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Druggable Pathophysiologic Targets in Alzheimer Disease: From Amyloid and Tau to Biomarker-Guided Multimodal Therapy

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ABSTRACT

Alzheimer disease (AD) is no longer viewed only as a clinical syndrome of memory impairment but as a biological disease continuum driven by interacting amyloid-β, tau, glial, vascular, metabolic, and synaptic mechanisms. This shift has practical therapeutic consequences. Symptomatic agents such as cholinesterase inhibitors and memantine remain useful for selected patients, but they do not directly modify the core neurodegenerative process. In contrast, amyloid-β monoclonal antibodies have provided proof that biomarker-confirmed early AD can be slowed, although the magnitude of clinical benefit is modest, treatment is restricted to carefully selected patients, and amyloid-related imaging abnormalities require structured monitoring. Tau pathology, neuroinflammation, blood-brain barrier dysfunction, mitochondrial and oxidative stress, and impaired proteostasis are therefore increasingly important druggable axes rather than secondary background phenomena. A staged, biomarker-guided druggability framework can evaluate each target by biological proximity to clinical decline, biomarker measurability, therapeutic modifiability, implementation feasibility, and suitability for sequencing or combination therapy. Validated and emerging targets are summarized with emphasis on how biomarkers reshape patient selection and outcome assessment and how anti-amyloid therapy can be integrated with stage-specific interventions targeting tau propagation, glial activation, vascular injury, clearance failure, and metabolic vulnerability. The central conclusion is that AD drug development should move from a single-target rescue model toward biomarker-guided, mechanism-matched, and combination-ready strategies that can be tested earlier in the disease course while maintaining realistic safety and implementation standards.

Keywords: Alzheimer Disease; Amyloid Beta-Peptides; Tau Proteins; Neuroinflammation; Biomarkers; Therapeutics

INTRODUCTION

Alzheimer disease (AD) is the leading cause of dementia and a major public-health challenge in aging societies.[1,2] Amyloid-β (Aβ), tau, neuroinflammation, oxidative stress, mitochondrial

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dysfunction, and blood-brain barrier (BBB) dysfunction are central, interacting therapeutic issues in AD. A clinically useful druggability framework must connect these mechanisms to biomarkers, patient selection, and clinical implementation.

The therapeutic landscape has changed substantially over the last several years. Cholinesterase inhibitors and memantine remain symptomatic treatments, while lecanemab and donanemab have demonstrated statistically significant slowing of decline in biomarker-confirmed early symptomatic AD. These advances do not prove that amyloid is a sufficient target; rather, they show that amyloid removal can alter the clinical trajectory in a restricted disease window while leaving substantial residual progression. The current task is therefore not to choose between amyloid and non-amyloid hypotheses, but to define when each mechanism is druggable and how targets should be sequenced or combined.[3-6]

Clinically relevant druggable pathophysiologic targets in AD can be interpreted in light of modern biomarker definitions, anti-amyloid treatment experience, and the 2025 development pipeline. This target-centered framework emphasizes implications for clinicians, pharmacists, and translational researchers, aligning with a clinical and translational scope while incorporating both Korean and international implementation issues.[6-8]

SEARCH SCOPE AND CONCEPTUAL FRAMEWORK

Recent clinical trials, consensus criteria, appropriate-use recommendations, diagnostic-biomarker studies, and representative mechanistic reviews were prioritized. The conceptual framework is organized around five linked questions: whether the target is biologically proximal to AD progression, whether it can be measured or enriched by biomarkers, whether therapeutic modulation is feasible without unacceptable toxicity, whether the intervention can be implemented in real-world clinical pathways, and whether the target is best approached alone, sequentially, or in combination. This framework treats AD as a staged and multidirectional network in which proteinopathy, glial activation, vascular injury, metabolic stress, proteostasis failure, and synaptic dysfunction interact through feedback loops rather than through a purely linear cascade.

