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Review Article

Molecular Mechanisms of FDA-Approved Drugs for the Treatment of Alzheimer's Disease: A Comprehensive Review

Aimen Shahid[1], Uzair Ahmad[2]

[1] Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan
[2] Department of Biosciences, COMSATS University Islamabad, Islamabad, Pakistan
*__Correspondence:__ aimen_shahid.scps@stmu.edu.pk

Abstract

Alzheimer's disease (AD) is characterized by progressive degeneration of neurons. It is a complex and multifactorial disorder. Symptomatic modulation of neurotransmitter pathways and disease-modifying treatments are the current therapeutic approaches in molecular medicine. The efficacy of Food and Drug Administration (FDA)-approved medications for AD has improved over time. Among the classes of drugs, cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate receptor (NMDAR) antagonists are used for symptom management. The combination of these treatments improves understanding about neurotransmitter abnormalities in AD. Although their processes differ, they complement each other in terms of effectiveness. The mechanistic evidence remains underexplored for these interactions. With time, treatment advancement introduced anti-amyloid monoclonal antibodies. This shifted the therapeutic focus toward targeted intervention. These drugs selectively target pathogenic amyloid plaques and clear them from brain tissues, which further clears amyloid in the bloodstream. The immune-mediated process provided by this class of drugs differs in both efficacy and downstream biological pathways. These steps in the mechanism are critical; emerging observations need to inquire regarding their treatment specificity, biological variability, and safety mechanisms in neural and cellular safety signaling pathways. In this review, therapeutic classes with distinct mechanisms are explored at the molecular level, where immune activation, aggregated protein clearance, and symptomatic modulation intersect. The review discusses a combination of these molecular-level understandings of AD pathology and how treatments interact with biological systems across conventional and innovative therapeutic options.

Keywords: Alzheimer's disease, molecular mechanisms, acetylcholinesterase inhibitors, NMDAR antagonists, antibodies

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by memory loss and cognitive impairments, where symptoms vary according to AD stages. There are no clear symptoms shown in pre-clinical stages, whereas in early stages, AD is marked by symptoms such as forgetting recent events and difficulty in planning or organizing tasks. Patients with AD face difficulties when symptoms are severe enough to interfere with daily routine activities (Zvěřová 2019). AD is the major form of dementia and is ranked fifth in fatal diseases. Epidemiology of AD suggests its rise from 5.8 million to 13.8 million in the United States.

It is a growing global public health challenge, where the prevalence of AD reports higher cases in women than in men. The prevalence is reported to be higher in low-and middle-income countries (LMICs) due to population dynamics (He et al. 2025). The increase in prevalence of AD has significant societal effects, highlighting the need to understand its underlying molecular

mechanisms. At the molecular level, amyloid-beta (Aβ) aggregation and tau hyperphosphorylation are the key characteristics of AD, where Aβ oligomers initiate the molecular cascade disrupting neuronal signaling. Aβ aggregation triggers neuroinflammatory responses. Tau hyperphosphorylation at multiple serine and threonine residues mediates kinases in the signaling cascade. Aβ-induced toxicity reinforces a synergistic pathogenic loop (Zhang et al. 2021).

The therapeutic strategies for AD were primarily symptom-based. The cholinergic hypothesis, where loss of cortical acetylcholine (ACh) contributes to cognitive decline, was considered as a therapeutic strategy for AD. Similarly, glutamatergic (Glu-related) dysregulation and excitotoxicity prompted the use of N-methyl-D-aspartate-receptor (NMDAR) antagonists to protect neurons from excessive calcium influx (Danysz and Parsons 2003). In Figure 1, the drug target sites are illustrated alongside the pathology of AD. This historical context provides insights into the development of acetylcholinesterase inhibitors (AChEIs), where, despite their wider use, their long-term efficacy and potential for early intervention continue to be investigated (Hampel et al. 2019).

Currently, the therapeutic options have shifted towards disease-modifying treatments, where anti-amyloid monoclonal antibodies (mAbs) were first approved, serving as the optimal means of halting cognitive decline. These antibodies target the underlying molecular pathology, besides treating symptoms (Alkhalifa et al. 2025). This review examines the molecular mechanisms underlying AD in the context of Food and Drug Administration (FDA)-approved therapies. By providing the molecular evidence, it aims to enhance understanding of emerging therapeutic targets and pathways modulated by these drugs, Aβ metabolism, tau pathology, synaptic integrity, and neuroinflammatory processes.

