Journal of Health, Wellness and Community Research
ISSN: 3007-0570

OPEN ACCESS

JHWCR

Type: A Narrative Review
Published: 09 September 2025
Volume: III, **Issue:** XII
DOI: https://doi.org/10.61919/4892av69

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Received 04-08-25 **Accepted** 06-09-2025

Authors' Contributions
Concept: AK; Design: ZY; Data Extraction: AK; Analysis: ZY; Drafting: AK, ZY

Declarations
No funding was received for this study. The authors declare no conflict of interest. The study received ethical approval. All participants provided informed consent.

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Possible Targets for the Treatment of Alzheimer's Disease – A Narrative Review

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ABSTRACT

Background: Alzheimer's disease (AD) accounts for 60–70% of dementia cases worldwide, with over 55 million people currently affected and numbers projected to triple by 2050. Despite extensive research, most therapies remain symptomatic, and the global burden continues to rise. Objective: To narratively synthesize recent evidence on approved and investigational therapies for AD, emphasizing mechanisms, efficacy signals, safety, and clinical implementation challenges. Methods: Literature from PubMed/MEDLINE, ClinicalTrials.gov, and FDA/EMA regulatory documents published between 2019 and 2025 was reviewed. Priority was given to pivotal randomized controlled trials, regulatory labels, and high-quality systematic reviews. Data were extracted on mechanisms of action, clinical outcomes, adverse effects, and monitoring requirements, and narratively synthesized. Results: Acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA antagonist memantine consistently improve cognitive scores by 1–3 points on standard scales, with benefits lasting 6–12 months before decline resumes. Combination therapy yields marginally greater effects but is limited by tolerability and cost. Aducanumab demonstrated amyloid reduction but failed to show consistent clinical benefit and was discontinued in 2024. In contrast, lecanemab (CLARITY-AD, n≈1800) slowed cognitive decline by ~27% on the CDR-SB over 18 months and achieved FDA approval in 2023, while donanemab (TRAILBLAZER-ALZ-2, n≈1700) reduced decline by ~35% and gained approval in 2024, though both carry a 20–30% risk of amyloid-related imaging abnormalities (ARIA) requiring MRI monitoring. Tau immunotherapies such as AADvac-1 and bepranemab show robust target engagement but have yet to demonstrate cognitive efficacy. Adjunctive approaches, including masitinib (tyrosine kinase inhibition), intranasal insulin, and albumin/plasma exchange (AMBAR study), report modest signals in exploratory endpoints but remain unconfirmed. Nanoparticle and exosome-based platforms improve blood–brain barrier penetration in preclinical models, though human translation is limited. Conclusion: Symptomatic therapies remain relevant but modest in impact. The approvals of lecanemab and donanemab mark a pivotal shift toward disease-modifying treatment, albeit with safety and implementation challenges. Tau-directed strategies, anti-inflammatory agents, metabolic modulators, and regenerative approaches are promising but unproven. Future progress will depend on integrating biomarker-driven diagnosis, rigorous ARIA management, equitable health-system planning, and development of multimodal therapeutic combinations.

Keywords
Alzheimer's disease; dementia; amyloid-beta; tau; monoclonal antibodies; ARIA; neuroinflammation; nanomedicine; disease-modifying therapy.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia and a growing global public-health priority. More than 55 million people currently live with dementia worldwide, a figure projected to rise steeply as populations age, straining care systems and economies (1). The largest proportional increases are expected in low- and middle-income countries where diagnostic capacity, specialist services, and caregiver support may already be limited, underscoring equity and access challenges that run in parallel with scientific progress (2). Although disease-modifying monoclonal antibodies have recently entered clinical use for early AD, most individuals remain untreated or undertreated, and many health systems are only beginning to organize safe, scalable pathways for biomarker-guided diagnosis and therapy. These realities motivate a narrative synthesis that balances mechanistic advances with real-world implementation considerations. (1,2)

Burden & trajectory

Contemporary estimates place the global dementia population above 55 million; projections consistently forecast a doubling by 2030 and ~139–153 million by 2050, depending on model assumptions (1–3). Beyond prevalence, dementia carries profound societal costs through loss of independence, caregiver burden, and health-system expenditures; these impacts escalate nonlinearly as disease advances. For South Asia and other low- and middle-income regions—including Pakistan—the demographic shift toward older age structures means that absolute case counts will

surge, with the majority of new cases arising where resources are scarcest (2). Framing AD within this trajectory clarifies why incremental symptomatic benefits are insufficient; therapies must ultimately bend long-term disability curves and be deliverable at scale. (1–3)

