Initiating Early Intervention Through Biomarker Targeted Therapies to Slow Alzheimer's Disease Progression

Bhumi Rao

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Alzheimer's disease (AD) is a common form of dementia that affects approximately one in nine people in the United States over the age of 65. As AD progresses, patients experience symptoms of dementia including increased deficits in memory and problem-solving abilities, as well as behavior changes that result from severe neuronal death. Although specific causes of the disease remain unknown, AD is primarily characterized by abnormalities in two proteins: amyloid beta (Aβ) and tau, which can appear up to years before the onset of dementia symptoms. Because of the early appearance of protein biomarkers, it is important to initiate early intervention of AD– to target tau and Aβ before significant neuronal death and cognitive decline associated with later stages of AD. Current interventions largely target late-stage AD, resulting in only symptomatic alleviation rather than slowed disease progression. Some drugs such as Aβ-targeting antibodies are currently on the market and are able to slow AD progression, but still cause many adverse effects in patients. Due to the shortcomings of current interventions, further research and development of therapies targeting Aβ and tau protein in the early stages of AD to slow disease progression is necessary. Future interventions are currently being developed to target these biomarkers early on, and hold promising results for the future of AD. Developing medications that target Aβ and tau protein in early-stage AD can lead to slowed disease progression and symptom onset, resulting in a better quality of life for AD patients.

Key terms: Alzheimer's disease (AD), early intervention, amyloid beta (Aβ), tau, neurofibrillary tangles (NFT), mild cognitive impairment (MCI), positron emission tomography (PET), neurofilament light chain (NfL)

1 Introduction

AD is a neurodegenerative disease characterized by progressive cognitive decline. AD progresses in stages. Early stages of AD include preclinical AD, in which patients exhibit no symptoms, and AD characterized by mild cognitive impairment (MCI), which is a slight decline in an individual's memory and thinking abilities, but not enough to interfere with daily life. MCI is a clinical diagnosis based primarily on cognitive symptoms, while early AD diagnosis is based on both clinical signs and the presence of AD-specific biomarkers. Late-stage AD is characterized by the onset of dementia. In this stage, patients encounter severe difficulties with memory and language abilities [1,2]. Most patients are diagnosed and treated in late-stage AD. However, current late-stage AD treatments are only able to target symptoms of AD rather than the neuropathological changes associated with AD, such as the formation and aggregation of Aβ plaques and NFTs. These treatments are unable to slow AD progression due to significant neuronal death in late-stage AD.

However, new diagnosis strategies and treatments that target AD biomarkers in early stages of the disease, such as the presymptomatic and MCI stages, are changing the field of AD treatment because they are able to slow disease progression unlike previous late-stage treatments. There are two primary protein hallmarks of AD which early-stage treatments target-amyloid-beta plaques, composed of Aβ protein and neurofibrillary tangles (NFT) composed of tau protein [3,4]. These biomarkers can appear in early-stage AD, several years before the onset of cognitive symptoms, and can be detected through positron emission tomography (PET) and various blood tests. Treating AD by targeting biomarkers in early-stage AD has the potential to slow disease progression before the onset of severe cognitive symptoms, unlike late-stage treatments that have been used in the past and have been largely ineffective [5].

Interventions such as some Aβ targeting antibodies including lecanemab and donanemab have been approved by the FDA for use in early stage AD. Although they have demonstrated high efficacy in clinical trials, Aβ targeting antibodies continue to have widespread adverse effects [6]. Other drugs such as cholinesterase inhibitors have also been approved for use in early stages of AD, but do not target biomarkers of AD, making them ineffective for slowing disease progression. Because biomarker targeting interventions have proven to be more effective at slowing disease progression, several antibodies, vaccines and other treatments are currently being developed to slow disease progression in

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early-stage AD pateints. These interventions largely target tau and Aβ and hold promising results for the future of early-stage AD treatments[7]. However, there are still many research gaps in early-stage AD and possible intervention methods due to the uncertainty regarding the exact neuropathological causes of AD, and the difficulties surrounding the diagnosis of early-stage AD. More research in this area will allow for a better understanding of how to slow or prevent cognitive decline before significant neuronal death to improve the quality of life for AD patients and possibly reverse or prevent disease progression.

This review outlines the biomarkers associated with early-stage AD and how imaging techniques can detect these biomarkers to diagnose AD in early stages. The review then considers current late-stage AD drugs and evaluates their inefficacy in comparison to early-stage AD drugs, which target AD biomarkers. Lastly the review examines several early-stage treatments for AD that are currently approved and still under development, which hold a promising future for the slowing of AD progression. By analyzing biomarkers present in early-stage AD and current and future early interventions, this review aims to address the current gap in literature regarding early AD intervention to highlight the need for these interventions and stimulate further research.

