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ALZHEIMER'S DISEASES INSIGHTS: FROM MECHANISM TO TREATMENT

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ABSTRACT

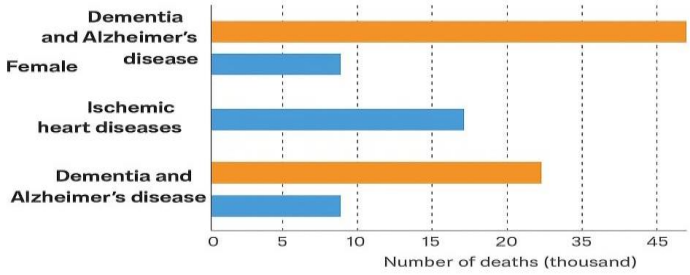
Alzheimer's disease is the progressive neurodegenerative disease leading cause of dementia, slowly destroying memory, thinking, and independence until daily basic life becomes impossible. WHO stated Alzheimer's been the most fatal disease and occurring older adults. The Alzheimer's disease follows the hypothesis which are amyloid hypothesis and Tau hypothesis. Fragment of a protein called amyloid accumulates outside neurons, forming sticky plaque. These plaques disturb communication between cells, trigger inflammation, and set off toxic chemical reaction that damage brain tissue. Hand in hand amyloid comes in tau pathway, tau is a protein that normally stabilize the cell internal transport system. In Alzheimer's tau becomes abnormally modified, clumping together into twisted tangles inside neurons. These tangles block the transport of nutrients and signals, causing the affected cells to weaken and die. Treating Alzheimer's has always been difficult because the disease involves many damaging processes at once. The first treatment focus on symptom relief drugs like-donepezil, rivastigmine, and galantamine boost acetylcholine to support memory, while memantine helps protect neurons grom glutamate overload. These provide temporary benefits but do not stop progression. More recently, therapies have turned to the roots of the disease. Antibody drugs such as Aducanumab and donanemab target and clear amyloid plaques, showing some ability to slow decline, though side effects remain a concern. Hence current treatments only aim to slow decline, not to regenerate or repair damaged neurons. This review is covered based on the information subject to various source for scientific, technical, and medical research like science direct, Scopus, Web of science, PubMed etc.

KEYWORDS: Alzheimer's disease, etiology, oxidative stress, apolipoprotein, western diet, APPswe.

INTRODUCTION

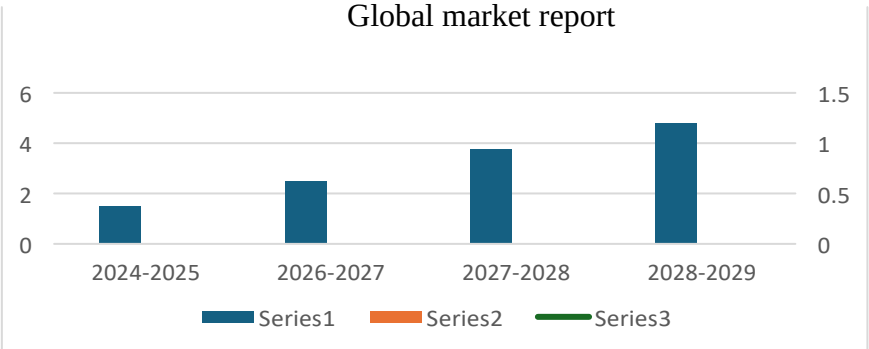
Alzheimer's disease (AD) is a chronic, progressive neurodegenerative condition and remains the primary cause of dementia across the globe. Clinically, it is manifested by a gradual deterioration in memory, thinking abilities, and behavioural functions, which progressively interfere with everyday activities and independence. Since its first description by Alois Alzheimer in 1906, the disorder has become one of the greatest health challenges associated with population aging and increased life expectancy.[1][2] At the neuropathological level, AD is defined by the abnormal accumulation of extracellular β-amyloid plaques, intracellular tangles of hyperphosphorylated tau protein, disruption of synaptic integrity, and widespread neuronal death. These alterations predominantly affect the hippocampus and cortical regions, which are essential for memory processing and higher cognitive functions.[5][6][7] The prevalence of AD increases sharply with advancing age. According to recent estimates from the World Health Organization, more than 55 million people worldwide currently live withdementia, and Alzheimer's disease accounts for about 60–70% of these cases. Approximately 10million new cases are diagnosed every year, and projections indicate that the number of people affected by dementia will climb to 78 million by 2030 and nearly 139 million by 2050. Furtheranalyses suggest that in eight major economies, Alzheimer's disease cases are expected to grow from 15.99 million in 2023 to 22.51 million in 2033, with an annual growth rate exceeding 4%. Despite significant scientific progress, no curative treatment for Alzheimer's disease exists. Currently available therapies are limited to symptomatic management and modest slowing of disease progression.[6][8][9] This reality underscores the urgent need for novel therapeutic strategies, early diagnostic biomarkers, and preventive Approaches. In view of the substantial personal, social, and economic burden caused by Alzheimer's disease, it is essential to critically review its underlying mechanisms, diagnostic advances, and therapeutic developments. This article aims to provide an updated perspective on current knowledge while also exploring emerging opportunities for effective intervention.[10][12][13]