Etiology & risk snapshot

AD pathogenesis is multifactorial, integrating aberrant amyloid-β processing and clearance, tau hyperphosphorylation and propagation, synaptic failure, neuroinflammation, and vascular/ blood–brain barrier dysfunction. Age remains the strongest non-genetic risk factor. Among genetic influences, the apolipoprotein E ε4 (APOE ε4) allele is the most robust susceptibility factor for late-onset AD at the population level, modifying amyloid and lipid biology and interacting with inflammatory pathways; importantly, ε4 carriage is neither necessary nor sufficient for disease, which supports a probabilistic—rather than deterministic—view of genetic risk (4). Across the life course, modifiable vascular-metabolic exposures contribute meaningfully to incident dementia. The Lancet Commission highlights a set of modifiable risk factors—hypertension, diabetes, obesity, smoking, hearing loss, low education, physical inactivity, depression, and social isolation—whose cumulative reduction could delay or prevent a substantial fraction of cases; recent updates add untreated vision loss and high low-density lipoprotein cholesterol to this list, emphasizing cardiometabolic health and sensory restoration as prevention opportunities (5,6). Taken together, these data argue for an integrative model in which genetic susceptibility, aging biology, and modifiable vascular-metabolic factors converge to drive neurodegeneration. (4–6)

Purpose & scope

Given this burden and the multifactorial biology, a multimodal therapeutic strategy is the logical next step. This narrative review therefore aims to: (i) summarize currently approved symptomatic therapies and place them in context; (ii) synthesize near-term disease-modifying pipelines with emphasis on the anti-amyloid monoclonal antibodies now approved for early AD and on tau-directed candidates nearing pivotal readouts; (iii) highlight adjunct approaches—targeting neuroinflammation, metabolic pathways, and blood–brain barrier drug delivery (including nanocarriers)—that may complement core disease-modifying agents; and (iv) outline practical implementation, including biomarker confirmation, APOE ε4 counseling, amyloid-related imaging abnormality (ARIA) risk management, MRI monitoring logistics, and health-system capacity. This scope is designed to bridge mechanistic progress with bedside realities so that clinicians, patients, and health services can navigate evidence-based options while anticipating the move toward rational combination therapy. (1,2)

METHODS (SEARCH STRATEGY & SCOPE)

This narrative review synthesized evidence from PubMed/MEDLINE, ClinicalTrials.gov, and regulatory documents from the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) published between January 1, 2019 and September 5, 2025, in English (1–3). Search strings combined keywords and MeSH terms for “Alzheimer*,” “disease-modifying,” “lecanemab,” “donanemab,” “aducanumab,” “tau immunotherapy,” “BACE,” “ARIA,” “APOE,” “intranasal insulin,” “plasma exchange,” “nanoparticle*,” “exosome*,” and “drug delivery,” using Boolean operators AND/OR. Inclusion prioritized regulatory labels and prescribing information, pivotal randomized controlled trials, and high-quality systematic reviews/meta-analyses; large observational cohorts and mechanistically informative translational studies were considered secondarily where they clarified safety, eligibility, or implementation (4–6). Case reports and small uncontrolled series were excluded unless they introduced a clearly novel mechanism or safety signal. For included sources, we extracted indication, population, diagnostic requirements (e.g., amyloid confirmation), dosing/monitoring (including MRI schedules), cognitive and functional outcomes, and adverse events (with emphasis on ARIA). Evidence was integrated via narrative synthesis; no quantitative meta-analysis or formal risk-of-bias scoring was undertaken, and the review was not prospectively registered. References are organized in Vancouver style by order of appearance. (1–6)

PATHOPHYSIOLOGY SNAPSHOT

Alzheimer’s disease (AD) emerges from intersecting biological axes rather than a single lesion, which helps explain both its heterogeneity and the partial effects of monotherapy. In the amyloid pathway, amyloid precursor protein (APP) is cleaved by β-secretase (BACE1) and γ-secretase to generate amyloid-β (Aβ) peptides; soluble oligomers perturb synaptic receptor signaling, while fibrils accumulate into plaques (7).