2 Methods

This manuscript reviews primary research papers covering the biomarkers involved in AD, current intervention methods and future interventions. Literature searches were conducted largely through Pubmed, although some references were found through Google Scholar. Clinical trial searches were also conducted on clinicaltrials.gov to identify clinical studies that have been conducted to support the efficacy of drugs that were mentioned in the early and future intervention sections. Searches on pubmed were conducted through the use of keywords such as "Alzheimer's disease" and "early interventions" as well as "amyloid beta" and "tau" and "MCI". Papers published before the past five years were excluded. Key findings regarding study results and drug efficacy were included in the review. Keywords utilized to search for clinical trials on clinicaltrials.gov were names of various AD drugs such as "lecanemab" and "donanemab" and all other included interventions. Clinical trials involving patients with severe AD were excluded.

3 Early biomarkers and disease progression

In spite of substantial research that has been done in the field, the primary driving factors of AD remain unknown due to the complex interplay of various genetic, environmental and molecular factors that contribute to its pathogenesis. However, current research holds that the most common neuropathological hallmarks of AD are amyloid plaques and NFTs, composed primarily of abnormal accumulation of Aβ protein and tau protein, respectively[8]. Misfolding and self-assembly of extracellular Aβ deposits results in the formation of aggregates in neural tissue in the brain and cerebral vasculature leading to neuronal loss and synaptic dysfunction[9]. CSF Aβ is the most sensitive biomarker for AD and has a sensitivity of around 96.4% for AD detection[10]. NFTs are the result of hyperphosphorylation, resulting in abnormal buildup of tau proteins as they detach from microtubules, leading to neuronal damage[11]. Because of this, tau levels are elevated in individuals with AD, and total tau in the CSF has a sensitivity and specificity of approximately 90%[12]. Additionally, blood-based biomarkers such as Aβ42 and p-tau are present in the plasma and can serve as highly specific minimally invasive biomarkers, with sensitivity levels of approximately 88% and 79% respectively and specificity levels of 81% and 94% respectively, in patients with MCI[13]. Another blood-based biomarker, neurofilament light chains (NfL) located in the plasma can serve as a biomarker for axonal damage and is associated with AD[14]. Due to their role in maintenance of axon structure, NfLs are commonly present in higher levels in individuals with neurodegenerative disease, such as AD, which is characterized by axon degeneration[15]. However, although they are correlated with AD and have proven to, these biomarkers are associated with several uncertainties due to a variety of external factors being able to influence tau, Aβ and NfL levels within the CSF and plasma. Additionally, there still remains high variability in biomarker measurements among and within laboratories, meaning that there is still uncertainty regarding universal cut-off values for AD biomarkers[16].

Detection through PET screening allows for clear visualization of location and severity of Aβ and tau aggregates in the CSF allowing for targeted early intervention[17]. Radiotracers such as F-FDDNP are used to detect both NFTs and amyloid plaques and can be used to quantify AD. The most common radiotracer for detecting Aβ plaques, 11C-PiB has a high affinity, selectivity and specificity to fibrillary Aβ, allowing for the visualization of Aβ in the neural tissue[18]. Additionally, the radiotracer [18F]-flortaucipir was recently approved by the FDA to be used to detect tau pathology in the neural tissue. In a diagnostic study involving terminal illness patients with varying degrees of dementia, [18F]-flortaucipir was able to successfully detect NFTs in patients with and without dementia, with high sensitivity levels of 92.3% to 100.0%, indicating that it can be used to detect neuropathological changes associated with AD, in both early and late stages[19]. Due to high sensitivity levels and affinity towards AD biomarkers in the CSF, PET screening should be utilized to screen patients for AD pre-symptomatically or during MCI to allow for interventions to be administered before significant cognitive decline occurs.

Because PET scans are expensive and may not be accessible to everyone, alternative diagnostic tests for early-stage detection

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of AD include blood tests, which target blood-based biomarkers, and are generally more cost effective and accessible than other imaging techniques. The Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio is the first diagnostic blood test for AD and was recently FDA approved for detection of AD in patients demonstrating symptoms, including those with MCI. The Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio is used to detect pTau217 and Aβ 1-4 in the human plasma[20]. Because this blood test can successfully detect tau and Aβ in the plasma of early-stage AD patients with MCI, and is minimally invasive, it serves as a useful tool for detection and intervention of early AD.