TABLE: Alzheimer's affecting world wide.



Alzheimer's disease treatment Global market report 2025

Globally Alzheimer's disease treatment expense going to increases double by the upcoming four years.



In Billion dollars

years	$ billion
2025	5.93
2026	6.42
2027	6.87
2028	7.46
2029	8.35

1. Alzheimer's impact on aging

Alzheimer's disease (AD) is an irreversible neurodegenerative condition strongly linked to aging and stands as the leading cause of dementia. Current understanding of AD emphasizes the abnormal processing of amyloid precursor protein (APP), which results in the accumulation of harmful amyloid-β (Aβ) deposits in the brain.[13][14][15] Despite extensive research, treatment options remain limited, largely due to incomplete knowledge of its underlying causes and the influence of environmental factors. Recently, lifestyle choices—particularly diet—have drawn growing attention for their possible role in brain health. One dietary pattern under scrutiny is the Western diet (WD), known to contribute to age-related disorders. This study aimed to determine whether metabolic imbalances triggered by WD could speed up brain inflammation and amyloid formation during the early stages of AD.[19][20][23] For this, transgenic mice carrying human APP mutations associated with AD were fed WD starting at three months of age. Their outcomes were compared withAPPswe mice subjected to short-term inflammation through lipopolysaccharide (LPS) injection and with untreated APPswe controls. Analyses were carried out when the animals were 4, 8, and 12 months old. At 4 and 8 months— representing early pre-plaque phases—WD-fed mice already showed clear brain changes.[23][24][25] By 4 months, they displayed heightened astrocyte activity (astrogliosis) like that triggered by LPS treatment, while at 8 months, activation of microglia was also evident. Importantly, WD exposure accelerated Aβ buildup, detected as early as 8 months. These neurological alterations coincided with metabolic disturbances, including elevated cholesterol levels at 4 months, progressing to severe hypercholesterolemia and fatty liver disease by 8 months.[28][29][32]

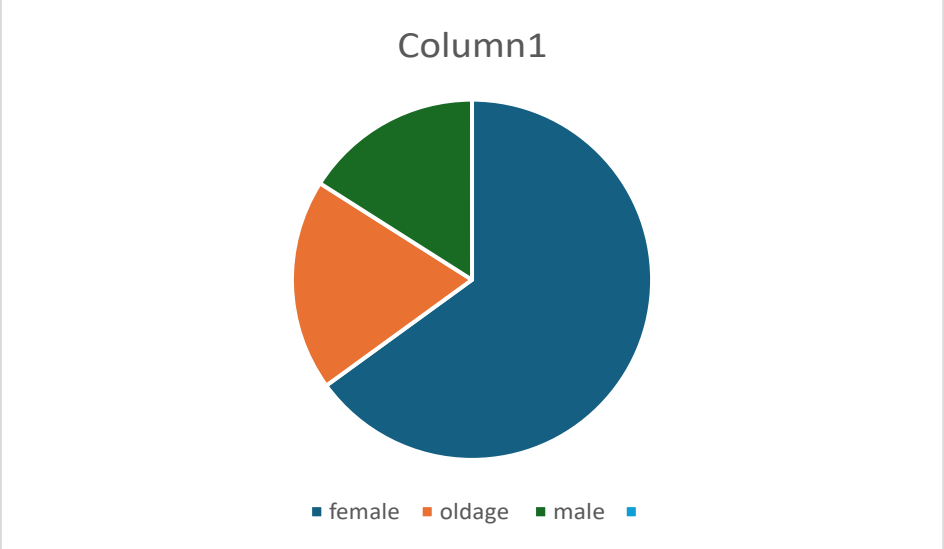
Overall, the findings highlight that a Western-style diet acts as a significant, modifiable risk factor for AD. In contrast, adopting a healthy and balanced diet may be one of the most effective strategies for reducing the risk and slowing the progression of this devastating disorder.[33][37][39]

