzheimer’s and Parkinson’s disease, although larger long-term trials are still needed. However, accessibility, cost, geographic limitations, and individual variability—including age, sex, genetics, and disease severity—affect outcomes. Sleep and circadian rhythm

regulation also play a critical preventive role, as adequate sleep supports glymphatic clearance of neurotoxic proteins such as amyloid-β and phosphorylated tau, whereas sleep disruption promotes oxidative stress, neuroinflammation, neurotransmitter imbalance, reduced BDNF, and accelerated neurodegeneration in disorders like Alzheimer's, Parkinson's, and Huntington's disease. Therapeutic strategies such as melatonin supplementation, consistent sleep schedules, light exposure management, and lifestyle modifications help restore circadian balance and provide antioxidant and neuroprotective effects, though benefits are more evident in early disease stages and require long-term adherence, patience, and support from patients and families.[19]

CONCLUSION

Alzheimer's disease (AD) remains the most prevalent cause of dementia worldwide and represents a growing global public health crisis due to its rising incidence, progressive nature, and profound socioeconomic burden. Despite decades of research, currently available therapies—including cholinesterase inhibitors and NMDA receptor antagonists—provide only symptomatic relief and fail to halt or reverse the underlying neurodegenerative process. Advances in understanding AD pathophysiology have highlighted multiple interconnected mechanisms, including amyloid-β accumulation, tau hyperphosphorylation, neuroinflammation, oxidative stress, mitochondrial dysfunction, neurotransmitter imbalance, and genetic susceptibility such as APOE4, emphasizing that AD is a complex multifactorial disorder rather than a single-pathway disease.Emerging disease-modifying strategies, particularly anti-amyloid monoclonal antibodies such as lecanemab and donanemab, BACE1 inhibitors, anti-tau immunotherapies, microglial-targeted agents, and novel anti-inflammatory pathways, represent significant progress toward modifying disease progression. However, mixed clinical outcomes, safety concerns such as ARIA, and variability in patient response underscore the need for improved patient selection, early diagnosis, biomarker-guided therapy, and long-term evaluation of safety and efficacy. In parallel, stem cell therapy and gene-based approaches offer regenerative and precision-based possibilities, though translational challenges remain. Importantly, non-pharmacological interventions—including dietary modification, cognitive training, physical activity, sleep regulation, and lifestyle optimization—provide supportive and potentially preventive benefits, particularly in early stages of the disease. These strategies, while not curative, may enhance cognitive reserve, reduce neuroinflammation, and slow pathological progression when combined with pharmacological treatments. Overall, the future management of AD will likely require a

multimodal and personalized approach that integrates early biomarker-driven diagnosis, targeted disease-modifying therapies, neuroprotective strategies, and sustainable lifestyle interventions. Continued interdisciplinary research, large-scale clinical trials, and equitable global healthcare access are essential to reduce the burden of Alzheimer's disease and improve quality of life for patients and caregivers worldwide.

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