Both tau and Aβ deposition, measured through PET can appear up to two decades prior to severe cognitive symptoms in individuals with AD[21 22]. Individuals tested for cerebrospinal fluid (CSF) and blood biomarkers such as Aβ tested positive without demonstrating any cognitive symptoms, indicating that AD occurs in stages separately characterized by Aβ formation and aggregation and symptom onset, which occurs later[23]. Similarly, NFTs, although less commonly than Aβ, can appear pre-symptomatically as CSF tau protein concentration has been shown to increase up to fifteen years prior to symptom onset in autosomal dominant AD patients[24]. Tau oligomers, which are the small soluble forms of tau proteins, also appear early on in AD, several years before onset of dementia symptoms[25]. When using PET scans to detect tau positivity, approximately 46.5% of MCI AD patients with Aβ positivity were also tau PET positive in the temporal meta-region of interest, regions in the neural tissue with elevated tau-PET levels in AD[26]. Additionally, NfLs increase in the CSF and plasma ten to twenty years before symptom onset in AD patients[27]. The appearance of protein biomarkers such as Aβ, tau aggregates and NfL in early-stage AD illustrates the need for intervention strategies earlier in disease progression.

As AD progresses past its early-stages, biomarker concentration in the blood and CSF can begin to plateau. Aβ has higher accumulation rates in earlier stages as it follows a sigmoidal time function in individuals with AD[28]. After rapidly increasing, Aβ levels in the CSF level off as AD pathology increases in a preclinical AD model[29]. This plateau in Aβ deposition at a later age demonstrates that aggregation and growth of protein biomarkers occurs in earlier stages and plateaus in later stages of neurodegeneration, roughly around the same time cognitive symptoms arise in AD patients. Tau deposition spreads across the brain as AD progresses[30]. Earlier stages of AD in which individuals remain cognitively unimpaired are marked by tau protein aggregation in the transentorhinal cortex region of the brain, indicating that tau protein can act as a biomarker for pre-symptomatic AD[17]. The appearance and accumulation of AD biomarkers well before cognitive decline arises implies that AD pathogenesis largely occurs pre-symptomatically, signifying a need for intervention in early-stage AD, when Aβ and tau biomarker formation is occurring. This will allow for the prevention of the neuronal dysfunction and death associated with Aβ and tau aggregates.

4 Downfalls of treating AD in later stages

There are various downfalls to initiating intervention of moderate to severe AD, emphasizing the need for early treatment. Current treatments such as memantine that are given to late-stage AD patients are only able to target symptoms of AD rather than the neuropathological changes that are associated with AD. Treatments that are given to late-stage AD patients typically target chemicals and neurotransmitters involved in memory and cognitive function rather than protein biomarkers that appear in earlier stages such as Aβ and tau[31]. Memantine acts as an antagonist to inhibit overexcitation of NMDA receptors, which only provides symptomatic alleviation of AD[32]. When tested on moderate to severe AD patients in a randomized, double-blind, placebo-controlled study, although it relieved some cognitive symptoms of AD such as comprehension, conversation and ability to follow commands, memantine wasn't successful in slowing disease progression, indicating synaptic dysfunction and neuronal death continued to occur. Disease progression occurred at the same rates as placebo patients in the control group[33].

Cholinesterase inhibitors prevent the breakdown of acetylcholine[31] (Figure 1). These drugs, although primarily prescribed to early-stage AD patients, have been shown to have decreased efficacy in late-stage AD patients, proving that initiating intervention in early-stage AD is more effective.

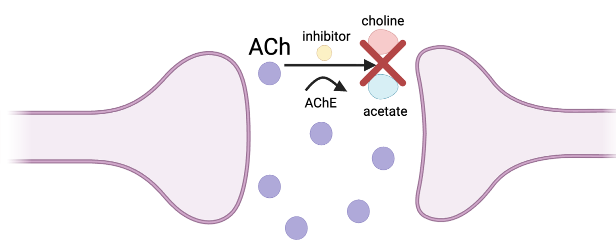

Fig. 1 Mechanism of action of cholinesterase inhibitors

The cholinesterase inhibitor blocks the enzyme acetylcholinesterase (AChE), which inhibits the breakdown of ACh, a neurotransmitter associated with learning and memory, into choline and acetate. This raises levels of ACh in AD patients, allowing for improved learning, memory, and overall cognitive funciton[34]

In an interventional randomized study with 61 participants with late-stage AD and dementia, patients who continued the treatment of cholinesterase inhibitors demonstrated slightly higher scores of cognitive function in a six-item screener. However, AD progression continued at the same rate, indicating that cholinesterase inhibitors are able to reduce symptoms but not stop or slow disease progression altogether when given to late-stage AD patients[35]. Because late-stage AD drugs are only able to slightly reduce cognitive symptoms without targeting AD pathogenesis, early intervention treatment options would be more beneficial as they can target early biomarkers to slow disease progression.

