***Review Article***

**Cracking the Code of Alzheimer’s: Advances of Neurology and Drug Advancement**

**ABSTRACT**

Alzheimer's disease (AD), a progressive and unrelenting memory loss, gradually weakens cognitive and independent functioning. There is currently no cure despite decades of research, and existing medicines simply alleviate symptoms. A complex interaction between hereditary variables (APOE ε4, PSEN1, PSEN2) and controllable risks (e.g., obesity, hypertension, and sleep disorders) leads to the disease. Fundamentally, tau tangles, amyloid-beta (Aβ) plaques, neuroinflammation, and mitochondrial dysfunction are what cause AD and eventually cause the death of neurons. A major obstacle in treating AD is ensuring drugs can penetrate the brain’s protective barrier. To combat this, innovative drug delivery methods include liposomes and nanoparticles, that would ensure therapeutic brain levels and reduce adverse effects are being investigated. Disease. Disease-modifying treatments, involving monoclonal antibodies such as aducanumab and lecanemab, are beginning to show promise in slowing disease progression.

Another frontier in AD management is early detection. Diagnoses can be made more quickly and accurately thanks to advanced biomarkers in blood and cerebrospinal fluid (CSF) and advanced imaging methods. There are still issues, though, such as late-stage detection, high drug trial failure rates, and financial limitations. Biomarker-driven therapies, tailored therapy, and advanced technology like digital health monitoring and artificial intelligence are the future of AD research. Integrating interdisciplinary work in neurology, genetics, and bioengineering brings us one step closer to turning AD from an incurable illness into a treatable one. Although there are obstacles in the way, cooperation and innovation hold out hope for a better future in the battle against Alzheimer's.

***Key Words:*** *Alzheimer's disease (AD), Tau tangles, Amyloid-beta (Aβ) plaques, Neuroinflammation, Monoclonal antibodies*

**Graphical Abstract**

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**1. INTRODUCTION**

Alzheimer's, the most common type of dementia, is a neurological illness that causes 60–80% of all dementia cases[1]. Difficulty in problem solving, wandering and disorientation, losing or misplacing items in unusual settings, mood and personality changes, and an increased level of anxiety and hostility are the features of the disease. Memory loss is another feature of AD that interferes with daily living, making it more difficult to perform everyday routine duties. Buildup of extracellular Aβ plaques and the development of intracellular neurofibrillary tangles composed of hyperphosphorylated tau are distinctive sign of AD neuropathology. The existing 50 million cases of AD dementia will quadruple to 150 million cases worldwide by 2050 with most of those affected living in low- and middle-income countries[2]. Current therapies, such as memantine and cholinesterase inhibitors, enhance quality of life but neither alter nor delay the progression of the disease; however, biomarkers sourced via cerebrospinal fluid (CSF) with positron emission tomography (PET) can improve the accuracy of diagnosis [3,4]. Although the exact causes of this illness are still being studied, the "cholinergic hypothesis" is the main emphasis. The disruption of cholinergic signaling in the cerebral cortex and hippocampal regions is linked to the cholinergic hypothesis[5]. The three main paths that can be used to get beyond the BBB and facilitate drug administration to the brain are "crossing," "avoiding," and "disrupting." Drugs can first penetrate the blood-brain barrier by taking advantage of several routes, including paracellular and transcellular ones. Additionally, avoiding the BBB refers to any other administration channels that do not involve direct physical perturbation of BBB but instead exploit invasive parenteral methods, including surgical, intrathecal, intracerebral, and intracerebroventricular. Moreover, BBB disruption is an example of non-invasive techniques including radiation, targeted ultrasound sonication, and the application of surfactants and hyperosmotic agents[6]. If patients are diagnosed with AD early, they may be able to collaborate with their doctors, family, caregivers, and other healthcare professionals to create advanced care plans. Crucially, it also makes it possible for patients to seek early intervention through risk-reduction strategies, lifestyle changes to maintain quality of life, and symptomatic therapy, which can lead to clinically meaningful declines in functional, and behavioral and cognitive abilities. Early diagnosis of AD can save around $7 trillion, according to a research by the Alzheimer's Association. It can also assist lower healthcare system expenses and limitations. Treating the underlying pathophysiology of active AD and identifying and staging therapies for those with preclinical, or asymptomatic, AD are the goals of current research[7].

**2. ETIOLOGY**

The development of AD is influenced by genetic and environmental risk factors, which can be divided into controllable and inherent components[8].

**2.1. Inherent risk Factors**

Numerous studies indicate that gender, lifespan, and Apolipoprotein E (APOE-ε4) allele are the main inherent risk factors for AD[8].

**2.1.1. Life Span**

Increased life expectancy correlates with higher AD risk due to changes in brain structure and DNA damage. Neurons are particularly vulnerable to aging, and lifestyle factors like diet and exercise may help limit progression[9].