A druggable target in AD should not be defined only by its presence in pathology. Many molecular events are associated with AD brains but are difficult to modulate safely, occur too late to change clinical course, or lack reliable biomarkers for patient selection. Conversely, a target may be clinically important even if it is not disease-specific, such as neurovascular dysfunction or metabolic stress, when it amplifies neurodegeneration and creates an actionable therapeutic window. This distinction is essential because the history of AD drug development is marked by biologically plausible targets that failed when tested in heterogeneous or late-stage populations.[6,9,10]

A BIOLOGICAL DISEASE CONTINUUM: DIAGNOSIS BEFORE SYMPTOMS

A major recent development in AD research and clinical practice is the integration of AD biomarkers. Current research frameworks increasingly define AD biologically by core pathology rather than by dementia severity alone. Amyloid positron emission tomography

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(PET), tau PET, cerebrospinal fluid (CSF) Aβ and phosphorylated tau (p-tau), and emerging blood biomarkers allow clinicians and investigators to separate AD pathology from other causes of cognitive impairment and to identify the stage at which a given intervention is most plausible.[8,11-13]

Blood-based biomarkers are especially relevant to future clinical practice and trial systems because they may reduce diagnostic bottlenecks before anti-amyloid therapy and clinical-trial enrollment. Plasma p-tau217 assays have shown high accuracy for identifying AD pathology, and the U.S. Food and Drug Administration cleared the first blood-based test to aid AD diagnosis in 2025. However, real-world interpretation must account for assay heterogeneity, including platform differences, antibody epitopes, calibration methods, pre-analytical handling, cutoff selection, comorbid kidney or vascular disease, and whether the test is intended for rule-out, rule-in, or triage use. These assays are not stand-alone unsupervised screening tools, but they support a stepwise diagnostic pathway in which accessible blood tests triage patients for confirmatory amyloid PET or CSF testing within locally validated workflows.[11-15]

Biomarker staging also changes how druggable targets are interpreted. Aβ accumulation may begin decades before dementia, tau spread correlates more closely with symptom progression, and neuroinflammatory or vascular responses may shift from compensatory to harmful depending on disease stage. Therefore, drug development should pair each intervention with an appropriate disease phase: amyloid-directed prevention or early symptomatic therapy, tau-directed strategies near the onset of neurodegeneration, and glial, vascular, or metabolic interventions across broader windows depending on mechanism and safety.[8,10,14]

Aβ: VALIDATED BUT INCOMPLETE

Aβ remains the most clinically validated disease-modifying target in AD, but it requires careful contemporary interpretation. Aducanumab is best viewed as a historical and limited anti-amyloid therapy because commercial development was discontinued after controversy and limited uptake. In contrast, lecanemab and donanemab represent current anti-amyloid monoclonal antibodies with trial evidence in early symptomatic, biomarker-confirmed AD.[3-5,16]

Lecanemab, an antibody directed preferentially against soluble protofibrils, slowed decline on the Clinical Dementia Rating-Sum of Boxes in early AD over 18 months and later received traditional U.S. Food and Drug Administration approval. Donanemab, directed against pyroglutamate Aβ plaques, similarly slowed cognitive and functional decline in TRAILBLAZER-ALZ 2 and was approved in 2024. These trials are important because they provide clinical proof of principle that amyloid reduction can change disease course. However, they also show the limits of a single-target approach: treatment effects are partial, eligibility is narrow, and progression continues despite amyloid clearance.[3,4,9,17]

Safety and implementation are central to the druggability of Aβ. Amyloid-related imaging abnormalities (ARIA), especially vasogenic edema and microhemorrhage, require baseline and serial magnetic resonance imaging (MRI), careful review of anticoagulant use and cerebral amyloid angiopathy risk, and counseling about apolipoprotein E (APOE) ε4-associated risk. Korean appropriate-use recommendations for lecanemab emphasize mild

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cognitive impairment (MCI) or mild dementia due to AD with positive amyloid biomarkers, APOE genotyping for risk prediction, and regular MRI monitoring.[5,18,19]

Small-molecule Aβ production inhibitors remain scientifically informative but clinically problematic. β-secretase 1 (BACE1) inhibitors reduce Aβ generation, yet prior clinical trials were limited by cognitive worsening, neuropsychiatric adverse events, or lack of benefit, likely reflecting the physiological roles of BACE1 substrates and the challenge of intervening after downstream pathology is established. Future Aβ approaches may therefore focus on safer antibodies, active or passive immunization, brain-shuttle delivery, and earlier treatment windows rather than broad suppression of amyloid production.[6,10,20]