Antidepressant drugs are widely used to target and reduce dementia associated behavioral symptoms of late-stage AD, such as depression, anxiety, and agitation[36]. Sertraline, citalopram, escitalopram, and mirtazapine are few of the commonly used antidepressants among dementia patients. Sertraline, citalopram, and mirtazapine are selective serotonin reuptake inhibitors and mirtazapine is a tetracyclic antidepressant. However in a national cohort study in Sweden with over 18740 patients, antidepressant drugs did not reduce cognitive decline in dementia patients and even showed to be associated with faster cognitive decline, especially in severe dementia patients[37]. Because severe dementia is associated with late-stage AD, late-stage interventions targeting behavioral symptoms such as antidepressants are largely ineffective in controlling disease progression or slowing cognitive decline.

Furthermore, difficulties surrounding treatment of late-stage AD also stem from the issues involving the recruitment and assessment of individuals with moderate to severe AD. Many individuals with late-stage AD and their families are reluctant to enroll in clinical trials because they feel it is too late in the disease trajectory to face any improvements. Patients and families may also experience hesitancy to enroll in trials due to the advanced and meticulous care that late-stage AD patients require[38]. Moreover, individuals with moderate to severe AD face issues with cognition including decision-making problems, lack of cooperation and poor communication skills[39]. This creates difficulty when assessing subjects for late-stage AD treatments, as researchers often rely on cognition tests requiring communication from the patient to evaluate treatment efficacy.

The primary reason as to why late-stage AD treatments are less effective is due to the extent of neuronal damage that has occurred by this stage. Late-stage AD is marked by severe neuroinflammation and microglial activation, which leads to neuronal damage from cytotoxicity[40]. Neuronal damage increases greatly as AD progresses ultimately leading to severe neuronal death and brain atrophy, resulting in the shrinkage of the gyri by over 50%[5]. Because of this extreme neuronal impairment, medications that reduce hallmarks of AD like Aβ plaques and tau aggregates and are administered in late-stage AD patients often cannot reverse the neurodegeneration and cognitive decline that has already resulted from AD progression, as the neural tissue is too-far damaged for these drugs to work. This makes late-stage intervention in AD less beneficial for further research than early intervention, as early intervention can target protein hallmarks of AD before the development of significant neuronal death.

5 Current early intervention strategies

The development of various Aβ-targeting antibodies has helped to treat AD in its early stages[41]. In recent years, two of these antibodies, lecanemab and donanemab have been approved by the FDA for early-stage AD patients. Lecanemab is a humanized monoclonal IgG1 antibody medication that binds to soluble aggregated Aβ protofibrils rather than plaques (Figure 2). In an 18-month, multicenter, double-blind, phase 3 trial involving individuals 50 to 90 years of age with early AD, persons that received intravenous injections of lecanemab showed a significant reduction in cognitive decline compared to placebo treated control patients, indicating slowed disease progression. However, lecanemab is associated with adverse effects like infusion-related reactions and amyloid-related imaging abnormalities (ARIA) with edema or effusions[42]. with higher rates of these side effects occurring in individuals with the APOE4 allele[43]. After 18 months of administration of lecanemab, ARIA occurrences decrease along with dosage in non carriers of APOE4[44]. Additionally, lecanemab may have reduced efficacy in women[45]. Early-stage AD patients are also treated with donanemab, a humanized monoclonal IgG1 antibody that binds to a modified form of Aβ protein, N3pE-Aβ, found in Aβ plaques (Figure 2). In a randomized clinical trial that included 1736 participants with early symptomatic Alzheimer disease and amyloid and tau , individuals that were administered donanemab showed significantly slowed disease progression and improved cognition compared to placebo groups. Groups treated with donanemab had a -6.02 change in score in the integrated Alzheimer Disease Rating Scale, while placebo groups had a change of -9.27, with lower scores indicating worse cognitive function[46]. Long term administration was associated with ARIA, with higher rates in individuals with the APOE4 allele[47]. Although lecanemab and donanemab have demonstrated efficacy clinically, it is important to note that Aβ antibody treatments are considered to be expensive medications and therefore may not be an accessible or affordable treatment option for all early-stage AD patients.