**2.1.2. Hereditary Risk Factor**

Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) or Amyloid precursor protein (APP) are among the genes linked to amyloid metabolism that can be mutated to cause AD, while APOE gene variant is the main hereditary risk factor for serious AD[8].

***2.1.2.1. APP:*** Alterations in APP gene have been linked to an earlier development of AD, producing Aβ1-42 in plaques and Aβ1-40 in micro-vessels[10].

***2.1.2.2.* PSEN1/2:** Mutations in the **PSEN1/2** genes are common in cases of inherited AD with early onset (EOAD**)**. PSEN1 influences processing of APP, resulting in elevated Aβ deposition. PSEN1 mutations can also promote apoptosis through amyloid-independent pathways[11]. CRISPR-Cas9 studies on PSEN1 mutations show promise for future gene therapies. PSEN2 mutations, like Val214Leu and p.His169Asn, have been linked to EOAD in different populations[12].

***2.1.2.3. APOE:*** **APOE** gene variations, especially allele ε4, are major risk factors for AD. APOE plays a role in cholesterol metabolism, and its structure affects amyloid and tau pathologies, influencing AD progression[13].

**2.1.3. Gender**

Women are more affected, possibly due to longer lifespan and vascular differences. Some studies suggest women experience more rapid cognitive decline, while others show no significant gender influence[14].

**2.2. Controllable risk Factors**

**2.2.1. Hypertension**

Long-term studies shows high blood pressure elevates the menace of AD, particularly when it occurs in middle age. Hypertension can damage arterial walls, leading to ischemia, hypoxia, and reduced blood flow, which triggers the production of presenilin, APP, and Aβ, contributing to AD. Hypertension may also damage the blood-brain barrier, further promoting AD development[15].

**2.2.2. Sleep Disturbance**

AD can disrupt sleep patterns by affecting brain areas controlling the circadian rhythm, particularly the galaninergic neurons in the intermediate hypothalamus. Loss of these neurons is linked to sleep fragmentation, with greater fragmentation associated with fewer remaining neurons in autopsied AD brains[16].

**2.2.3. Obesity and Dementia**

Obesity, linked to low-grade inflammation, is connected with a menace of AD. While midlife obesity increases dementia risk, a high BMI in old age may boost cognition. Contradictory findings show that very obese individuals (BMI > 40) may have a lower dementia risk, whereas underweight people (BMI < 20) face a higher risk. Overall, studies suggest a U-shaped relationship between obesity and cognitive decline, with obesity often correlating with cognitive impairment[17].

**3. PATHOGENESIS**

Each of the brain's billions of neurons has many dendrites and an axon. To be healthy, neurons need to communicate, metabolize, and repair themselves. AD interferes with each of these three vital jobs. Neurofibrillary tangles (NFTs) and neurotic plaques/Ν-amyloid plaques are two of AD's characteristic lesions[18,19].

**3.1. Amyloid Plaques**

There is increasing research on the link between Aβ and glial cells, which play a critical role in neuroinflammation. Neuroinflammation may initiate or compensate for Aβ imbalance, with microglia removing Aβ clumps and dead cells. TREM2 modulates the microglial response to Aβ plaques[20], while proteases implicated in Aβ breakdown can improve clearance. Microglia are activated by Aβ plaques, which can cause brain alterations and neurite dysfunction. In mouse models, Aβ42 injection accelerated tau spread and neuron death, indicating that it speeds up tau propagation. Furthermore, Aβ is associated to neuronal hyperexcitation, perpetuating a cycle of hyperactivation. Secreted APP (sAPP) interacts with GABABR1a, preventing synaptic release, which may aid in neuronal circuit stability. Research indicates that Aβ is essential for the progression of AD and neurodegeneration[21].

**3.2. Neurofibrillary Tangles**

A characteristic of AD is the formation of NFTs by tau protein aggregates. Stage IV of NFTs spread to the temporal and frontal cortices after first forming in the hippocampus (stage III) and entorhinal cortex. The hippocampus is affected in "limbic stages." Later on, in what are referred to as "isocortical stages"[22], NFTs extend to further neocortical regions, including as the primary cortex. Stages V and VI of NFTs are associated with significant symptoms of dementia. Neuronal death results from aberrant tau phosphorylation and redistribution, leaving behind "ghost tangles" that interact with Aβ and microglia. Cognitive decline is exacerbated by tau pathology, and frontotemporal dementia and other related illnesses are brought on by tau gene mutations (MAPT)[23].

**3.3. Cholinergic Insufficiency**

The "Cholinergic Hypothesis of AD" suggests that a major contributing factor to AD is the death of cholinergic neurons which produce acetylcholine (Ach). Ach is crucial for learning, memory, and cognitive functions. It is released into the synapse and binds to receptors like nicotinic and muscarinic receptors. Acetylcholine esterase (AchE) breaks down excess Ach, and choline is recycled back into neurons for resynthesis of Ach. Some choline is also used to maintain cell membrane integrity. The degeneration of cholinergic neurons disrupts these processes, contributing to dementia in AD[24].