1.1 Table

Age group In years	Europe 2000	USA 2007	CHINA 2007	BRAZIL 2008
65-69	1.5	1.0	0.5	2.0
70-74	2.0	2.0	1.0	2.5
75-79	3.0	4.0	2.5	7.0
80-84	8.0	10.0	6.0	13.0
85-89	17.0	22.0	15.0	21.0
90+	22.0	30.0	20.0	23.0

Alzheimer's also effects more female population than males. The single biggest risk factor for Alzheimer's is age. Women, on average, live longer than men. Because they survive into the age groups where Alzheimer's is most common, their chances of developing the disease are naturally higher.[43][44][45] Estrogen, the primary female hormone, plays a protective role in the brain. It supports memory, learning, and communication between brain cells. After menopause, estrogen levels drop sharply, and this loss may leave the brain more vulnerable to changes that lead to Alzheimer's. Research suggests that women may accumulate more of the harmful proteins—amyloid plaques and tau

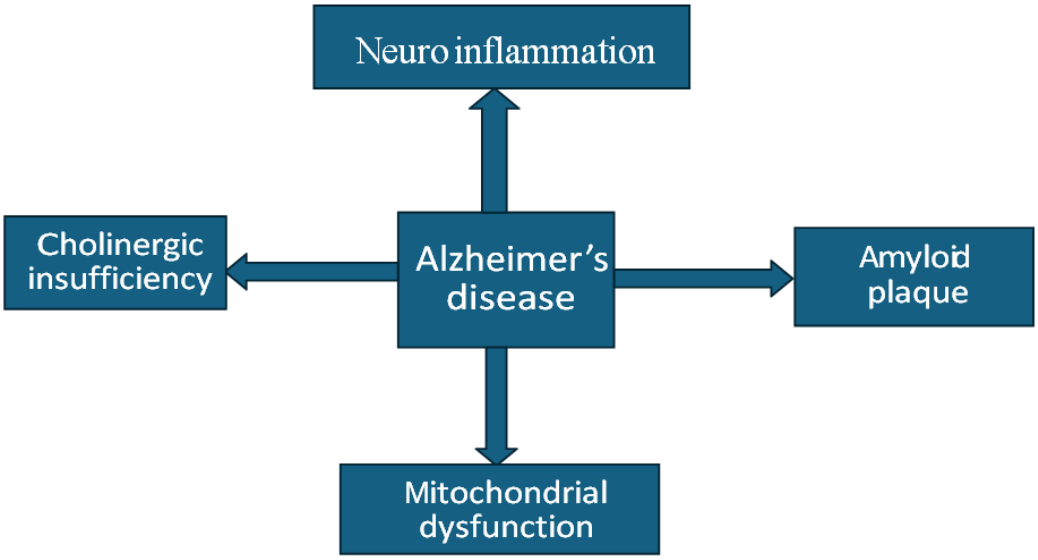
tangles—that damage brain cells in Alzheimer's. This biological difference could partly explain the higher prevalence in females.[46][47][49]