TAU PATHOBIOLOGY: CLOSER TO CLINICAL DECLINE

Tau is a central therapeutic axis because tau aggregation and spread correlate more closely with neurodegeneration and cognitive decline than amyloid plaque burden alone. Hyperphosphorylated tau forms paired helical filaments and neurofibrillary tangles, but the druggable process is broader than visible tangles: tau misfolding, seeding, propagation across connected networks, synaptic toxicity, and impaired clearance all provide potential intervention points.[10,21,22]

The main limitation is that tau has not yet produced an approved disease-modifying therapy. Anti-tau antibodies, aggregation inhibitors, kinase modulators, phosphatase modulators, antisense oligonucleotides, and microtubule-stabilizing approaches remain under investigation. Past failures may reflect late intervention, inadequate brain exposure, target heterogeneity, or insufficient engagement of toxic tau species. These failures should not be interpreted as evidence that tau is irrelevant; rather, they highlight the need for better patient staging and target engagement biomarkers.[6,10,14]

Within a druggable-target framework, tau represents both a pathobiological mediator and a potential treatment-selection axis. Amyloid can be viewed as an early trigger or permissive pathology, tau as a mediator of regional neurodegeneration, and glial/vascular stressors as amplifiers. This framing avoids the oversimplified amyloid-versus-tau debate and instead presents AD as a temporally evolving network disease.[8,10,21]

NEUROINFLAMMATION AND GLIAL TARGETS

Neuroinflammation and glial activation are central components of contemporary AD pathobiology. Microglia and astrocytes are not merely bystanders responding to plaques; they shape synaptic pruning, phagocytosis, cytokine release, complement activation, tau propagation, and neuronal resilience. Genetic evidence involving APOE, triggering receptor expressed on myeloid cells 2 (TREM2), cluster of differentiation 33, complement receptor 1, and other immune-related loci further supports the relevance of innate immunity to AD risk and progression.[23-26]

The therapeutic challenge is that glial activation is context-dependent. Microglia can clear debris and contain pathology in early phases, but chronic activation may promote synaptic loss, oxidative injury, and inflammatory amplification. Therefore, a simple anti-inflammatory

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strategy is unlikely to be sufficient. Drug development is moving toward pathway-specific modulation such as TREM2 signaling, complement inhibition, NOD-like receptor protein 3 inflammasome modulation, colony-stimulating factor 1 receptor strategies, and regulation of astrocytic reactivity.[6,24-26]

These translational considerations connect molecular targets to patient stratification and biomarker development. Neuroinflammatory therapies will need biomarkers beyond amyloid and tau, including fluid markers of glial activation, neurofilament light, inflammatory proteomics, or imaging of microglial activation. They may also be especially relevant for combination therapy after amyloid removal, when residual tau-mediated and glial-mediated progression remains.[6,14,24]

NEUROVASCULAR, METABOLIC, AND OXIDATIVE AXES

Oxidative stress, mitochondrial dysfunction, and BBB dysfunction can be integrated into a single neurovascular-metabolic axis. The BBB and neurovascular unit regulate amyloid clearance, immune-cell trafficking, nutrient delivery, and protection from plasma proteins. BBB breakdown, cerebral amyloid angiopathy, small-vessel disease, and impaired glymphatic or perivascular clearance may all worsen AD progression and increase the risk of treatment complications such as ARIA.[18,27,28]

Mitochondrial dysfunction and oxidative stress are also druggable, but antioxidants alone should not be described as proven disease-modifying treatments. Mitochondrial injury contributes to synaptic energy failure, reactive oxygen species generation, impaired calcium handling, and inflammatory signaling. However, translation has been difficult because generic antioxidant supplementation rarely matches the timing, compartment, or mechanism of neuronal injury. More plausible strategies include improving mitochondrial quality control, reducing ferroptosis or lipid peroxidation, targeting metabolic resilience, and treating vascular and sleep-related contributors.[10,29,30]