Aβ targeting antibodies, such as donanemab and lecanemab, lead to the degradation of Aβ. Lecanemab binds to the soluble Aβ protofibril before it constitutes Aβ plaque. Donanemab binds to the Aβ plaque itself. Macrophages recognize these antibodies and engulf the Aβ protofibril or the Aβ plaque. It is then degraded in the lysosome of the macrophage, helping clear Aβ build up[48,49].

Cholinesterase inhibitors have also been FDA-approved and are currently being prescribed to early-stage AD patients. However, these drugs do not target the protein biomarkers associated with the neuropathology of AD. Rather, they function by

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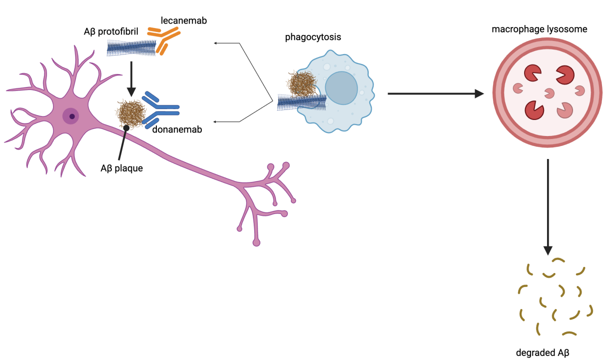

Fig. 2 Antibody based Aβ degradation

preventing the breakdown of acetylcholine by inhibiting acetylcholinesterase[50]. Cholinesterase inhibitors have not been guaranteed to slow disease progression and are instead intended to alleviate cognitive symptoms of AD by helping to restore excitatory neuron function[51]. There are currently three FDA-approved cholinesterase inhibitors for AD: donepezil, galantamine, and rivastigmine. Donepezil is a cholinesterase inhibitor approved for all stages of AD that has shown to enhance cognitive abilities particularly in early-stage AD patients[52]. Galantamine is another cholinesterase inhibitor that is safe and tolerable in early and moderate AD patients, and is available in the form of oral tablets. AD patients given galantamine showed higher cognitive scores than placebo groups[53]. However, there is no distinct evidence demonstrating that galantamine is effective in patients with MCI or early-stage AD[54]. Rivastigmine is available in oral forms and through a transdermal patch intended for patients with early to moderate AD. When tested on patients with early-stage AD with rivastigmine showed slight improvement in cognitive performance[55]. Although these drugs can potentially improve MCI in early AD patients, they do not target Aβ and tau protein aggregation, allowing for continued progression of AD.

In addition to drugs, several behavioral therapies are currently being used in early-stage AD patients. Cognitive stimulation therapy (CST) is a form of behavioral therapy used for early-stage AD and dementia patients to maintain cognitive function and slow cognitive decline[56]. A study on men with mild to moderate dementia to test the overall effectiveness of CST shows that mild dementia groups receiving CST treatment maintained Mini-Mental State Examination (MMSE) and AD Assessment Scale scores, while groups not receiving the treatment had slight decreases in these scores over the period of the study[57]. Additionally, cognitive rehabilitation (CR) is also used as a form of behavioral therapy for early-stage AD patients. CR typically involves the practice of performing specific tasks to improve certain cognitive functions. Early-stage AD patients receiving CR treatment showed significant improvements in quality of life and in the orientation subscale of the MMSE when compared to the control group not receiving the treatment[58].