2. Etiology of Alzheimer's disease

The causes of Alzheimer's disease (AD) are highly complex, and scientists still do not fully understand the exact mechanisms behind its onset. While the buildup of amyloid-β (Aβ) plaques and tau tangles are central to the disease, many other biological factors are thought to contribute. These include reduced acetylcholine levels, chronic neuroinflammation, oxidative stress, imbalance of essential brain metals, disrupted glutamate signalling, insulin resistance, gut microbiome changes, cholesterol imbalance, mitochondrial dysfunction, and problems with cellular waste clearance (autophagy).[45][46][55] Collectively, these factors not only influence how the disease develops but also serve as important foundations for diagnosis and treatment. Biomarkers are particularly valuable in this context—they help detect AD in its earliest stages, track disease progression, and evaluate how well drugs are working. Theories around these pathogenic factors have also guided drug development. However, finding effective treatments has proven extremely challenging. For example, the first approved drug, tacrine, had to be withdrawn due to liver toxicity.[54][55][56] Current medications such as donepezil, rivastigmine, galantamine, memantine, and the combination drug namzaric can help ease or stabilize symptoms for a time but do not halt the disease's long-term progression and often cause side effects. Recently, new therapies such as sodium oligomannate (GV-971), aducanumab lecanemab, and donanemab have been developed with the aim of slowing or altering the course of the disease. Although promising, their full clinical impact is still being assessed. More than a century has passed since AD was first identified in 1906, and while our understanding of its biology, diagnostic tools, and treatment approaches has advanced greatly, current options still fall short of fully addressing the devastating decline in memory and cognition. This review therefore focuses on the interconnected framework of AD research—prevention, diagnosis, and treatment. t explores the mechanisms driving the disease, the role of biomarkers, clinical trial progress, and the potential of next-generation small-molecule drugs. Importantly, it emphasizes the urgent need for safer and more effective therapies. Innovative approaches—such as selective inhibitors, dual-target inhibitors, allosteric modulators, covalent inhibitors, PROTACs, and protein–protein interaction modulators—offer exciting possibilities to transform scientific discoveries into real clinical benefits for patients.[55][59][60][61]

2.1 figure



3. Causes and risk factor

3.1 Amyloid beta plaque deposition

One of the most influential explanations for Alzheimer's disease (AD) is the amyloid beta (Aβ) hypothesis, first introduced by John Hardy and David Allsop. This theory suggests that the buildup of Aβ is the initial trigger for a chain of damaging events in the brain, including the formation of neurofibrillary tangles, neuronal death, vascular problems, and ultimately dementia. Aβ peptides are produced when a larger protein, known as the amyloid precursor protein (APP), is cut by enzymes. Normally, this process is harmless and produces fragments important for nerve cell function.[33][35] However, when β-secretase (BACE) first cuts APP at the N-terminal site, it generates a fragment called sAPPβ and leaves behind a carboxy-terminal segment (CTF99/89). This fragment is then cleaved by γ-secretase, producing different Aβ peptides, mainly Aβ40 and Aβ42. Among these, Aβ42 is longer and has a higher tendency to clump together. While large plaques of Aβ are well-known features of AD,research now points to Aβ oligomers— small clumps of Aβ peptides—as the more harmful form. These oligomers interfere with nerve cell communication and damage synapses, leading to cognitive decline.[45][46][47][48] The exact reason why Aβ begins to accumulate is not fully understood, but genetics plays a critical role. Mutations in the genes for APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have been linked to rare cases of early-onset, inherited AD. These mutations often shift the balance of Aβ production, favouring the longer Aβ42 form that aggregates more easily. For example, certain APP mutations increase Aβ42 oligomer formation, speeding up disease progression. In total, about 25 known APP mutations can cause autosomal dominant AD, each influencing the ratio of Aβ42 to Aβ40 and the way peptides aggregate. Mutations in PSEN1 (chromosome 14) and PSEN2 (chromosome 1) also alter the way APP is processed, again leading to excess Aβ production. Beyond these rare familial cases, the apolipoprotein E (APOE) gene is the most important genetic risk factor for the more common late-onset AD. Located on chromosome 19, APOE exists in three main forms—ε2, ε3, and ε4. Carrying the ε4 version significantly raises the likelihood of developing AD. One copy of ε4 increases the risk, while two copies make it much higher. APOE ε4 not only encourages Aβ to build up but also slows its removal, while promoting inflammation and greater neuronal injury.[66][67] Together, these findings strongly support the amyloid hypothesis, highlighting how genetic mutations and risk factors influence Aβ production, aggregation, and clearance, ultimately driving Alzheimer's disease. However, when overwhelmed, they become overactive, releasing inflammatory