2. Cholinesterase Inhibitors

Due to the degeneration of basal forebrain cholinergic neurons in AD, cholinergic neuronal loss and dysregulated signaling occur. AD is characterized by alterations in neurotransmitters such as glutamate (Glu) and ACh (Auld et al. 2002). ACh is an important neurotransmitter; its degradation causes impaired cognition, where inhibitory control efficiency is reduced in AD (Sabandal, Saldes, and Han 2022). In the cholinergic hypothesis, AD pathology focuses on impaired ACh signaling and synthesis. The hypothesis does not account for disease progression, only emphasizing symptom generation.

Two related enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), are involved in the degradation of ACh. BuChE provides a broader role in regulation, whereas AChE hydrolyzes ACh through an enzymatic process. The molecular mechanisms provide the basis of AD pathology, where decreased activity and increased BuChE make them suitable targets for new therapies (Cavdar et al. 2019). Primarily, synaptic ACh hydrolysis is done by AChE. In mice models, in the absence of AChE enzyme, BuChE provided protection of nerve terminals, where it partially compensated for the hydrolysis of AChE at the neuromuscular junction (NMJ) (Hung et al. 2025). Inhibition of these enzymes provides the rationale for the AD treatment, where ACh levels can be restored (Arcone et al. 2023). There are several ways of this inhibition, where enzymes can be covalently modified, or their activity can be blocked for a shorter time. Restoration duration of ACh within the synapse depends upon these mechanistic differences, which influence the extent of synaptic ACh availability and provides insights into the treatment of AD (Moss 2020).

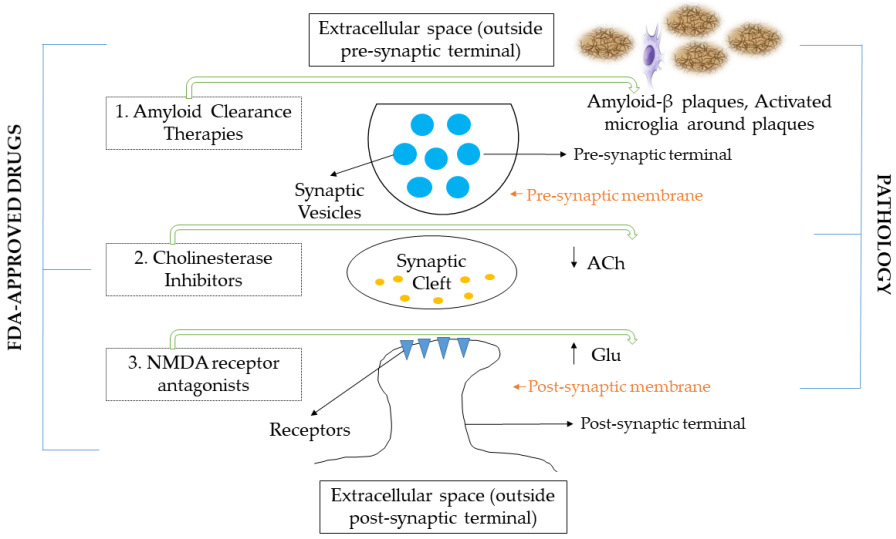

Figure 1: Schematic diagram of AD brain pathology and drugs targeting pathological sites.

2.1. Donepezil

Donepezil is a reversible AChE inhibitor. The U.S. FDA approved donepezil for the treatment of mild, moderate, and severe stages of AD. It binds in the hippocampal and cortical regions of the brain of the Central Nervous System (CNS) and selectively inhibits AChE, where it increases the concentration of ACh (Jelic and Darreh-Shori 2010). The binding affinity is 1200 times higher than that of BuChE. Strong binding affinity and high selectivity are the key factors for its preferred use in treating mild-to-moderate AD (Yiannopoulou and Papageorgiou 2020). By inhibiting the hydrolysis of ACh, it increases its availability and transmission at the synapse.