6 Future early intervention strategies

In addition to FDA-approved drugs that are currently used, several drugs are undergoing development for future treatment of early-stage AD. Because tauopathy is a characteristic of early-stage AD, it is being targeted by various immunotherapy methods for early AD patients. Vaccines aim to induce antibodies that can clear tau protein aggregates. AADvac1is a vaccine intended to produce antibodies that target the microtubule-binding region of tau in patients with increased plasma phosphorylated-tau217 (p-tau) levels. Phase I trial results have shown that AADvac1 is safe and tolerable by patients. Phase II trials indicate that the drug can reduce tau levels; however, overall cognitive function remains unimpacted in AD patients, and further research is required to advance this drug as an early treatment for AD[59]. Another vaccine, ACI-35.030, is engineered to stimulate antibody production against p-tau. It has undergone phase II trials and has shown to be safe when tested on patients AD with MCI. The efficacy of this vaccine is still being tested, however it was able to activate the immune system of subjects between 50 and 75 years with MCI due to AD or mild AD with an antibody response against p-Tau[60]. Virus-like particle (VLP) based immunotherapy vaccines can be used to target p-tau in early AD patients. One of these vaccines, Qβ-PHF1, targets the phosphorylation sites Ser396 and Ser404. Qβ-PHF has been shown to diminish cognitive deficits and reduce soluble and insoluble p-tau and reactive microgliosis in rTg4510 mice[61]. In addition to vaccines, tau aggregation inhibitors are also on the horizon for early AD interventions by directly targeting tauopathy. For example, hydromethylthionine mesylate has been shown to prevent tau aggregation and disaggregate existing NFTs in early-stage AD patients in several phase III trials. This drug can be administered orally and does not present any major safety concerns or adverse effects when taken in low dosages[62]. Another tau aggregation inhibitor, curcumin has shown to reduce soluble tau protein and prevent the formation of NFTs. Using light scattering analysis, it was found that curcumin can bind to adult tau and fetal tau with dissociation constants of 3.3 ± 0.4 and 8 ± 1 μM, respectively, and inhibited the formation of tau oligomers[63].

New drugs in early phases of clinical trials may hold promising results for the slowing of amyloid plaque formation. Remternetug, an experimental monoclonal antibody that targets the pyroglutamate-modified Aβ component of amyloid plaques present in AD, is currently under phase III development. In a phase 1 trial in AD patients with mild to moderate dementia, remternetug was able to reduce Aβ plaques significantly[64].

New interventions on the horizon such as antisense oligonucleotides (ASOs) are being researched. ASOs target RNA transcripts and modify them, which can reduce levels of toxic tau and Aβ protein. ASOs, when tested on cortical neurons differen-

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Treatment	AD Indication (stage)	Status	Efficacy
Lecanemab	Early (MCI)	FDA approved	• Can slow disease progression by binding to Aβ plaques
Donanemab	Early (MCI)	FDA approved	• Can slow disease progression by binding to Aβ protofibrils
Cholinesterase inhibitors	Early to moderate	FDA approved	• Can enhance cognitive function • Cannot slow disease progression
Antidepressants	Early to moderate	FDA approved	• Can reduce behavioral and mood changes • Cannot slow disease progression
Memantine	Late Stage	FDA approved	• Can alleviate certain cognitive symptoms • Cannot slow disease progression
Behavioral therapies (CST, CR)	Early to moderate (MCI)	Approved	• Can increase cognitive function • Cannot slow disease progression
AADvac1	Early (MCI)	Phase II trial	• Can reduce total tau levels • Overall cognitive function remains unimpacted
ACI-35.030	Early (preclinical stage)	Phase II trial	• Able to activate the patients immune system with an antibody response against p-Tau
Qβ-PHF1	Early	Preclinical	• Unknown efficacy in humans • Reduces cognitive decline and soluble and insoluble p-tau in mice
Remternetug	Early	Phase II trial	• Able to reduce Aβ plaques
ASOs (MAPTRx)	Early	Phase II trial	• Able to reduce tau levels

Table 1: Early AD interventions. This table shows various AD interventions, which stage of AD they are used for, their status in the drug approval process and their overall efficacy.

tiated from human induced pluripotent stem cell lines with three copies of the amyloid precursor protein (APP) gene, showed significant decrease in APP[65]. A tau-targeting ASO, MAPTRx, inhibits expression of the microtubule associated protein tau gene. When intrathecal bolus administrations were given to patients with mild AD, dose dependent reduction of total tau levels in the CSF showed to be greater than 50% compared to baseline, 24 weeks after the final dose was administered[66]. This significant reduction in tau levels is promising and demonstrates a need for additional research in RNA therapy to intervene in early-stage AD. Early-stage interventions have proven to be successful in reducing levels of AD protein biomarkers such as Aβ and tau. This indicates a need for further development of drugs and therapies to treat AD in its earlier stages, as these interventions target neuropathological causes rather than symptoms of AD.

7 Discussion

Early appearance and aggregation of Aβ and tau aggregates in the neural tissue of AD patients suggests early interventions targeting and blocking these AD biomarkers may be effective in preventing AD progression. Medications that treat late-stage AD provide only symptomatic relief rather than curing or slowing disease progression. Some current early interventions are less effective in early-stage AD patients and target symptomatic relief,

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such as cholinesterase inhibitors and behavioral therapies. Early interventions such as Aβ targeting antibodies can slow disease progression successfully. However, these antibody interventions are associated with adverse effects especially in individuals with the APOE4 allele. Furthermore, future interventions that are currently under development targeting Aβ and tau aggregates hold promising results in slowing AD progression.