signals that damage neurons. This figure highlights possible therapeutic strategies: preventing or treating infections that trigger Aβ buildup, blocking excessive inflammasome activity, enhancing fibril uptake by microglia, improving their ability to degrade Aβ, and reducing harmful overactivation. By supporting microglia in this balance, researchers aim to slow Alzheimer's progression and protect brain health.[45][46][47]

3.2 Tau hypothesis

Tau, a protein that helps stabilize microtubules inside brain cells, does not stay in its raw form. Like many proteins, it undergoes several post-translational modifications—changes that happen after it is made. These include phosphorylation, glycosylation, ubiquitination, glycation, polyamidation, nitration, truncation, and aggregation. Among all these, phosphorylation of tau is most closely tied to Alzheimer's disease (AD).[28][66][67] Scientists discovered as far back as 1977 that tau is a phosphoprotein—meaning phosphate groups can attach to it.[12][51][61] A few years later, Lindwall and Cole showed that when tau is phosphorylated, its ability to help microtubules assemble is reduced. This finding became crucial when researchers realized that the main component of the twisted fibers (paired helical filaments, or PHFs) inside Alzheimer's brains was abnormally hyperphosphorylated tau. In a healthy brain, tau carries about 2–3 phosphate groups per molecule. But in Alzheimer's, tau is 3–4 times more phosphorylated, with more than 40 phosphorylation sites identified so far. Differentphosphorylation sites affect tau differently: At positions like Ser262, Thr231, and Ser235, phosphorylation reduces tau's ability to bind to microtubules by 10–35%. At sites like Ser199/Ser202/Thr205, Thr212, Ser262/Ser356, and Ser422, phosphorylation transforms tau into an "inhibitor" that pulls normal tau and other microtubule proteins (MAP1, MAP2) away from microtubules.[4][17][41] Phosphorylation at Thr231, Ser396, and Ser422 promotes tau's tendency to clump into filaments. Mutations that mimic phosphorylation at Ser396, Ser404, or Ser422 make tau even more likely to form fibrils. phosphorylation in certain regions gradually weakens tau's normal stabilizing function while encouraging it to aggregate. When tau is phosphorylated in the proline-rich region, it only moderately affects microtubules.[16][34][37] But when phosphorylation occurs at the C-terminal tail and binding regions, tau nearly loses its ability to support microtubules and instead begins to disrupt them. Interestingly, the story does not end with tau simply "losing function." Tau knockout mice—genetically engineered to lack tau—do not show major defects, suggesting that other proteins can compensate.[3][7][28] Instead, the real problem in Alzheimer's seems to be a toxic gain of function: hyperphosphorylated tau not only fails to support microtubules but also actively damages cells by sequestering normal tau and other MAPs. Importantly, if hyperphosphorylated tau is dephosphorylated, it loses this toxic ability. For years, researchers believed that neurofibrillary tangles (NFTs)—the visible clumps of tau in Alzheimer's brains—were the main culprits behind dementia. This made sense because the number of NFTs correlated with dementia severity. But more recent evidence suggests the opposite: the smaller, Soluble forms of abnormal tau (oligomers) may be more toxic than the large tangles.[15][22][56]

3.3 Neuroinflammation

Microglial cells are often called the resident macrophages of the brain—they act like immune guardians, constantly scanning the environment to keep things balanced and safe. Under normal conditions, they are neuroprotective: they help maintain homeostasis, support metabolism, and even fine-tune synaptic plasticity, which is essential for learning and memory. But this protective role has a flip side.[6][13] When microglia encounter harmful triggers—such as toxins, genetic changes, or infections—they switch into an activated state. Instead of protecting, they begin releasing inflammatory molecules and contribute to neuroinflammation, a process linked to Alzheimer's disease (AD) and other brain disorders. Research shows that this over-activation of microglia does not just play a role in Alzheimer's.[51][53][62]