**3.4. Mitochondrial Dysfunction**

Mitochondria are essential for brain functions like energy production, calcium balance, synaptic plasticity and calcium balance. In AD, mitochondrial dysfunction leads to neuronal damage and cell death, often due to increased reactive oxygen species (ROS)[25]. In AD, mitochondria typically go through more fission than fusion. Exposure to Aβ may reduce Drp1, a protein regulating fission. Uncoupling proteins (UCP2 and UCP3) help protect mitochondria from oxidative stress, but overexpression of APP or mutated APP weakens this protection, worsening mitochondrial dysfunction and ROS production[26].

**3.5. Autophagy Dysfunction**

AD is associated with defective autophagy. In AD, autophagosomes as well as autolysosomes accumulates in brain, suggesting a block in autophagic flux. This is due to reduced Beclin-1 and down-regulated PI3P synthesis, which are essential for autophagy. Studies show that enhancing neuronal autophagy can protect against protein buildup in AD[27]. Microglia, which help clear Aβ and other debris, rely on both autophagy and phagocytosis to maintain brain health. These processes share common molecular mechanisms, helping immune cells like microglia and macrophages degrade harmful molecules and prevent neurodegeneration in AD[28].

**4. list 1 : FDA APPROVED DRUGS AND CURRENT TREATMENTS [29]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug Name** | **Class** | **Mechanism of Action** | **Stage of AD treated** |
| Donepezil | Cholinesterase Inhibitor | raises the amount of acetylcholine | Mild to severe |
| Rivastigmine | Cholinesterase Inhibitor | enhances the action of neurotransmitters | Mild to Moderate |
| Memantine | NMDA Receptor Antagonist | Lowers toxicity via controlling glutamate | Moderate to Severe |
| Aducanumab | Monoclonal Antibody | Cuts down on Aβ-plaques | Early – Stage AD |
| Lecanemab | Anti- Amyloid Therapy | takes aim at plaques to slow down cognitive degeneration. | Early – Stage AD |

**5. VARIOUS POSSIBLE ROUTES OF ADMINISTRATION**

**5.1. Oral DDS**

Oral extended-release (ER) formulations, such as tablets and capsules, provide controlled medication release, lowering dosage frequency and enhancing patient compliance. They offer advantages like as consistent drug levels and fewer side effects, but they can also have disadvantages such as slower peak plasma levels and the danger of dose dumping. Oral disintegrating tablets (ODTs) disintegrate fast on the tongue, providing convenience, a better flavor, and discreet ingestion; however, they are more expensive and may not be appropriate for patients with swallowing problems[30]. The ALC study underlines the potential of oral delivery to be feasible option for AD treatment, with both oral and intravenous methods displaying effective brain penetration. This supports the hypothesis that oral medicines can be equally successful as IV treatments in certain situations, if the drug is capable of penetrating the BBB get to the neuronal systems in the brain[31].

**5.2. Intravenous (IV) administration**

Intravenous (IV) injection provides rapid systemic medication distribution, resulting in immediate therapeutic effects. This approach is especially beneficial for drugs such as aducanumab (Aduhelm™), a monoclonal antibody that designed to address amyloid plaque accumulation in the brain a defining feature of AD. By binding to these plaques, aducanumab aids in their removal, perhaps reducing disease development. IV delivery ensures that the medicine enters the bloodstream immediately and is effectively delivered to the brain, where it exerts its effects. However, aducanumab's IV infusion necessitates careful dosing schedules and monitoring for side effects such as brain swelling or microhemorrhages, making it critical to adhere to strict medical procedures during therapy. This form of administration ensures the drug's potency and lowers dangers, allowing individuals with intermediate AD to access it[32].

**5.3. Nose to brain DDS**

The ability to directly reach the brain through intranasal administration to the nasal cavity's olfactory area has shown promise in avoiding the blood-brain barrier (BBB). With this method, systemic adverse effects can be minimized and the necessary therapeutic dose can be decreased. As a promising approach, intranasal administration improves drug distribution and targeting to the brain, circumvents the blood-brain barrier, and helps prevent hepatic first-pass metabolism[33]. Nasal powders are desirable formulations because of their superior medication stability than solutions or suspensions and the absence of preservatives[34].

**5.4. Transdermal Drug Delivery**

Oral administration has various disadvantages, including first-pass metabolism, limited efficacy, and low bioavailability, making it challenging to treat Alzheimer's-like diseases. Transdermal administration is an alternate approach that permits active substances to diffuse over time, avoids first-pass metabolism, and decreases systemic adverse effects. The FDA authorized five medications for Alzheimer's disease. Rivastigmine functions as a cholinesterase inhibitor, while tacrine, donepezil, galantamine, and memantine act as NMDA receptor antagonists. This increases patient compliance and allows the medications to be used for a longer period of time[5].