Practitioners should utilize screening techniques such as PET scans and new blood tests, which have higher affordability and accessibility, as ways to detect abnormal Aβ and tau in the CSF and plasma, as potential biomarkers for AD in pre-symptomatic and MCI patients. The administration of Aβ monoclonal antibodies, although expensive, is also advisable to slow cognitive decline in early AD patients.

The ability for new pharmacological interventions to slow AD progression has vast implications for the future of AD treatment. Therapies which target the neuropathological biomarkers of AD, unlike previous symptom-targeting treatments, could improve the lives of AD patients by slowing the onset of cognitive and physical symptoms in late-stage AD. Additionally, slowing disease progression reduces burdens on caregivers and reduces societal costs associated with advanced stages of AD significantly[7], furthering the need for early interventions.

Studies included in this review are largely conducted in western cohorts, particularly in Europe and North America. Although these studies have contributed largely to the understanding of AD and early interventions, it is important to consider that they may not entirely capture the diversity of variables such as age, sex, and ethnicity might influence treatment response and biomarker profiles. Because a majority of AD research is conducted in western cohorts due to higher resource availability and funding organizations, future research can aim to be more inclusive by engaging all populations affected by AD to assess the effects and benefits of early-stage AD treatments in relation to diverse demographic factors[67].

Due to the potential societal and individual benefits of slowing AD progression through the developments of various biomarker-targeting early interventions, more research should be conducted in this area. Further research regarding antibodies which bind to soluble Aβ can stimulate the creation of new monoclonal antibodies that can degrade Aβ aggregates before plaque formation occurs in the neural tissue and cerebral vasculature, with fewer adverse effects than current treatments. Additionally, more research on tau aggregation and its appearance in early-stage AD can help create new vaccines, aggregation inhibitors and antibodies targeting tau tangles. ASOs which target RNA transcripts rather than the proteins themselves can also work to reduce tau and Aβ dysregulation in AD patients. Further research will allow for the creation of new intervention therapies that target protein build up associated with early-stage AD. Other modalities in early development such as stem cell therapies and gene therapies are on the horizon for the treatment of AD in early stages. Stem cell therapies have the ability to replace damaged neurons and target neuroinflammation to reverse AD progression[68]. Gene therapies can alter genes involved in AD pathology to possibly prevent or slow disease onset[69]. These advancements have the potential to ultimately slow AD progression, providing AD patients with new opportunities to restore cognitive function and improve overall quality of life.

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Table 2: Study Summary. This table includes all preclinical and clinical trials, observational studies, longitudinal studies and meta-analysis included in the review. The study name along with year, intervention, participant information, type of study and key findings are mentioned.

Study	Year	Intervention	Participants	Study type	Key findings
PET Imaging With [18F]flortaucipir and Postmortem Assessment of AD Neuropathologic Changes	2020	[18F]-flortaucipir (PET radiotracer)	Terminal illness patients	Diagnostic study	ET imaging with [^{18}F]flortaucipir could be used to identify density and distribution of AD-type tau pathology and \AD neuropathological change
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease	2012	N/A	128 participants with autosomal dominant AD	Prospective longitudinal study	Autosomal dominant AD was associated with a series of changes over decades in CSF AD biomarkers and progressive cognitive impairment
The impact of demographic, clinical, genetic, and imaging variables on tau PET status	2021	N/A	2338 participants (430 Aβ+ AD dementia, 381 Aβ + MCI, 370 non-AD, and 1157 CU)	Meta-analysis	Tau PET positivity in the temporal meta-ROI was 88.6% for AD dementia, 46.5% for MCI, 9.5% for non-AD, and 6.1% for CU
Effect of Memantine on Functional Communication in Patients With Alzheimer's Disease	2009	Memantine	264 participants with moderate to severe AD	Interventional Clinical trial	Improvements in functional communication and language abilities in memantine group. No reduction in disease progression.
Cholinesterase Inhibitor Discontinuation (CID)	2015-2019	Cholinesterase inhibitors	72 participants with dementia AD	Interventional clinical trial	No significant difference in cognitive function/disease progression when cholinesterase inhibitors were discontinued
Antidepressant use and cognitive decline in patients with dementia: a national cohort study	2007-2018	Antidepressants	18740 patients with all levels of dementia	National cohort study	Antidepressant use was associated with faster cognitive decline
Lecanemab in Early Alzheimer's Disease	2022 (18 month)	Lecanemab	Participants 50 to 90 years of age with early Alzheimer's disease	Clinical trial	Lecanemab reduced markers of amyloid in early AD and resulted in less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events