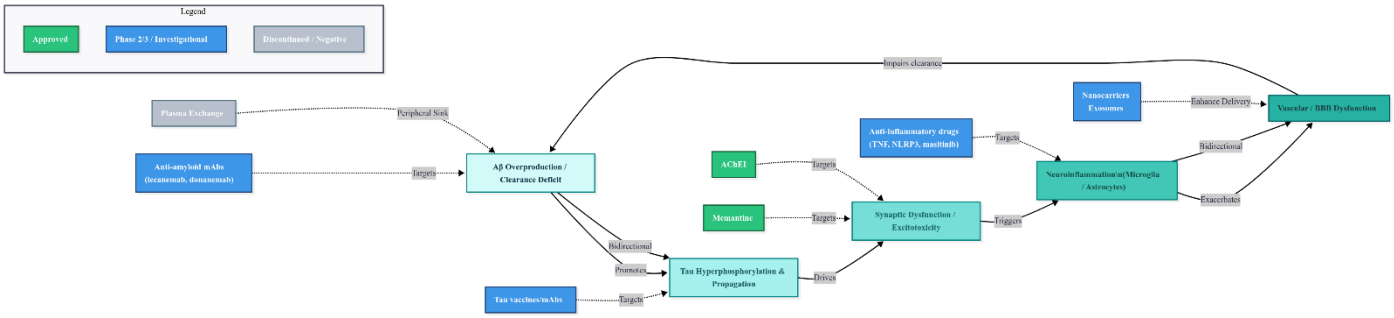

Figure 1 Figure 1. Pathophysiological Axes of Alzheimer’s Disease and Therapeutic Entry Points

Clearance normally occurs via microglial phagocytosis, enzymatic degradation, glymphatic flow during sleep, and blood–brain barrier (BBB) transport (LRP1-mediated efflux; RAGE-mediated influx); aging, APOE ε4, and cerebrovascular disease impair these routes and promote parenchymal and vascular deposition (8,9). Tau pathology begins as site-specific hyperphosphorylation by kinases such as GSK3β and CDK5, followed by misfolding, aggregation, and trans-synaptic spread of pathogenic tau “seeds”; the topography of tau, more than amyloid, aligns closely with clinical decline (10). At synapses, Aβ oligomers and pathological tau disrupt NMDA receptor and mGluR5 signaling, calcium homeostasis, and long-term potentiation, driving early network dysfunction before overt neuronal loss (11). Neuroinflammation is not merely epiphenomenal: microglia (shaped by risk genes including TREM2) and reactive astrocytes engage complement (C1q/C3) and inflammasome pathways (e.g., NLRP3), amplifying synaptic pruning and injury (12). Parallel vascular injury—including cerebral amyloid angiopathy, endothelial and pericyte

dysfunction, BBB leakage, and glymphatic failure—links systemic cardiometabolic risk to brain accumulation of toxic proteins and hypometabolic stress (13). Together, these processes—Aβ dyshomeostasis, tau propagation, synaptic failure, inflammatory amplification, and vascular/BBB breakdown—form a self-reinforcing network that drives progressive cognitive and functional decline (7–13).

THERAPEUTIC ENTRY POINTS (ALIGNMENT FOR FIGURE 1)