**5.5. Intracerebroventricular Drug Delivery**

The ICV STZ Model mimics sporadic Alzheimer's disease by producing glucose hypometabolism, cerebral insulin resistance, and cognitive impairment. Used in preclinical drug testing for treatments that target brain metabolism.

ICV MSC Treatment: Phase I study looked at hUCB-MSCs in patients with mild-to-moderate AD using an Ommaya reservoir over three injections. The results were safe and practicable, with the most prevalent side effects being fever, headaches, and nausea. There are no toxicities that limit the dose.

Results: Temporary reduction in Aβ, tau, and enhanced neuroprotective markers. PET scans showed that the amyloid burden has decreased.

ICV administration has potential for Alzheimer's disease treatment, particularly in targeting metabolic dysfunction. Repeat dosages may be required, and additional trials are needed to determine clinical efficacy[35,36].

**6. NOVEL DRUG DELIVERY OPTIONS**

**6.1. Nanoparticles(NPs)**

Nanotechnology has emerged as a transformative technique to drug delivery research. It improves medication stability, biodistribution, and pharmacokinetics, allowing for more control over release. Nanoparticles (NPs) have the ability to overcome drug resistance, solubilize both hydrophilic and hydrophobic medicines, and respond to intrinsic and extrinsic stimuli to deliver therapeutic agents precisely in terms of time and space. These characteristics make NPs highly useful in improving the efficacy and safety of conventional treatments, particularly for neurological illnesses like Alzheimer's[37].

**6.2. Lipid-derived NPs**

Solid lipid nanoparticles (SLNs) and liposomes are examples of lipid-derived nanoparticles that are stable coupled with biocompatible. Liposomes include a hydrophilic core, whereas SLNs can solubilize lipophilic compounds. Despite their low toxicity and immunogenicity, lipid-based NPs require enhancement in terms of stability and drug loading capacity. Although unmodified liposomes have difficulty crossing the blood-brain barrier (BBB), functionalized or modified liposomes can boost their penetration by targeting specific receptors and improving their ability to deliver medications to brain areas, particularly in Alzheimer's disease[38].

**6.3. Polymeric NPs**

Polymeric nanoparticles (both synthetic and natural) have drawn a lot of interest because of their adaptable structure, biocompatibility, along with capacity for delivering drugs in a regulated manner. These nanoparticles shield therapeutic drugs from enzymatic and hydrolytic breakdown, allowing for better drug transport across the BBB. Polymeric NPs boost brain penetration, raise medication concentrations in target regions, and improve therapeutic efficacy by encapsulating them. They have been extensively employed for a broad range of medication delivery systems, particularly in treating neurological illnesses[39].

**6.4. Magnetic NPs (SPIONs)**

Superparamagnetic iron oxide nanoparticles (SPIONs) have been employed in medication therapy since the 1960s, and they provide numerous advantages for targeted drug delivery. They have magnetic properties that may be triggered by an external magnetic field, allowing for fine spatial control with few side effects. The surface of SPIONs can be changed to allow active targeting, making them especially suitable for crossing the BBB. SPIONs have been effectively employed to promote drug penetration into the brain, providing a technique for more efficient drug distribution and better treatment effects in neurological diseases[40].

**6.5. Solid Lipid Nanoparticles (SLNs)**

SLNs are a next-generation drug delivery device made up of a solid lipid core surrounding by a biocompatible surfactant layer. SLNs have a high drug loading capacity, superior stability compared to other lipid carriers, and biocompatibility. They are suitable for delivering hydrophobic medicines, proteins, and peptides, and show great promise for brain-targeted therapy. SLNs are currently being investigated as a vehicle for delivering medications to treat neurological illnesses including Alzheimer's disease due to their advantageous features, which include higher stability and less toxicity[41].

**6.6. Curcumin-loaded NPs**

Curcumin, a naturally occurring antioxidant and anti-inflammatory chemical, has showed promise in the management of AD due to its capacity to bind amyloid and tau proteins. It also suppresses tau hyperphosphorylation, making it a potentially useful therapeutic treatment. Curcumin, on the other hand, has low stability, bioavailability, and brain penetration due to its sensitivity to hydrolysis, oxidation, and photodegradation. Researchers are developing curcumin-loaded nanoparticles to increase its stability, pharmacokinetics, and bioavailability, hence increasing its therapeutic potential for neurological illnesses[42].

These novel drug delivery systems based on nanoparticles hold great promise for improving the therapy of neurological conditions, particularly AD, by enhancing therapeutic stability, targeting specific areas of the brain, and increasing drug efficacy while minimizing side effects.

**7. BIO MARKERS FOR AD TREATMENT**

A biomarker is a crucial metric for evaluating the course of a disease, normal biological processes, and the results of therapy. Biomarkers are used to assess the health of elderly adults with AD[43]. Aβ plaque accumulation and the brain's hyperphosphorylated tau protein aggregation are the two main pathogenic characteristics of AD and are both essential to the disease's progression[44].