Metabolic risk and vascular comorbidity are particularly important because they are clinically actionable even when disease-specific drugs are unavailable or inaccessible. The 2024 Lancet Commission emphasized that modifiable risk factors contribute substantially to dementia burden. Disease modification in AD should not be limited to antibodies; it also includes rigorous management of hypertension, diabetes, dyslipidemia, sleep disorders, hearing loss, depression, and vascular risk when these factors interact with AD biology.[7,10,27]

GENETICS, PROTEOSTASIS, AND SYNAPTIC RESILIENCE

Genetic risk is important because it connects molecular pathogenesis to therapeutic risk stratification. APOE ε4 increases the likelihood of amyloid deposition and is also associated with vascular and BBB vulnerability. TREM2 and other immune-related variants support the concept that microglial response states influence disease onset and progression. These genetic associations do not yet translate into routine genotype-directed therapy, but they guide target discovery and help explain why patients with similar amyloid burden may differ in clinical progression and treatment risk.[23,24,28]

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Table 1. Druggable pathophysiologic axes in Alzheimer disease

Pathophysiologic axis	Representative druggable targets	Biomarkers or enrichment tools	Key translational issue
Aβ	Soluble protofibrils, plaques, BACE1, γ-secretase modulation	Amyloid PET; CSF Aβ42/40; plasma Aβ- or p-tau-based assays	Validated by antibodies; benefit is partial; assay cutoffs and ARIA monitoring are required
Tau	Tau phosphorylation, aggregation, seeding, propagation, clearance	Tau PET, CSF/plasma p-tau181/217/231	Biologically proximal to decline, but no approved therapy yet
Glial inflammation	TREM2, complement, NLRP3 inflammasome, astrocytic reactivity	Fluid glial markers; inflammatory proteomics; microglial imaging; NfL	Protective versus harmful glial states require stage-specific biomarkers
Neurovascular/BBB	Endothelial integrity, pericytes, cerebral amyloid angiopathy, transport systems	MRI microbleeds, white-matter disease, vascular imaging	Important for progression, ARIA risk, and real-world anti-amyloid safety
Metabolic/oxidative stress	Mitochondrial quality control, lipid peroxidation, insulin signaling, proteostasis	Metabolic risk profile, oxidative markers, neurodegeneration markers	Generic antioxidants are insufficient; mechanism-specific and comorbidity-focused targeting is needed

BACE1: β-secretase 1, PET: positron emission tomography, CSF: cerebrospinal fluid, Aβ: amyloid-β, p-tau: phosphorylated tau, ARIA: amyloid-related imaging abnormalities, TREM2: triggering receptor expressed on myeloid cells 2, NLRP3: NOD-like receptor protein 3, NfL: neurofilament light, BBB: blood-brain barrier, MRI: magnetic resonance imaging.

APOE status is already clinically relevant for anti-amyloid therapy because APOE ε4 carriers, especially homozygotes, have a higher risk of ARIA. This does not mean that APOE genotyping should be used to deny treatment categorically; rather, it should inform shared decision-making, MRI monitoring intensity, and counseling about uncertainty. This connection illustrates how molecular pathophysiology, safety pharmacology, and bedside implementation converge in anti-amyloid treatment decisions.[5,16,19]

Proteostasis is another underemphasized druggable domain. AD is characterized by failure to clear misfolded Aβ and tau through autophagy-lysosomal pathways, ubiquitin-proteasome systems, microglial phagocytosis, and perivascular drainage. Therapeutic concepts include enhancing autophagy, improving lysosomal function, stabilizing endosomal trafficking, and supporting glymphatic or vascular clearance. These approaches remain mostly investigational, but they may become important when combined with antibodies that mobilize protein aggregates and increase the need for safe clearance mechanisms.[10,23,27]

Synaptic dysfunction should also be framed as more than a downstream consequence. Synapse loss is one of the strongest correlates of cognitive impairment, and Aβ oligomers, tau mislocalization, complement-mediated pruning, mitochondrial failure, and glutamatergic excitotoxicity all converge at synapses. Symptomatic drugs modulate synaptic neurotransmission, but future disease-modifying strategies may aim to preserve synaptic plasticity, prevent maladaptive pruning, or improve neuronal network resilience.[10,25,31]