Therapies map onto these axes at distinct nodes. Cholinesterase inhibitors increase cortical acetylcholine to partially compensate for early cholinergic denervation and improve signal-to-noise at synapses; they do not alter core pathology (14). Memantine, a low-to-moderate affinity uncompetitive NMDA receptor antagonist, mitigates excitotoxicity and calcium overload that follow oligomer-induced receptor dysregulation, with symptomatic benefits in moderate–severe stages (15). Anti-amyloid monoclonal antibodies (e.g., lecanemab, donanemab) bind soluble protofibrils or deposited fibrils and promote microglial Fc-mediated clearance, lowering plaque burden and modestly slowing clinical decline in early AD; their class-specific risk—amyloid-related imaging abnormalities (ARIA)—likely reflects interactions between vascular amyloid, permeability, and immune activation along the neurovascular unit (16). Earlier secretase inhibitors (BACE1/γ-secretase) targeted Aβ production but were halted for safety/efficacy limitations, shifting emphasis toward clearance rather than upstream blockade (17). Tau-directed strategies intervene at phosphorylation (kinase inhibition), aggregation (anti-aggregants), or propagation (active/passive anti-tau immunotherapies) to reduce misfolded tau burden and spread; demonstrating cognitive benefit remains the pivotal hurdle despite encouraging target engagement (10,18). Neuroinflammation modulators aim at microglial phenotype (TREM2 signaling, CSF1R), complement, or inflammasome (NLRP3) to dampen maladaptive pruning and cytokine cascades (12,19). Metabolic and systemic interventions—such as intranasal insulin—seek to normalize brain insulin signaling and synaptic metabolism (20). Vascular/BBB-focused approaches include risk-factor control and investigational methods that enhance efflux or reduce influx of Aβ (e.g., LRP1/RAGE axis); plasma exchange operates as a peripheral "sink," potentially shifting Aβ gradients to favor brain efflux (21). Finally, drug-delivery innovations—polymeric nanoparticles, liposomes, and exosome-like carriers—leverage receptor-mediated transcytosis (e.g., transferrin or LDL receptor pathways) to overcome BBB barriers and increase CNS exposure of both symptomatic and disease-modifying agents (22). Figure 1 (schematic) will depict these nodes and arrows: production vs clearance of Aβ; tau modification and spread; synaptic receptors and calcium flux; microglia/astrocyte-complement loops; and the vascular/BBB interfaces through which risk factors and therapeutics exert their effects (7–22).

SYMPTOMATIC THERAPIES (CURRENT STANDARD)

Symptomatic drugs remain cornerstone options for many patients but provide modest, time-limited improvements in cognition, function, and global ratings without altering disease progression. Current guidance recommends acetylcholinesterase inhibitors (AChEIs) for mild–moderate Alzheimer's disease (AD) and memantine for moderate disease when AChEIs are contraindicated/intolerant or for severe AD; use in non-AD dementias is limited to specific scenarios (1).

Acetylcholinesterase inhibitors

Donepezil, rivastigmine, and galantamine produce small but clinically meaningful gains on cognitive scales and global impression in mild–moderate AD, with some benefit on activities of daily living; there is no consistent superiority among agents (2). Common adverse effects are gastrointestinal (nausea, vomiting, diarrhea, anorexia/weight loss) and cholinergic (bradycardia, syncope), with insomnia/vivid dreams occasionally seen with donepezil; careful titration and dosing with food can improve tolerability (1,2). Rivastigmine transdermal patch offers similar symptomatic benefit with lower GI intolerance and can aid adherence in patients who struggle with swallowing or multiple daily dosing, although application-site reactions (erythema, pruritus) and dermatitis can occur (1,3,4). (1–4)

NMDA receptor antagonist (and combination use)

Memantine—an uncompetitive NMDA receptor antagonist—is indicated for moderate–severe AD (or moderate AD when AChEIs are not suitable). Trials and meta-analyses show modest improvements in global status, cognition, behavior, and daily function versus placebo, with a generally favorable tolerability profile; common adverse effects include dizziness, headache, confusion, and constipation (5–7). In patients already on donepezil, adding memantine yields small additional benefits on global/functional outcomes in moderate–severe AD, though the effect size is limited and should be weighed against pill burden, cost, and individual tolerability (6,7). (5–7)

Editing notes applied: drug names standardized (generic first), claims restricted to symptomatic relief, tolerability summarized qualitatively, and adherence considerations highlighted for the rivastigmine patch.

AGENTS NO LONGER PRORESSING / NEGATIVE

BACE1 inhibitors. Multiple oral β-secretase (BACE1) inhibitors have been discontinued after late-stage failures and/or safety concerns. Verubecestat failed to improve outcomes and was associated with worsening cognition and function in prodromal AD (APECS) despite amyloid lowering; the earlier EPOCH mild–moderate AD study had already been stopped for futility (23,24). Umibecestat (CNP520) was halted across the Generation prevention program after interim unblinding indicated an unfavorable risk–benefit profile, including cognitive worsening on some measures (25,26). Elenbecestat's Phase 3 MISSION AD1/AD2 trials were terminated on Data Safety Monitoring Board advice for safety and lack of benefit; the sponsor ended the open-label extension as well (27–29). Collectively, these outcomes have shifted the field away from upstream Aβ production blockade toward clearance strategies, with renewed emphasis on patient selection and safety monitoring.