AD is characterized by the build-up of tau tangles, amyloid plaques, and neuronal damage, each of them can be assessed through biomarkers. These biomarkers, including amyloid beta (Aβ), tau proteins, neurofilament light chain (NfL), and blood-brain barrier (BBB) dysfunction indicators, are critical for diagnosing AD, tracking disease progression, and evaluating therapeutic responses[45].

1. Aβ related biomarkers
2. Tau related biomarkers
3. Neuronal damage related biomarkers
4. Synaptic dysfunction related biomarkers
5. BBB dysfunction related biomarkers
6. CSF biomarkers.

**7.1. Aβ‑related biomarkers**

Amyloid Beta (Aβ) Biomarkers: The cleavage of the APP produces Aβ peptides, which in turn cause Aβ plaques, primarily Aβ42 and Aβ40. In a healthy brain, Aβ peptides are cleared via cerebrospinal fluid (CSF) or blood. However, impaired clearance or overproduction leads to plaque formation, with Aβ42 being the predominant component in plaques. Lower levels of Aβ42 or a decreased Aβ42/Aβ40 ratio in CSF predict amyloid plaque presence, aiding in the prompt detection of AD along with preclinical stages. Measurement concerning these biomarkers can be achieved using mass spectrometry or immunoassays[46].

**7.2. Tau‑related biomarkers**

Tau proteins are crucial in the pathophysiology of AD, especially in neurofibrillary tangles. Several tau-related indicators are useful for detecting and monitoring AD.

Full-length tau (fl-tau) Elevated fl-tau concentration in CSF indicate neuronal injury followed by degeneration. Phosphorylated (p-tau) Specific phosphorylated variants of tau, such as p-tau181 and p-tau217, are significantly associated to AD pathology and detectable in both CSF and blood, enabling the possibility of non-invasive diagnosis[47].

Plasma Tau: Plasma tau levels, especially brain-derived tau, represent a promising blood-based biomarker that correlates with CSF biomarkers and cognitive function, making it a less invasive diagnostic tool.

Tau PET imaging with particular tracers permits visualization of tau deposition, which distinguishes AD from other neurodegenerative disorders[48].

**7.3. Neuronal damage‑related biomarkers**

A possible biomarker for neuronal injury is neurofilament light chain (NfL), which leaks into CSF when neurons or axons are injured. NfL is closely associated with a number of neurodegenerative illnesses, however it is not unique to AD[49]. When used in combination with other biomarkers, it is most beneficial. The significant correlation between CSF and blood NfL levels allows for early identification, even before symptoms manifest, especially in autosomal dominant AD[50].

**7.4. Synaptic dysfunction‑related biomarkers**

Synaptic Dysfunction and Metabolic Imaging: Synaptic loss occurs early in the progression of AD, and fluorodeoxyglucose (FDG) PET is used to detect hypometabolism in brain regions such as the praecuneus and cingulate cortex. FDG PET is beneficial for early Alzheimer's disease detection and differential diagnosis[51].

**7.5 BBB dysfunction‑related biomarkers**

BBB disruption contributes significantly to AD pathogenesis. Several biomarkers show BBB impairment:

Thrombin and HMGB1: Elevated levels of these molecules indicate BBB failure and inflammation, acting as clinical indicators of disease development.

Soluble Thrombomodulin (sTM): Increased sTM levels indicate endothelial injury, shedding light on BBB integrity in AD patients[52].

Increased neuroinflammation and BBB permeability are associated with the APOE ε4 allele, which can contribute to AD pathogenesis.

CSF biomarkers such as Aβ peptides and tau proteins can help diagnose and monitor BBB integrity and neuronal damage[53].

Recent Research Developments:

Focused Ultrasound for BBB Opening: Researchers are employing MR-guided focused ultrasound to temporarily open the BBB in order to increase drug transport to the brain and hence improve therapeutic efficacy in Alzheimer's disease.

Blood-Based Biomarkers: Advances in detecting blood-based biomarkers, such as plasma tau and NfL, offer a non-invasive method for early AD detection and monitoring[54].

**7.6. CSF biomarkers**

CSF markers, including Aβ1-42, full-length tau, and hyperphosphorylated tau, plays crucial role in diagnosing AD. Moderate cognitive impairment is indicated by lower levels of Aβ1-42 and greater levels of tau proteins. Combining Aβ1-37 with Aβ1-42 levels could improve sensitivity in predicting MCI-to-AD development. Correlations between CSF biomarkers and amyloid plaque formation or tau tangles are inconsistent and impacted by factors including APOE ε4 allele status and age. Recent meta-analyses reveal that Aβ1 - 42, tau proteins have modest sensitivity in detecting preclinical AD. However, inconsistencies across studies highlight the need for future research into additional biomarkers. The use of numerous biomarkers and imaging modalities can improve diagnostic accuracy, allowing for earlier and more reliable detection of AD.

These advancements in biomarker identification and understanding BBB dysfunction are essential to the early detection, tracking, and development of AD treatments[55].