A narrow space of about 18 - 20 angstroms, named as "gorge" is an active site of AChE. In this region, aromatic residue presence causes cations - π interactions, providing stability to the positively charged ACh as they move towards the active site (Dvir et al. 2010). Donepezil binds along the gorge that spans around the peripheral anionic site (PAS). It can adopt multiple orientations while binding the catalytic site (CAS). This interaction of donepezil represents competitive inhibition as it occupies the site where ACh usually binds. Through its outward orientation, PAS can interact with residues at the gorge entrance, leading to the non-competitive inhibition (Silva, Kiametis, and Treptow 2020). Conformational analysis suggests that the indanone ring of donepezil participates in π- π interactions with tryptophan residues (Trp279). This interaction is mainly responsible for the noncompetitive component of donepezil, where it blocks substrate binding. The dual site of donepezil involves Trp84 and Phe330 residues at CAS, while Trp279 is in PAS. This dual binding behavior supports donepezil as a potential multifunctional anti-Alzheimer's drug (Piemontese et al. 2018).

In-vitro studies of purified AChE, on the kinetic mechanisms of donepezil, confirm its reversible mixed-type inhibitor nature, where it can interact in the form of an enzyme-substrate complex or as a free enzyme. In vitro studies on donepezil show that it protects neurons from excitotoxic stress. Receptors are internalized by the activation of nicotinic acetylcholine receptors (nAChRs). The downregulation of these receptors prevents the neuronal death by controlling excessive calcium influx under pathological conditions, reducing excitotoxic, cellular and oxidative damage (Wang et al. 2025).

2.2. Rivastigmine

Rivastigmine, an FDA-approved drug for AD, is approved as a patch delivery system as well as the oral formulation to treat moderate symptoms of AD. Rivastigmine works effectively in the treatment of AD by working as an inhibitory enzyme for AChE and BuChE, so ACh levels can be maintained. BuChE activity increases with age in people with AD; however, AChE is not directly correlated. Rivastigmine inhibits both AChE and BuChE in a concentration-dependent manner. In experimental studies, its effectiveness has been proven when extracellular ACh is increased. Cerebrospinal Fluid Analysis (CFA) and clinical trials also confirm rivastigmine's greater effectiveness compared to other drugs due to its dual inhibitory molecular mechanisms (Kandiah et al. 2017). The Structure - Activity Relationship (SAR) study of rivastigmine reveals that it contains a carbamate group, where its role as a pharmacophore is proven in anti-cholinesterase activity. The inhibitory mechanism falls under pseudo-irreversible inhibition, where it is the temporary inactivation of the enzyme facilitated by prolonged hydrolysis by the carbamyl group. Carbamylated residue on the enzyme forms after the binding of rivastigmine to the CAS, where active residues such as His447, Glu335, and Ser203 cause the cleavage. After carbamylation, ACh can no longer binds and this binding is pseudo-irreversible (Singh et al. 2023). Given a longer duration of action compared to reversible inhibitors, it is effective at all stages of AD.

2.3. Galantamine and Benzgalantamine

Galantamine, an FDA-approved drug, works as a positive allosteric modulator of nAChRs. Mainly, it works as an ACh inhibitor, where it targets AChE to increase ACh levels. The modified version, benzgalantamine, acts as a prodrug with improved tolerability and minimal gastrointestinal side effects (Neureiter et al. 2025). The two types of mechanisms for inhibition, competitive inhibition and allosteric modulation of nAChRs in these drugs, work in a complementary manner. Through competitive inhibition of ACh, galantamine slows down its breakdown. The available neurotransmitter helps in memory and cognitive improvement. It binds to different sites on nicotinic receptors through allosteric modulation, where it has a complementary effect on receptor activity by increasing their sensitivity, ultimately mediating cholinergic signaling. Its effect on amyloid aggregation includes its inhibition through modulation of non-amyloidogenic processing. Decrease in toxicity provides protection against Aβ neurotoxicity (Castillo and Aristizabal-Pachon 2017). Table 1 provides a comparative analysis of cholinesterase inhibitors (ChEIs) on the basis of structure, IC50 values, and selectivity profiles.

3. NMDAR Antagonists

For Alzheimer's, one specific type of NMDAR antagonist works for the modulation of Glu-mediated NMDAR activity. These receptors, when overproduced, cause Glu toxicity in neuronal cells, leading to their death. NMDAR antagonists work by blocking these receptors and stopping Glu excitotoxicity.