These domains broaden the therapeutic framework beyond an antibody-centered model. Successful AD treatment may require reducing upstream proteinopathy while simultaneously protecting synapses, improving clearance, and limiting inflammatory or vascular amplification. This is especially important for patients who present after decades of pathology, when removing one protein species may be insufficient to restore neuronal function. The relationship among the major pathophysiologic axes, druggable targets, biomarkers, and therapeutic implications is summarized in **Fig. 1** and **Table 1**.[6,10,15]

TREATMENT LANDSCAPE AND PHARMACOLOGIC IMPLICATIONS

Current pharmacologic management can be divided into symptomatic therapy, disease-modifying anti-amyloid therapy, and emerging mechanism-based interventions (**Table 2**).

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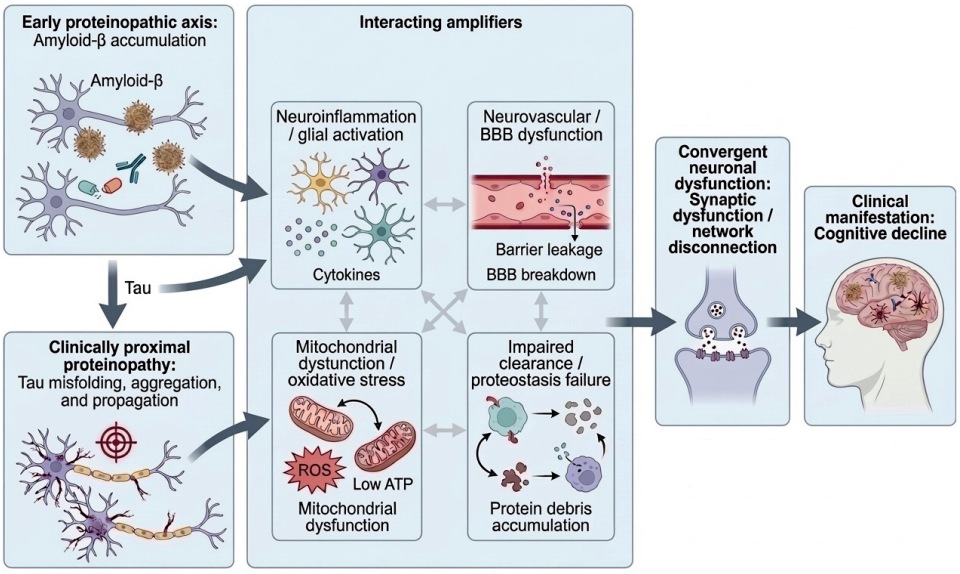

Fig. 1. Integrated multidirectional pathophysiology-to-druggability map for Alzheimer disease. The diagram depicts amyloid-β accumulation and tau misfolding, aggregation, and propagation as proteinopathic axes linked to neuroinflammation/glial activation, neurovascular/BBB dysfunction, mitochondrial dysfunction/oxidative stress, and impaired clearance/proteostasis failure. These interacting amplifier axes converge on synaptic dysfunction/network disconnection and cognitive decline. Solid arrows indicate predominant directional influences, and double-headed arrows indicate reciprocal interactions among pathophysiologic axes.
BBB: blood-brain barrier, ROS: reactive oxygen species, ATP: adenosine triphosphate.

Cholinesterase inhibitors increase synaptic acetylcholine and may provide modest symptomatic benefit in mild to moderate AD. Memantine, an N-methyl-D-aspartate receptor antagonist, may be useful in moderate to severe disease or in combination with cholinesterase inhibitors. These agents should be described as symptomatic rather than disease-modifying.[10]

Anti-amyloid antibodies require a different clinical workflow. Before treatment, patients need confirmation of amyloid pathology, assessment of disease stage, MRI evaluation for hemorrhagic risk, review of antithrombotic therapy, and shared decision-making about expected benefit and risk. During treatment, infusion reactions and ARIA monitoring require neurologic assessment and serial MRI. This makes the pharmacist's role important in medication reconciliation, anticoagulant-risk assessment, adverse-event education, and coordination of infusion logistics.[5,16]