**8. FUTURE EMERGING**

**8.1. CSF1R**

Because of its critical function in microglial control and neuroinflammation, the colony-stimulating factor 1 receptor (CSF1R) is thought to be promising therapeutic target in AD. Dysregulated microglial activity leads to AD pathogenesis, like Aβ plaque buildup as well as tau induced neurodegeneration. CSF1R inhibition has been investigated as an approach for controlling microglial function and reducing neuroinflammatory responses.

Preclinical studies show that CSF1R inhibitors like PLX5622 and PLX3397 can lower microglial proliferation, alter detrimental microglia-amyloid interactions, and improve cognitive performance in AD animals. JNJ-40346527, a brain-penetrant CSF1R inhibitor, has showed potential in treating tau-induced neurodegeneration and is presently in clinical studies Phase I for AD. While these data emphasize the therapeutic potential of CSF1R inhibition, more research is needed into the long-term effects of microglial suppression.

CSF1R targeting is a unique method in Alzheimer's disease therapy that addresses neuroinflammation and microglial dysfunction. Ongoing research and clinical studies will assess the efficacy and safety of CSF1R inhibitors, which could open up new routes for disease-modifying therapy in Alzheimer's[56].

**8.2. Anti-Amyloid Therapy**

Anti-amyloid treatments have become popular in AD therapy due to their ability to reduce cognitive loss by targeting amyloid-beta (Aβ) plaques, which are a hallmark of AD pathology. Monoclonal antibodies like lecanemab and donanemab have shown promise in decreasing Aβ plaques and slowing disease development. In phase 3 trials, lecanemab (CLARITY-AD) delayed cognitive decline by approximately 25% over 18 months, whereas donanemab (TRAILBLAZER-ALZ2) reduced disease progression by 35%. Despite these advances, anti-amyloid medications still face obstacles, including amyloid-related imaging abnormalities (ARIA), which encompass conditions like cerebral edema and microhaemorrhages. Lecanemab and donanemab have reasonably good safety profiles, although close patient monitoring is required to reduce hazards. Furthermore, many medicines require biomarker-assisted testing, such as CSF analysis paired with amyloid Positron tomography imaging, to confirm Aβ accumulation and ensure appropriate patient selection.

While these therapies do not cure AD, they represent a major step forward in disease-modifying treatments. Future research will focus on optimizing their use, identifying patients who benefit most, and exploring combination approaches with tau-targeting and neuroinflammatory therapies. The integration of these therapies into clinical practice marks a significant shift in AD treatment, providing hope for slowing disease progression and improving patient outcomes[57].

**8.3. Genetic Intervention**

**8.3.1. Nerve Regeneration Molecule (NRM)**

Throughout their lives, CBF neurons rely on an ongoing flow of NRM to maintain and survive. The cerebral cortical neurons and hippocampus that express p75NTR and TrkA receive the NRM produced by these neurons. NRM forms a complex with TrkA in these areas, which is stabilized by p75NTR. To aid in signal transduction, this NRM/TrkA combination is subsequently returned to the basal forebrain. A sharp age-dependent decrease of CBF neurons is shown in transgenic mice that express anti-NRM antibodies, underscoring the crucial function of NRM in maintaining neurons[58].

**8.3.2. Brain Nourishment Factor (BNF)**

A homodimeric amino acid complex called BDNF is mostly located in the hippocampus and cerebral cortex of the brain and is essential for memory and learning. Neuronal survival is supported by activating its low-affinity receptor p75NTR and high-affinity receptor TrkB, especially dopaminergic and cholinergic neurons. Lower BDNF levels are associated with AD, research has shown that AD brain areas have lower BDNF, which affects memory through decreased BDNF-TrkB signaling. In rat, mouse, and primate models, gene therapy to supply BDNF has demonstrated promise in reversing neuronal damage and recovering memory, indicating its potential as a treatment for AD[59].

**8.3.3. Viral Vectorization**

The majority of clinical trials for gene therapy aimed at neurological illnesses have employed AAV-based vectors. AAV serotypes are important in determining biodistribution, tissue tropism, and the susceptibility to neutralizing antibodies in vivo, among other critical elements for the effectiveness of AAV-based gene therapy. Knowing how various AAV serotypes transport gene cargo to particular tissues is crucial to creating a dependable and consistent gene therapy strategy. Here, studies have demonstrated that intracerebral administration of AAV2 (nerve growth factor) is well tolerated and can help treat cognitive loss in dementia caused by AD[60,61].

**9. CHALLENGES AND LIMITATIONS**

**9.1. Challenges**

Combination medicines that target various pathways in AD, like inflammation, tau, and amyloid, offer promise for enhancing treatment outcomes and minimizing side effects. These medicines, such as the memantine and donepezil combination, are successful for middle to later stages of AD, improving cognitive together with social features, although being more expensive than monotherapy. AD treatment challenges include restricted alternatives, a significant economic burden, difficulties in early detection, and uncertain biological processes, particularly in women. Despite promising discoveries, high failure rates in CNS drug development, a dearth of good anti-inflammatory medications, and difficulties identifying effective combinations underscore the complexities of AD and demands for novel therapies[62,63].