It also contributes to depression, dementia, and cognitive decline. One reason this becomes more important with age is that microglia in older brains behave differently than those in younger ones.[62] For example, studies on mice have shown that aged microglia release higher levels of pro-inflammatory cytokines like IL-6 and TNF-α, while also losing some of their ability to clear harmful proteins such as amyloid-β (Aβ). They also show reduced antioxidant defences, such as lower glutathione levels. In short, microglia in older individuals are more "primed" to overreact, making the brain more vulnerable to inflammation and damage.[49] It is not that microglia fundamentally change with age, but rather that they respond more strongly to certain signals, such as interferon-gamma (IFN-γ). This exaggerated response pushes them toward a pro-inflammatory state, which, over time, contributes to neurodegeneration and cognitive dysfunction. microglia exist in two main functional states: M2 microglia – protective and supportive.[57][64] They clear debris, provide nutrients, and help preserve synaptic plasticity. M1 microglia – inflammatory and damaging. They release proinflammatory cytokines, impair synaptic connections, and contribute to neuronal injury.[88][54][74][76] The problem in Alzheimer's and aging is that microglia tend to shift more toward the M1, neurotoxic state. This has made scientists think of new treatment strategies: if a drug could prevent microglia from switching from M2 to M1, or calm down excessive activation, it might serve as a powerful neuroprotective therapy. microglia are like the brain's firefighters— but as we age, they become more like overreactive fire alarms, setting off unnecessary inflammation that damages the very system they are meant to protect.[3][12][21][38]

3.4 Glutamate toxicity

Glutamate is one of the most important neurotransmitters in the brain. Often called the brain's "excitatory messenger," it plays a central role in communication between neurons, learning, and memory. In normal amounts, glutamate is essential for healthy brain function. But when its levels become too high or uncontrolled, glutamate can turn from friend to foe, leading to what is known as excitotoxicity.[41][43][61] In Alzheimer's disease (AD), glutamate toxicity has emerged as a key factor in the cascade of events that damage neurons. Normally, after glutamate is released at the synapse, it is quickly cleared away by transporters, preventing overstimulation. In AD, however, this balance is disrupted. Amyloidβ deposits, oxidative stress, and inflammatory changes impair glutamate uptake, leading to excess glutamate lingering around synapses.[12][25][27][33][39] This persistent glutamate overstimulates NMDA receptors (N-methyl-D-aspartate receptors), which are normally responsible for controlled calcium entry into neurons. But under excitotoxic conditions, these receptors allow too much calcium to flood the cell, triggering a harmful chain reaction: Activation of destructive enzymes, Mitochondrial dysfunction, Increased free radicals and oxidative stress Progressive neuronal injury and death.[44]

Over time, this glutamate-driven excitotoxicity contributes to the loss of synapses and neurons that characterizes Alzheimer's disease, especially in areas critical for memory and cognition, such as the hippocampus. Interestingly, glutamate toxicity not only damages neurons directly but also interact with other pathological processes.[45][62][63] For example, excessive glutamate can worsen amyloid-β toxicity and tau phosphorylation, creating a vicious cycle that accelerates neurodegeneration. Because of this, glutamate regulation has become a therapeutic target. One well-known drug, memantine, works by partially blocking NMDA receptors. Unlike a full blocker, which would disrupt normal brain activity, memantine gently reduces the overactivation caused by excess glutamate, protecting neurons while allowing normal signaling to continue.[66]