Table 2. Current and emerging pharmacologic categories relevant to AD

Therapeutic category	Examples	Current role	Practical caution
Symptomatic cognitive therapy	Donepezil, rivastigmine, galantamine, memantine	May improve or stabilize symptoms in selected patients	Do not present as disease-modifying
Anti-amyloid monoclonal antibodies	Lecanemab, donanemab	Disease-modifying option for biomarker-confirmed early symptomatic AD	Requires amyloid confirmation, MRI monitoring, ARIA counseling, and risk stratification
Historical/limited anti-amyloid therapy	Aducanumab	Important proof-of-concept and controversy, but not a routine current option	Commercial development discontinued; avoid listing as active standard therapy
Emerging disease-modifying agents	Tau-directed, glial, synaptic, metabolic, vascular, and delivery-enhanced therapies, including investigational brain-shuttle anti-amyloid approaches such as trontinemab	Clinical-trial candidates and future combination components	Need stage-matched biomarkers, target-engagement evidence, safety testing, and delivery validation
Behavioral/neuropsychiatric symptom therapy	Antidepressants, antipsychotics, agitation-directed agents	Symptom management and caregiver support	Separate from core disease modification; monitor geriatric safety

AD: Alzheimer disease, MRI: magnetic resonance imaging, ARIA: amyloid-related imaging abnormalities.

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Cognitive disease modification should also be separated from behavioral and neuropsychiatric symptom control. Agitation, depression, psychosis, insomnia, and caregiver burden are clinically important, but drugs for these symptoms do not target the core amyloid-tau-neurodegeneration continuum. Clear separation prevents symptomatic benefits from being overstated as disease modification.[10]

IMPLEMENTATION ISSUES FOR CLINICIANS AND PHARMACISTS

Practical implementation is essential because the arrival of disease-modifying therapy changes the clinical pathway. Patients must be identified early enough, receive biomarker confirmation, be screened for contraindications, and understand that treatment slows decline rather than reverses established dementia. This is different from the traditional model in which AD drugs were started after a clinical diagnosis and monitored mainly for gastrointestinal, cardiovascular, or neuropsychiatric adverse effects.[5,10,16,32]

Medication review is a concrete pharmacologic contribution. Anticoagulants, antiplatelet combinations, thrombolytic exposure, uncontrolled hypertension, and MRI evidence of microhemorrhage or superficial siderosis may affect the risk-benefit discussion for anti-amyloid antibodies. Pharmacists can also help identify drugs that worsen cognition, such as strong anticholinergics, sedative-hypnotics, and inappropriate polypharmacy, which can obscure treatment response and increase falls or delirium.[5,18,19]

Another implementation issue is equity. Biomarker testing, PET imaging, repeated MRI, infusion capacity, and specialist follow-up create structural barriers. Blood-based biomarkers may reduce the bottleneck but should be used within validated pathways that specify intended use, local cutoffs, confirmatory testing thresholds, quality control, and referral routes, not as unsupervised population screening. Biomarker-guided therapy should therefore be understood not only as a molecular advance but also as a system-level challenge, as summarized in **Fig. 2**.[11-13,15,32]