**9.1.1. Limited Understanding of Disease Etiology**

Alzheimer's disease, unlike diseases with a well-defined origin (such as bacterial or viral infections), lacks a clear, singular cause. The "amyloid accumulation theory" posits that Aβ plaques and tau tangles are responsible, but it is unclear whether these are the root cause or a result of the disease. Other potential causes, including as inflammation, metabolic dysfunction, and vascular problems, make treatment development difficult[64].

**9.1.2. Complex Pathophysiology**

Alzheimer's is a chronic brain disorder distinguished as a complex interplay among genetic, environmental, and lifestyle effects. The condition advances over decades, making it difficult to determine when and how to intervene effectively. Early molecular alterations cause cell death, but symptoms only appear after major, irreversible brain injury.

**9.1.3. Lack of Effective Disease-Modifying Therapies**

Current treatments are mostly concerned with controlling symptoms (e.g., cognitive decline and behavioral difficulties), rather than slowing or reversing disease development. Most medications discovered to far have targeted amyloid-beta plaques, but their effectiveness in enhancing cognitive function has been limited. There is an increasing realization that tau pathology, neuroinflammation, and other variables may need to be addressed in therapeutic techniques.

**9.1.4. Difficulty in Early Diagnosis**

The disease starts 10-20 years before symptoms manifest, therefore many individuals are discovered too late for effective treatment. Clinical diagnosis is currently based on cognitive testing and medical history, which may not be effective in detecting early-stage disease.
New diagnostic methods, such as blood-based biomarkers and cerebrospinal fluid (CSF) and possess promise but have not yet established themselves as norms in clinical practice.

**9.1.5. Challenges in Drug Development**

Alzheimer's disease treatments are more difficult to develop than cancer, diabetes, or infections.
To determine if a treatment delays disease development, drug studies often require a lengthy follow-up period (commonly 5-10 years). Many medications fail in clinical trials, resulting in significant financial losses for pharmaceutical corporations and deterring investment in the industry[65].

**9.1.6. Regulatory and Financial Barriers**

Clinical studies are expensive, with costs totaling hundreds of millions of dollars per medication candidate. The extensive duration of studies, along with rigorous regulatory restrictions, make it difficult for novel therapies to enter the market rapidly. Government funding for Alzheimer's research has increased, but it is still lower than that for cancer or heart disease.

**9.1.7. Limited Diversity in Clinical Trials**

Alzheimer's disease disproportionately affects different racial and ethnic groups, but clinical trials frequently lack broad participation. Despite the fact that Black and Latino people are at a higher risk, just 3-8% of Alzheimer's study participants are from these communities.
Due to the lack of diversity in studies, therapeutic effectiveness and adverse effects may not be adequately understood for all populations.

**9.1.8. Disconnect Between Diagnosis and Treatment**

The majority of persons are diagnosed when they have moderate to severe symptoms, despite the fact that most investigational medications are intended for early intervention.
Physicians frequently rely on clinical symptoms rather than biomarkers to make diagnoses, which might cause therapy delays. Even potentially helpful treatments may be unable to restore the damage done if not administered early on.

**9.1.9. High Cost of Care**

As Alzheimer's progresses, individuals require higher degrees of care, ranging from in-home assistance to full-time nursing care. The financial impact on families and healthcare systems is substantial, with billions spent each year on caring and medical bills. Remote monitoring and AI-powered care solutions could be beneficial, but they have yet to be extensively adopted.

**9.1.10. Lack of Urgency in Policy and Research**

Even though AD is becoming more common, there hasn't been much progress made to speed up research and therapy approval. The answer to COVID-19 illustrated how quick scientific collaboration and government assistance can lead to speedy medical advancements. A comparable sense of urgency for Alzheimer's research could hasten advances in diagnostics and treatment.

**9.1.11. Possible Solutions to These Challenges**

* Increased funding in research to better understand disease pathways in the early stages.
* New clinical trial designs that test many medications simultaneously and shorten trial lengths.
* Biomarkers should be used more widely in early diagnosis to help identify at-risk patients sooner.
* Policy measures to expedite drug approval and boost investment in Alzheimer's research.
* Increased clinical trial diversity to guarantee that therapies are effective for all populations.
* Technological advances in caregiving and monitoring to alleviate the stress on families[66].

**9.2. Limitations**

Clinical overlap: AD symptoms are similar to those of other neurodegenerative illnesses, which might lead to a misdiagnosis. Comorbidities: Many Alzheimer's patients have other diseases, confounding the diagnosis. Biomarker Issues: Amyloid and tau biomarkers are detected in a variety of diseases, not just Alzheimer's. Post-mortem Diagnosis: Only 3-30% of Alzheimer's dementia cases exhibit pure AD pathology, limiting correct diagnosis. Variable Biomarker Expression: Biomarkers may not necessarily correspond to clinical symptoms[67].