3.5 Reactive astrocytes

Alzheimer's disease (AD) has long been viewed as a disorder centered on neurons, but in recent years, attention has shifted toward astrocytes—the star-shaped glial cells that support and protect neurons. Far from being passive bystanders, astrocytes undergo significant changes in AD, and their dysfunction contributes to the progression of the diseases.[17][31][40][51] Three major processes—apoptosis, ferroptosis, and senescence—define how astrocytes lose their normal roles and begin to harm rather than help the brain. One of the most striking features observed in AD brains is astrocyte apoptosis, or programmed cell death. In healthy conditions, apoptosis helps maintain balance by removing damaged cells. In AD, however, large numbers of astrocytes undergo apoptosis, particularly in brain regions like the temporal lobe.[22][29] These apoptotic astrocytes can be detected through DNA fragmentation and markers such as TUNEL positivity. Their degeneration often correlates with the presence of amyloid plaques, suggesting that astrocyte death and amyloid accumulation are closely linked. Elevated levels of caspase-3, a key executioner enzyme in apoptosis, further underscore the role of programmed astrocyte death in Alzheimer's pathology. Another pathway by which astrocytes are lost is ferroptosis, a form of iron-dependent, oxidative cell death. Unlike apoptosis, ferroptosis is driven by the toxic accumulation of lipid peroxidation products, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). Both human AD brains and animal models show increased numbers of astrocytes undergoing ferroptosis, along with elevated expression of NOX4, an enzyme that promotes oxidative stress.[55][67][71] In mouse models, genes tied to ferroptosis— including Ireb2, Cs, Rpl8, and Ptgs2—are upregulated, pointing to a genetic and biochemical basis for this destructive pathway. Since oxidative stress is already a well-established hallmark of AD, ferroptosis appears to be a central mechanism by which astrocytes contribute to neuronal injury. Beyond cell death, astrocytes in AD also undergo cellular senescence, a process where cells stop dividing, accumulate damage, and adopt a pro-inflammatory profile.[51] Senescence is a hallmark of aging—the greatest risk factor for Alzheimer's disease—and links the natural aging process to neurodegeneration. In the brains of AD patients, senescent astrocytes express high levels of p16INK4a (CDKN2A), a classic marker of aging.[11][19][29][33][47] They also show evidence of DNA damage, particularly through γH2AX, which appears in response to chromosome breaks. Animal studies support these findings: in transgenic mice that model tau pathology, astrocytes display increased senescence-associated gene expression.[60] Remarkably, when senescent astrocytes are selectively removed using nonlytic drugs like ABT263, tau pathology is reduced, highlighting the therapeutic potential of targeting cellular senescence. Taken together, these studies show that astrocytes in Alzheimer's disease are not mere spectators but active participants in neurodegeneration.[55][59][60] Through apoptosis, ferroptosis, and senescence, astrocytes lose their ability to support neurons and instead contribute to inflammation, oxidative stress, and synaptic failure. This shift in perspective reframes Alzheimer's as a disease not only of neurons but also of their supporting glial network.[17][28][45]

Alzheimer's disease: Treatments and Therapeutic Indices

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory impairment, cognitive decline, and behavioural disturbances.[44][56][61] The hallmark pathological features include extracellular amyloid-β plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Despite decades of research, therapeutic options remain limited, and most available agents provide only symptomatic relief rather than halting disease progression (Yiannopoulos & Papageorgiou, 2020).[31][34][52]

4. Symptomatic pharmacologic therapies

4.1 Acetylcholinesterase inhibitors (AChEIs)-: Symptomatic pharmacologic therapies

Agents: Donepezil, Rivastigmine, Galantamine. Indication: Mild to moderate AD (donepezil also used in severe disease per label). These agents increase synaptic acetylcholine and modestly improve cognition or slow symptomatic decline in some patients. Typical dosing (examples):

- Donepezil: 5 mg once daily, increasing to 10 mg once daily; some regimens use 23 mg for more advanced disease (label specifics vary).
- Rivastigmine: oral titration or transdermal patch formulations with stepwise titration.
- Galantamine: titrated oral dosing or extended-release formulations.[69]

Major adverse effects / safety: Predominantly cholinergic: nausea, vomiting, diarrhea, bradycardia, syncope; caution with asthma/COPD, urinary obstruction, and certain cardiac conduction disorders.[5][17][61] Therapeutic index (TI) commentary: Published numeric TI values in humans for AChEIs in AD treatment are not commonly reported in the clinical literature. Regulatory documents (FDA labels) and pharmacology reviews instead describe safety margins, observed adverse event rates, and dose-dependent tolerability. For clinical use, titration and monitoring of adverse events are the primary strategies to maintain an adequate safety margin.[26][27]