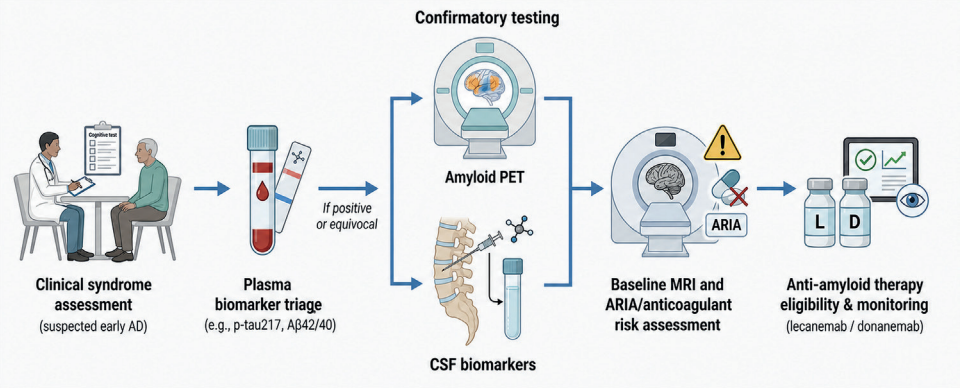

Fig. 2. Biomarker-guided treatment pathway for early symptomatic AD. The flow diagram begins with clinical syndrome assessment, proceeds to blood-based biomarker triage when locally validated assays are available, confirms amyloid pathology with amyloid PET or CSF testing, assesses MRI findings, anticoagulant exposure, and ARIA risk, and then guides discussion of lecanemab or donanemab eligibility and monitoring.
AD: Alzheimer disease, PET: positron emission tomography, CSF: cerebrospinal fluid, MRI: magnetic resonance imaging, ARIA: amyloid-related imaging abnormalities, p-tau: phosphorylated tau.

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In the Korean clinical context, the Korean Dementia Association's lecanemab appropriate-use recommendations provide particularly relevant guidance. These recommendations emphasize amyloid confirmation, APOE genotyping, MRI monitoring, ARIA risk counseling, and patient selection for biomarker-confirmed MCI or mild dementia due to AD.[5]

PIPELINE AND TRIAL DESIGN: FROM SINGLE TARGETS TO COMBINATIONS

The 2025 AD pipeline contains a broad set of agents targeting amyloid, tau, inflammation, synaptic function, metabolic pathways, neuropsychiatric symptoms, and other processes. This diversity supports the thesis that AD is a multifactorial disease requiring mechanism-matched and stage-matched therapy. Biomarkers are now used not only for diagnosis but also for trial eligibility, target engagement, and outcome assessment.[6]

A realistic future model is not a single universal cure but a layered approach. In preclinical or very early AD, amyloid lowering may be tested as prevention or delay. In early symptomatic disease, amyloid therapy may be combined with tau- or inflammation-directed interventions. In later disease, symptomatic, vascular, metabolic, and neuropsychiatric management may dominate while neuroprotective strategies are tested in enriched subgroups. This model parallels oncology and cardiovascular medicine, where combination and risk-stratified strategies replaced one-size-fits-all treatment (**Fig. 3**).[6,8,15]

Drug delivery remains a major bottleneck. Large antibodies reach the brain inefficiently, while small molecules must balance BBB penetration with off-target toxicity. Emerging approaches include receptor-mediated transcytosis, focused ultrasound-mediated BBB opening, intranasal delivery, nanoparticles, antisense oligonucleotides, and gene- or

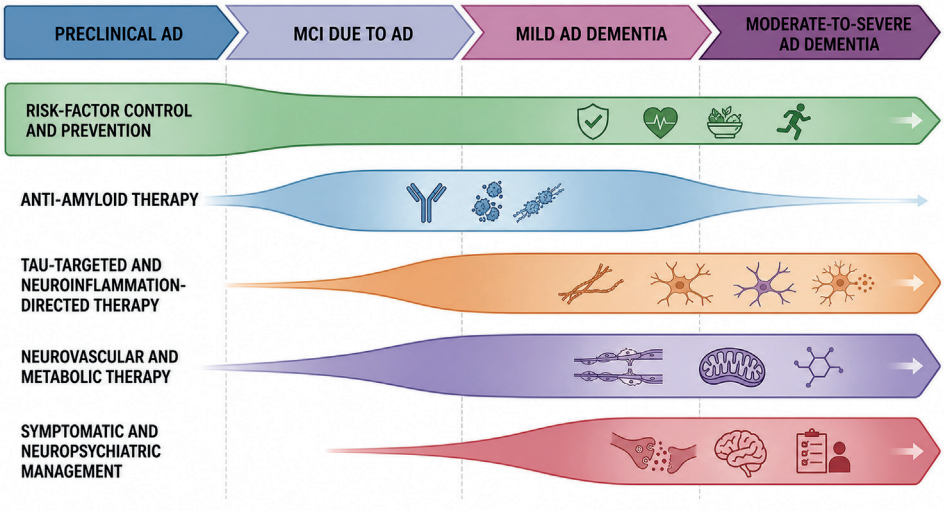

Fig. 3. Multimodal therapeutic strategy across the AD continuum. The timeline aligns preclinical, mild cognitive impairment, mild dementia, and later dementia stages with plausible intervention classes: risk-factor control and prevention, anti-amyloid therapy, tau and inflammatory modulation, neurovascular/metabolic therapy, and symptomatic or neuropsychiatric management. Overlapping bands and cross-links represent stage-specific therapeutic opportunity and multidirectional interactions, not quantitative efficacy or a fixed linear sequence. AD: Alzheimer disease.