Anti-amyloid monoclonals with negative Phase 3s. Gantenerumab did not meet the primary endpoint in GRADUATE I/II for early AD and Roche subsequently discontinued most gantenerumab trials (30,31). Crenezumab failed to slow clinical decline in the CREAD 1/2 Phase 3 studies and also did not meet coprimary endpoints in the autosomal-dominant AD Colombia prevention trial, despite acceptable tolerability (32,33). These results matter because they help calibrate target engagement versus clinical effect, highlight the importance of plaque removal magnitude, and inform trial design (population, stage, biomarker thresholds). In parallel, for the approved anti-amyloid antibodies, safety requirements are now codified on label with boxed warnings for ARIA and defined MRI schedules (e.g., baseline and early on-treatment scans; recent guidance moved an MRI earlier to before the third infusion for lecanemab), sharpening real-world risk management (39–41).

Tau-directed therapies (concise state-of-the-field)

Kinase/aggregation approaches. Early attempts to blunt tau hyperphosphorylation (e.g., GSK3β inhibitors) or prevent aggregation produced target engagement or biomarker signals without convincing cognitive benefit in Phase 2/3, often limited by dose, off-target effects, or inadequate brain exposure. The broader lesson is that downstream tau pathology tracks disability, but modulating a single kinase or aggregation step may be insufficient once multicentric propagation is underway and synaptic/vascular injury is entrenched (10). Recent work prioritizes propagation blockade and better patient staging (seed-rich, amyloid-positive early AD) to maximize signal detection.

Tau immunotherapies.

Active vaccines. AADvac-1 has shown immunogenicity with favorable safety and biomarker movement (e.g., plasma NfL and CSF tau) in Phase 2, though trials were not powered for definitive clinical endpoints—supporting larger, earlier-stage studies (34). ACI-35.030, a liposomal phospho-tau vaccine, has demonstrated robust anti-pTau antibody responses and maturation toward pathologic epitopes; a Phase 2b (Reτain) study in preclinical/early AD is planned to assess clinical signals (35).
Passive monoclonals. Tilavonemab (ABBV-8E12) did not show efficacy in a Phase 2 early-AD trial, underscoring challenges for N-terminal/epitope selection and dosing windows (36). Bepranemab (UCB0107), which targets mid-region tau to interrupt spread, completed a Phase 2a study in prodromal–mild AD with results presented at CTAD 2024 (clinical, safety, and imaging endpoints reported); full peer-reviewed efficacy data are awaited, and confirmatory trials will be required to establish cognitive benefit (37,38). Overall, tau programs are biologically on-target (binding and biomarker effects) but clinically unproven; success likely hinges on earlier intervention, optimized epitope/affinity, and possibly combination with Aβ-lowering to reduce upstream seeding pressure (10,18).

ADJUNCT & EMERGING STRATEGIES

Neuroinflammation targets.

Microglial and cytokine signaling remain attractive targets. Selective soluble TNF inhibition (eg, XPro/pegipanermin) has moved into phase-2 testing with mixed early readouts on cognition/white-matter biomarkers, while maintaining a plausible risk–benefit profile mechanistically distinct from non-selective TNF blockers (1). By contrast, perispinal etanercept is supported mainly by open-label/very small studies; robust randomized evidence is lacking and it is not recommended for routine care (2,3). Upstream innate-immunity approaches such as NLRP3 inflammasome inhibition (eg, dapansutrile and other candidates) have encouraging preclinical/early clinical safety packages but no efficacy data in AD yet (4–6).
Tyrosine-kinase modulation with masitinib (mast-cell/microglial inhibitor) showed a statistically significant ADAS-Cog advantage at 24 weeks in one phase-3 adjunctive trial (4.5 mg/kg/day arm), but requires confirmatory studies and careful AE management (rash, neutropenia, hypoalbuminemia) (7). Finally, the "bacterial protease" hypothesis targeting P. gingivalis gingipains (atuzaginstat) produced a negative/terminated phase 2/3 program due to hepatic AEs and failure on primary cognitive endpoints; this avenue remains investigational only (8).
Metabolic modulation. Intranasal insulin (INI) remains signal-generating rather than practice-changing. A multicenter phase 2/3 RCT (2014–2018) reported feasibility and safety but was confounded by device performance and did not demonstrate consistent cognitive benefit; pooled meta-analyses show mixed results with, at best, small effects and significant heterogeneity (9–12). Routine clinical use cannot be recommended outside trials.