3.1. Memantine

Memantine is the only FDA-approved drug for the treatment of moderate to severe AD that works through the mechanism of a non-competitive antagonist, where it binds to a site different from the binding site and blocks its activity. This blocking, followed by the unblocking, is rapid depending upon the voltage. This facilitates smooth ion flow to continue normal synaptic communication between neurons. Binding near the Mg^{2+} site within the associated channel further allows the selective shut off, through which normal NMDAR-mediated synaptic transmission is not

Table 1: Comparison of Cholinesterase Inhibitors by Structure, IC50 Values, and Selectivity Profiles

Drug	Chemical Structure	IC50 (BuChE)	IC50 (AChE)	Selectivity	References
Donepezil	Piperidine Ring (electrostatic interactions), Aromatic indanone and benzyl group (π- π interactions)	7000 - 7500 nM	6 - 9 nM	Higher selectivity for AChE	(Poeschl et al. 2020)
Rivastigmine	Carbamate functional group, small and less bulky, tertiary amine group (electrostatic interactions)	31 - 60 nM	4 - 10 nM	Dual inhibitor	(Bar-On et al. 2002)
Galantamine	Amaryllidaceae Alkaloid, Tertiary Amine (electrostatic interactions), tetracycl ring, hydroxyl group (hydrogen bonding), methoxy group (hydrophobic interactions)	11000 - 12000 nM	400 - 450 nM	Low selectivity for both AChE and BuChE	(Marucci et al. 2021)
Benzgalantamine	Benzoate ester derivative of galantamine (inertness)	500 - 1000 nM	300 - 3500 nM	Improved selectivity for AChE	(Okello and Mather 2020)

interfered with, which prevents excitotoxicity. Synaptic effect of the memantine involves in the reduction of Aβ-induced over-activation of NMDAR, providing protection against degeneration of cholinergic neurons in the basal forebrain and hippocampus neurons. Finally, in early cognitive abnormalities in AD, synaptic depression and cytoskeletal disruptions are averted.

In experimental studies and transgenic mouse models, the reduced levels of secreted Aβ peptides proved their protective role in synaptic function. The therapeutic role in the reduction of Aβ-mediated neurotoxicity in disease comes with infrequent adverse effects, where it may act synergistically with other ChEIs due to distinct mechanisms (Mucke and Selkoe 2012).

4. Combination Therapies

Combination therapies including memantine and donepezil provide mechanistic insights into the dual targeting role, where they tackle problems of glutamatergic excitotoxicity and cholinergic dysfunction. Due to their different chemical nature, these drugs have contrasting roles. Their combined efficacy is proven in pre-clinical and clinical studies. The complementary mechanistic roles of these drugs, where donepezil improves overall cognitive processing, and memantine protects neurons, allow coherent enhancement of neurotransmission. Clinical trials on patient safety indicate that patients can take combination therapy without experiencing frequent side effects (Michel and Staskin 2022). Doubly robust (DR) causal inference analysis of the combined therapy compared to monotherapy reveals additive survival benefits in patients with AD. The significant increase in five year survival probability of AD patients confirms the therapeutic potential of the synergistic effect (Yaghmaei et al. 2024). The effectiveness of this dual therapy on the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog) showed efficient results. The combination regimen outperformed placebo on the Clinical Global Impression (CGI) scale. These findings support that the complementary mechanism of action provides important therapeutic insights due to

the glutamergic modulation and simultaneous cholinergic enhancement (Isaac et al. 2022).

5. Anti-Amyloid Monoclonal Antibodies

Anti-amyloid mAbs are disease-modifying therapies where their role is the removal of amyloid plaques. Alzheimer's is characterized by the accumulation of Aβ, the early pathogenic event, targeted by this class of drugs. The reduction of cerebral Aβ through anti-amyloid mAbs therapy is rooted in the amyloid cascade hypothesis. Their selective binding to plaque-associated species, fibrils, and protofibrils highlights their direct role in combating AD (Cummings et al. 2024). Primarily, the mechanism of removing amyloid is related to phagocytosis and microglial activation. Anti-amyloid mAb therapy is thought to be superior to symptomatic treatments because it targets the root cause of AD instead of merely alleviating its symptoms (Maggiore et al. 2024).