**9.2.1. Treatment Limitations**

poor efficacy: Current treatments primarily target symptoms and have poor long-term effectiveness.
There are no disease-modifying therapies available to slow or reverse the condition.
Mixed Pathology Response: AD-targeted medications may not work for patients with other diseases.
Side Effects: Existing drugs have limited advantages and may produce adverse reactions.

**9.2.2. Biomarker and Diagnostic Method Limitations**

Lack of Standardisation: Biomarkers are not always reliable for diagnosis.
High Costs: Advanced diagnostic instruments are pricey and not generally available.
Late Diagnosis: Many patients are diagnosed too late to be treated effectively.

**10. CONCLUSION AND FUTURE PERSPECTIVES**

**10.1. Conclusion**

The prevalence of AD, a serious neurological ailment that impacts millions of individuals globally, is expected to rise significantly over the coming decades. Despite substantial research, the condition is still incurable, with current medications merely treating symptoms rather than preventing disease development. Advances in biomarker-based diagnostics, like PET imaging and CSF analysis, have improved early detection and enabled more targeted therapies. Novel treatment approaches, including as anti-amyloid and anti-tau medicines, immunotherapy, and gene-editing tools, present intriguing pathways for disease modification. Nanoparticles, liposomes, and transdermal applications are examples of drug delivery advances that attempt to improve therapeutic efficacy by enhancing blood-brain barrier penetration while lowering systemic side effects. However, problems remain, such as the intricacy of AD pathophysiology, late-stage diagnosis, high treatment costs, and the need for more effective combination therapies.

Future research should prioritize personalized medicine techniques that combine biomarker-based staging with targeted medicines. Additionally, advancements in neurotechnology, artificial intelligence, and wearable health monitoring technologies could transform early detection and patient care. Addressing these issues through multidisciplinary collaboration, greater research funding, and regulatory changes will be critical to creating effective therapies and, ultimately, a cure for Alzheimer's disease.

**10.2 Future Perspective**

The future perspective of Alzheimer’s disease (AD) staging focuses on advancing biomarker-based approaches for earlier detection and personalized treatment strategies. Here are the key points:

 **10.2.1 Multidimensional Biomarker-Based Staging**

The future of Alzheimer's disease staging will rely on in vivo biomarkers to track pathological changes from the asymptomatic to symptomatic phases. Biomarkers such as PET imaging, CSF, and plasma markers will give a comprehensive assessment of AD pathology, hence enhancing diagnostic accuracy.

 **10.2.2. Biological Staging Using PET Imaging**

Advances in molecular imaging (PET scans) will improve Alzheimer's disease classification methods by exploiting anatomical pathology distribution. Regional staging based on amyloid and tau accumulation may help to better track disease development.

 **10.2.3. Plasma and CSF Biomarkers for Early Detection**

Plasma-based assays for phosphorylated tau (pTau) are projected to provide a low-cost, non-invasive technique for detecting Alzheimer's disease. Combining numerous pTau markers in blood or CSF will allow for more precise disease staging and therapy methods.

 **10.2.4. Impact on Clinical Trials and Treatment**

Future clinical trials will choose patients based on biomarker-defined illness stages, hence boosting the efficacy of novel medicines. PET imaging can track the course of a disease and the effectiveness of treatments that modify it, like monoclonal antibody therapy for tau and amyloid.

 **10.2.5. Personalized and Preclinical Interventions**

There is a focus on diagnosing preclinical AD (before symptoms appear) in order to intervene at appropriate times. Biomarker-based staging systems will aid in identifying asymptomatic individuals who may benefit from early intervention.

 **Future Research**

More validation of pTau panels and biomarker thresholds is required to assure cross-population applicability. The integration of biological staging systems with cognitive assessments will be critical for therapeutic use.

**10.3. Technology and Personalized Innovation**

**10.3.1. Advances in Imaging** Imaging tools like PET and MRI can detect plaque buildup and neurofibrillary tangles, which lead to cognitive loss. Retinal imaging with optical coherence tomography is emerging as a non-invasive tool for detecting early indicators of Alzheimer's disease, potentially allowing for earlier intervention before symptoms worsen.

**10.3.2. Lab-on-a-Chip** Miniaturized handheld devices use antibody-based biomarker assays for fast, inexpensive, on-site diagnostics. These lab-on-a-chip devices enable real-time testing with results in less than 20 minutes, enabling for faster biomarker identification and therapy decisions.

**10.3.3. Smartphone Applications** The combination of biometric monitoring and smartphone apps provides a more accessible and ongoing way to tracking Alzheimer’s symptoms. These apps not only help with behavior modification and prescription reminders, but they also enable data collection and analysis, allowing for remote patient monitoring and prompt treatment modifications.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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