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Spontaneous ARIA-like Events in Cerebral Amyloid Angiopathy–Related Inflammation	2013-2017	Lecanemab/Aβ immunotherapy drugs	113 patients with early AD/ Aβ pathology	Longitudinal observational study	High rates ARIA-like events in Aβ driven diseases treated with antibodies like lecanemab. Higher rates in individuals with APOE4 allele.
Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial	2020-2021	Donanemab	1736 participants with early symptomatic AD	Clinical trial	In participants with early symptomatic AD and Aβ and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in those with low/ medium tau and in the combined low/ medium and high tau pathology population
Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial	2004	Donezepil	Patients with early-stage Alzheimer disease	Clinical trial	Significant treatment benefits of donepezil in early-stage Alzheimer disease, supporting the initiation of therapy early in the disease course to improve daily cognitive functioning
Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group	2000	Galantamine	653 patients with mild to moderate	Clinical trial	Galantamine is effective and well tolerated in AD. It slowed the decline of functional ability as well as cognition.
A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease	2000	Rivastigmine (patch)	Individuals with probable AD and a Mini-Mental State Examination (MMSE) score of ≥ 10 and ≤ 26	Clinical trial	Patients treated with the rivastigmine patch showed improvements on MMSE, ADCS-ADL, ADCS-CGIC and TMT-A scores
Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial	2003	Cognitive stimulation therapy	201 older people with dementia	Clinical trial	Although it doesn't target neuropathology and disease progression, CST groups may have worthwhile benefits for many people with dementia
Post hoc analysis of ADAMANT, a phase 2 clinical trial of active tau immunotherapy with AADvac1 in patients with Alzheimer's disease, positive for plasma p-tau217	2018-2023	AADvac1	Subjects with mild AD	Clinical trial	AADvac1 tau immunotherapy can reduce plasma biomarkers of neurodegeneration and neuroinflammation

A Study to Evaluate the Safety, Tolerability and Immunogenicity of Tau Targeted Vaccines in Participants With Early Alzheimer's Disease	2019-2023	ACI-35.030	Subjects between 50 and 75 years at screening with Mild Cognitive Impairment (MCI) due to AD or Mild AD	Clinical trial	ACI-35.030 is safe and tolerated in early AD and MCI patients. ACI-35.030 has the potential to be utilized as a treatment against AD tau pathology.
VLP-based vaccine targeting tau phosphorylated at Ser396/Ser404 (PHF1) site outperforms phosphorylated S199/S202 (AT8) site in reducing tau pathology and restoring cognitive deficits in the rTg4510 mouse model of tauopathy	2024	Ser199/Ser202 (Qβ-AT8) and Ser396/Ser404 (Qβ-PHF1) (VLP vaccines)	rTg4510 model of FTD	Preclinical	Only the Qβ-PHF1 vaccine was able to reduce tau pathology and rescue cognitive deficits.
Oral Tau Aggregation Inhibitor for Alzheimer's Disease: Design, Progress and Basis for Selection of the 16 mg/day Dose in a Phase 3, Randomized, Placebo-Controlled Trial of Hydromethylthionine Mesylate	2022	Hydromethyl-thionine mesylate	545 patients with probable AD or MCI-AD	Clinical trial	Hydromethyl-thionine mesylate provides a benefit for patients with mild AD by reducing cognitive decline
Curcumin Inhibits Tau Aggregation and Disintegrates Preformed Tau Filaments in vitro	2017	Curcumin	N/A	In vitro study	Curcumin inhibited the oligomerization of tau and could disaggregate tau filaments
A Study of LY3372993 in Participants With AD and Healthy Participants	2020-2024	LY3372993 (Remternetug)	33 participants with mild to moderate AD and healthy participants	Clinical trial	Remternetug is effective in clearance of amyloid protein.
APP antisense oligonucleotides reduce amyloid-β aggregation and rescue endolysosomal dysfunction in Alzheimer's disease	2024	Antisense oligonucleotides (ASOs) targeting APP gene	N/A	In vitro study	APP targeting ASOs significantly reduce both intracellular and extracellular amyloid-β-containing aggregates
Tau-targeting antisense oligonucleotide $MAPT_{Rx}$ in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial	2017-2022	$MAPT_{Rx}$ (ASO)	46 participants with mild	Clinical trial	Dose-dependent reduction in the CSF total-tau concentration was observed

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