The mode of action of this therapy underlies in two mechanisms, in which the direct microglial plaque clearance remains dominant due to higher efficacy and strong clinical evidence. In contrast, the mechanism where antibody penetration across the blood-brain barrier (BBB) is not mandatory, and disease modification merely depends upon lowering plasma Aβ levels through binding of anti-amyloid mAbs with soluble Aβ, does not have enough clinical validation, and representative drug shows weak efficacy, so the focus of this section will be on the drugs categorized into the primary mechanism (microglial clearance) (Cheng, Tian, and Wang 2020). Figure 2 illustrates the mechanistic action of amyloid clearance therapies. The use of anti-amyloid holds a therapeutic potential; however, the safety concerns, such as amyloid-related imaging abnormalities (ARIA), are notable, where they can exist in a form of ARIA-edema (ARIA-E) as well as ARIA-hemorrhage (ARIA-H) (Hampel et al. 2023). The two drugs, lecanemab and donanemab, with significant results are discussed below:

5.1. Lecanemab (Leqembi)

In AD, soluble Aβ protofibrils are reported as highly neurotoxic substances. The mechanism of selective binding to Aβ protofibrils allows leaving the healthy, monomeric Aβ in the blood. Protofibrils containing Aβ42 peptides can be eliminated through both direct clearance and peripheral trapping of soluble Aβ. Binding with soluble oligomers, insoluble plaques, and protofibrils after the intravenously administered lecanemab crosses the BBB triggers glial activation via fragment crystallizable gamma (Fcγ) receptors (FcγRs). This allows the removal of Aβ aggregation, hence causing plaque and neurotoxicity reduction (Anil et al. 2025).

Apart from selectivity, the binding conformation also plays a role, whereupon binding to Aβ, the drug forms an antibody-antigen complex in the Fc domain. When bound to plaques, this allows proper functioning of microglial FcγRs. The distinct microglial activation mediated through this Fc-mediated interaction facilitates the degradation of Aβ plaques. Transcriptomic analysis revealed AD-associated genes, such as HSPA5, MS4A6A, and SPP1 were up-regulated after Lecanemab treatment. This causes the enhanced response of microglia towards Aβ plaques, promoting enhanced amyloid recognition, uptake, and clearance. In functional pathway analysis, after lecanemab treatment, lysosomal and phagosome pathways are activated alongside changes in microglial recognition and activation through interferon (IFN) response, predominantly localized to regions around Aβ, indicating the drug's reprogramming of microglia into a specialized plaque clearance state. The antibody-amyloid binding provides valuable insight into the therapeutic potential while limiting excessive inflammatory responses and treatment-related adverse effects in patients overall (Park 2024).

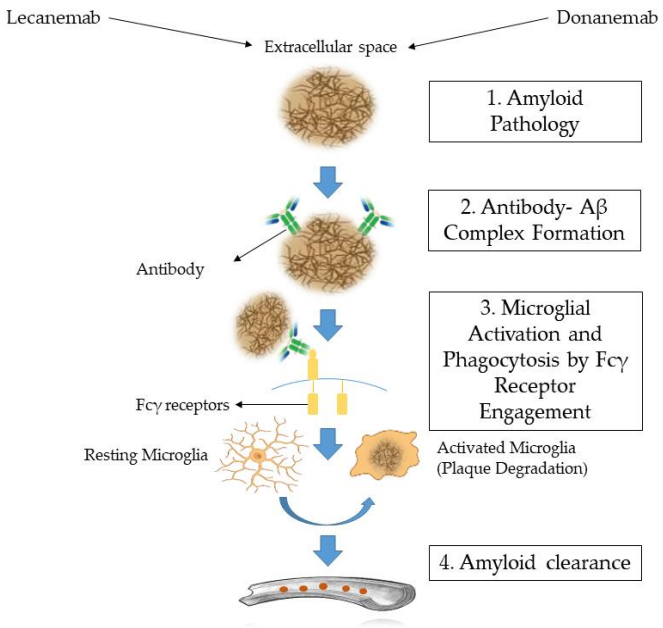

Figure 2: Mechanistic Action of Amyloid Clearance Therapies

5.2. Donanemab (Kisunla)

Donanemab, a class of anti-amyloid mAbs, acts as a disease-modifying therapy that targets settled amyloid plaques. This drug is designed for the mild stage, in which abnormal protein buildup can be detected in a positron emission tomography (PET) scan, employing radiolabeled tracers. The quantitative assessment of plaque burden before and during treatment allows discontinuation of therapy until it achieves a predefined threshold of amyloid reduction, thereby minimizing spare drug exposure. This drug, comparable to the fully human IgG antibodies, works better than conventional symptomatic treatments. This drug's unique where pE -modified Aβ are present. Upon binding, microglia activation occurs after microglial Fc receptors recognize the Aβ plaques. This triggers the engulfment and clearance of plaques from neuronal tissue, leading to neurotoxicity suppression. Immune modulation through this drug bears a therapeutic importance, where it partially reverses the dysfunctional microglial state and modulates the type 1 IFN signaling. The indirect influence on Amyloid Precursor Protein (APP) is processing pathways alter the post-translational modification, tau hyperphosphorylation and neurofibrillary tangles formation. The removal of amyloid plaques is notable, however donanemab does not substantially control early soluble Aβ oligomers, providing insight into implications for clinical outcomes and timeframes for treatment effectiveness (Jayaprakash and Elumalai 2025). Table 2 summarizes the comparison of anti-amyloid therapies on the basis of target epitopes, therapeutic impact, and safety risks.