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RNA-based platforms. Trontinemab illustrates the receptor-mediated transport strategy: it is an investigational Brainshuttle bispecific anti-Aβ monoclonal antibody engineered to use transferrin receptor 1-mediated transport to improve brain exposure, and Phase Ib/IIa data have shown rapid amyloid plaque reduction with a low reported frequency of ARIA-edema/effusion while Phase III TRONTIER studies are being developed for early symptomatic and preclinical AD. These approaches are promising but remain largely investigational for AD rather than established clinical solutions.[6,27,33]

LIMITATIONS AND CAUTIONS IN INTERPRETING CURRENT EVIDENCE

Several cautions are important when interpreting current evidence. First, statistically significant slowing of decline is not the same as clinical reversal, and the minimal clinically important difference for some trial outcomes remains debated. Second, trial participants are more selected than real-world memory-clinic populations; patients with extensive vascular disease, anticoagulation, advanced dementia, or atypical presentations are often underrepresented. Third, biomarker positivity confirms AD pathology but does not exclude mixed pathologies, which are common in older adults.[3-5,10,32]

Fourth, mechanistic plausibility should not be confused with therapeutic validation. Neuroinflammation, oxidative stress, mitochondrial injury, and BBB dysfunction are attractive targets, but many agents in these categories remain investigational or have failed to show clear clinical benefit. These axes should therefore be described as druggable and biologically important, but not as proven stand-alone treatments. A balanced interpretation is essential for clinically relevant translation of AD therapeutic strategies.[6,24,27,29]

FUTURE DIRECTIONS FOR A MULTIMODAL TARGET FRAMEWORK

Future AD therapy will likely require trials that are more adaptive than the classic single-agent model. A useful design would stratify patients by amyloid, tau, neurodegeneration, vascular burden, inflammatory activity, and APOE status, then test whether target-specific therapy changes the biomarker most directly linked to that pathway. This approach would reduce mechanistic noise and prevent therapies from being judged ineffective simply because they were tested in the wrong biological subgroup or disease stage.[6,8,14,32]

Combination therapy is a rational but still unproven direction. In principle, amyloid removal could be paired with tau propagation inhibitors, glial modulators, vascular protection, or metabolic support. In practice, combination trials must solve difficult safety questions, including additive edema or hemorrhage risk, immune activation, hepatic or renal toxicity, and the burden of repeated imaging and biomarker testing. Combination therapy is therefore best viewed as a future framework rather than a current standard.[5,6,18,19]

Finally, outcome measures should evolve with disease stage. Preclinical trials may require biomarker or digital cognitive endpoints over long follow-up, early symptomatic trials may combine global clinical scales with amyloid and tau markers, and later-stage trials may prioritize function, behavioral symptoms, caregiver burden, and safety. A staged endpoint

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strategy provides a clinically nuanced framework for both early diagnosis and long-term dementia care.[6,8,10,32]

CONCLUSIONS

AD druggability has entered a biomarker-guided era. Amyloid is clinically validated but incomplete; tau is biologically central and clinically proximal; neuroinflammation, BBB dysfunction, vascular injury, mitochondrial stress, and metabolic vulnerability are major amplifiers and potential combination targets. A clinically useful framework should synthesize these targets across disease stage rather than list mechanisms independently.

Accurate clinical translation requires avoiding outdated or imprecise statements, especially the implication that cholinesterase inhibitors slow disease progression or that aducanumab remains a routine contemporary treatment. The current therapeutic framework emphasizes early diagnosis, biomarker confirmation, realistic treatment effects, ARIA monitoring, Korean appropriate-use recommendations, and the need for multimodal interventions.

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