4.2 Memantine (NMDA receptor antagonist)

Agent: Memantine. Indication: Moderate to severe Alzheimer's disease (as monotherapy or combined with an AChEI).[51][63] Memantine is an uncompetitive NMDA receptor blocker that modulates pathological glutamatergic excitotoxicity. Typical dosing: Titrated to 10 mg twice daily (IR) or equivalent extended-release dosing per label.[23] Major adverse effects / safety: Dizziness, headache, confusion, constipation; generally considered to have a favorable tolerability profile at therapeutic doses. TI commentary: Like AChEIs, a single human TI number is rarely provided; regulatory labeling provides clinical safety data and toxicology summaries from which clinicians infer the therapeutic window. Clinical trials and post-marketing experience inform practical safety margins.[54][63][71]

4.3 Disease-modifying (amyloid-targeting) monoclonal antibodies

Agents: Aducanumab (ADUHELM), Lecanemab (LEQEMBI) — both target amyloid-beta with differing trial outcomes and regulatory histories. These agents reduce brain amyloid plaques; clinical benefit is modest and patient selection/safety monitoring is essential. Efficacy summary: Regulatory submissions showed plaque reduction; clinical benefit on cognitive scales is small to modest are mains an area of active discussion and confirmatory trials.[12][31][48] Continued (or traditional) approvals have been accompanied by requirements for confirmatory evidence and guidance on monitoring Major adverse effects / safety: Amyloid-related imaging abnormalities (ARIA), including ARIA-E (Edema/effusions) and ARIA-H (microhaemorrhage's/hemosiderin deposition),are a class safety concern requiring MRI monitoring and careful patient selection (consider ApoE ε4 status).[18][41][51] Recent regulatory updates have adjusted MRI monitoring timing for safety. TI commentary: For monoclonal antibodies, therapeutic index is operationalized via risk-benefit assessment rather than a single numeric TI. Dose selection, incidence of ARIA, and monitoring protocols delineated in prescribing information define safe use. Labelling and regulatory reviews provide detailed safety and monitoring recommendations.[11][29][55]

4.4 Non-pharmacologic & multimodal care

Evidence supports cognitive stimulation therapy, structured physical activity, vascular risk-factor control, sleep optimization, and caregiver support as integral parts of care —these interventions improve quality of life or reduce functional decline and are recommended alongside pharmacologic treatment. Guidelines emphasize individualized, multidisciplinary management.[14][15]63]

4.5 Therapeutic-index practical guidance for authors

Numeric TI data are rare for AD drugs in humans. Instead, reviewers should cite: (a) clinical trial adverse-event rates, (b) FDA prescribing information (safety sections), and (c) pharmacology/toxicology reviews that describe preclinical safety margins.[7][26][35]

When discussing "narrow" vs "wide" therapeutic index, use regulatory language (Dose-dependent adverse event profiles, need for titration, and monitoring requirements) rather than invented TI numbers. For disease-modifying antibodies the key safety metric is ARIA incidence and severity, tied to dosing and Apo Egeno type.[19][43][44]

CONCLUSION

Based on the review Alzheimer's disease remains complex and challenging issue among neurodegenerative diseases to understand and treat it's pathogenesis. Alzheimer's involves multiple interconnected mechanisms, including amyloid-beta plaque accumulation, tau protein hyperphosphorylation, oxidative stress, mitochondrial dysfunction, and neuroinflammation interpreting one reason alone is not commencing its onset; indicating multifactorial issue dependent upon genetic correlation age factors and environment Existing treatments giving symptoms relief via enzymatic inhibitions and NMDA receptor antagonists with limitations of not able to stop progression of neuronal damage. New therapeutic methods such as monoclonal antibodies targeting amyloid-beta, tau aggregation inhibitors, and anti-inflammatory agents indicating promising approaches but still need further evaluation on large-scale based clinical practices. There is also need of increased awareness campaigns, and support to research financial support for deeper investigations for more understanding, early diagnosis, and the development of more effective treatment strategies.

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