6. Discussion

Current FDA-approved AD medicines show therapeutic potential, despite significant differences in molecular targets and mechanisms of action. The key differences are noticeable. The primary action of ChEIs and NMDAR antagonists is symptomatic and does

Table 2: Comparison of anti-amyloid monoclonal antibodies in terms of target epitope, therapeutic impact, and safety risks.

Drug	Target Epitope	Therapeutic Impact	Safety Risks	References
Donanemab (Kisunla)	Pyroglutamate-modified Aβ	Disease modification; quick plaque removal	ARIA-E & ARIA-H, infusion-related reactions, possible interactions with particular food	(Rabinovici et al. 2025)
Lecanemab (Leqembi)	Soluble Aβ protofibrils	Slows cognitive deterioration; reduces plaque	ARIA (increased risk in people with two copies of the *APOE4* gene, the genetic risk factor), infusion-related reactions	(Rajič Bumber et al. 2025)

not capture the underlying pathology of AD, is in contrast to anti-amyloid antibodies. Targeted amyloid clearance through increased molecular specificity brought by anti-amyloid monoclonal antibodies provides disease-modifying treatment (Cummings 2023). Targeting specific amyloid-Aβ species can result in varying biological responses and off-target effects, including immunological activation. ARIA is mechanistically tied to antibody clearance, which is a key challenge. Lecanemab and donanemab treatment caused vasogenic edema and microhemorrhages due to Fc-dependent microglial activation (Loeffler 2023).

These findings, together with the minimal impact on overall disease management, indicate mechanistic limitations, since amyloid targeting alone may not be sufficient to eliminate tau pathology and synaptic abnormalities (Chundu et al. 2025). Given the multifactorial nature of AD pathology, therapies targeting multiple molecular pathways along patient selection with known amyloid burden and genetic modifiers such as *APOE* genotype are the current trending direction in therapeutics. For better disease modification while attenuating the need for combating amyloid clearance, integrating anti-amyloid therapies along with neuro- modulators and tau-directed agents provides insight into synergistic approaches to shift toward systemic intervention rather than centered on a single pathogenic pathway. Emerging evidence suggests that amyloid pathology interacts dynamically with tau aggregation and synaptic inflammatory responses and dysfunction. Combination-based approaches may therefore enhance therapeutic efficacy by simultaneously stabilizing signaling and reducing neurotoxicity.

7. Future Directions

The future of Alzheimer's treatment lies in finding new insight into novel mechanistic treatments and their proven effectiveness in pre-clinical and clinical trials. The shift in focus towards molecular mechanisms beyond tau pathology, neuroinflammation, synaptic dysfunction, and signaling abruption is a direction towards finding biomarkers for these mechanism-based treatments. Ongoing clinical trials are necessary to employ biomarker-enriched and combination designs where a mechanistic intervention provides a shift towards synergistic approaches and multiple pathways.

8. Conclusion

The current literature on the molecular mechanisms underlying AD therapies is comprehensively synthesized in this review. Drug that manage the symptoms modulates

neurotransmission, whereas disease-modifying therapy captures underlying Alzheimer's pathological process of amyloid clearance. The distinct mechanisms of action of each drug with their advances in target specificity are notable, however mechanistic limitations related to downstream pathology and immune activation remain a challenge. Therapeutic intervention with an integrated and multi-targeted strategies are likely required. The guidance provided by molecular biomarkers in an effective plan of action underscores the importance of mechanism-driven therapeutic development.

Conflict of Interest

The authors declare that they have no competing interests.

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NA

Data Availability

All the raw data related to this study are available with the authors.

Authors Contributions

AS conceptualized and organized the study, UA did the literature search and analysis, AS and UA wrote the initial manuscript, AS wrote the final manuscript, and supervised the project.

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