Plasma-derived interventions.

Albumin/plasma exchange (AMBAR) produced exploratory signals on function and survival in subsets of mild-to-moderate AD, but heterogeneity and multiple comparisons preclude firm conclusions; confirmatory, independently run trials are needed before clinical adoption (13,14).
Regenerative/growth-factor approaches. Neurotrophin strategies (eg, AAV2-NGF) showed acceptable safety and target engagement but no reproducible clinical efficacy to date (15,16). Mesenchymal stromal cell (MSC) products—including intravenous or intrathecal delivery—appear feasible and generally safe in early studies across neurologic indications; Alzheimer's-specific programs (eg, Lomecel-B) are in small phase 1/2 trials with preliminary signals that require larger randomized confirmation (17–20). At present these approaches remain investigational.

Drug-Delivery Innovations (Translational Lens)

Rationale. The BBB sharply limits CNS exposure for large biologics and many small molecules; strategies that increase brain bioavailability without systemic toxicity are essential for next-generation AD therapeutics (21,22). Platforms. Liposomes and polymeric/lipid nanoparticles can encapsulate cholinesterase inhibitors, anti-amyloid peptides, or nucleic acids and use receptor-mediated transport to improve CNS delivery in models (23,24). Exosomes/small extracellular vesicles offer native BBB transcytosis, immune stealth, and tunable surface ligands; multiple preclinical studies and early translational reviews highlight their potential to ferry small molecules and RNA cargo for neurodegeneration (25–29). In contrast, carbon-nanotube and other advanced vectors show impressive payload capacity but carry unresolved neurotoxicity/manufacturability and regulatory hurdles (22). Readiness level. Most nanocarrier/exosome programs are preclinical; a few have entered first-in-human or early feasibility phases in neurological conditions, but no platform yet has an approved AD indication. Bridging the translational gap will require standardized manufacturing/characterization, scalable quality control, and rigorous pharmacokinetic–pharmacodynamic correlations in humans (21,25–27,29).

Clinical Implementation, Safety & Future Directions

Eligibility & workup. For anti-amyloid mAbs, restrict to early symptomatic AD (MCI due to AD or mild dementia) with confirmed amyloid pathology. Labels specify confirmation before treatment (amyloid PET or CSF), with plasma biomarkers increasingly used as a triage step in clinical pathways. Discuss APOE ε4 status prior to initiation because ε4/ε4 homozygosity substantially increases ARIA risk and influences

monitoring and shared decision-making (30–33). Screen for comorbidities (uncontrolled hypertension, extensive microbleeds/siderosis, recent ICH) and concomitant antithrombotics.

ARIA risk management. Obtain a baseline MRI. Lecanemab: MRI before the 3rd, 5th, 7th, and 14th infusions (typically within ~1 week of dosing), plus symptom-triggered scans; boxed warning emphasizes rare but serious edema/hemorrhage and cautions around thrombolysis when ARIA-E is possible (30). Donanemab (Kisunla): MRI before the 2nd, 3rd, 4th, and 7th infusions; 2025 label update introduces a gradual titration intended to lower ARIA-E incidence (31–34). Many expert groups advise APOE genotyping and heightened caution/avoidance in patients requiring systemic anticoagulation or dual antiplatelet therapy (32). Provide clear patient education on ARIA symptoms and when to seek urgent care.

Health-system considerations. Implementation hinges on infusion capacity, MRI access, and payer requirements. In the U.S., Medicare coverage for lecanemab occurs under the National Coverage Determination using a registry-based "coverage with evidence development" model, which creates additional workflow and documentation steps (35–38). Early real-world experiences show feasibility but highlight resource demands and equity concerns (access to PET/CSF testing, rural MRI access, cost-sharing) (39–41).

Where the field is going. Expect movement toward combinations (eg, anti-Aβ + anti-tau ± anti-inflammatory), earlier intervention (preclinical/prodromal stages), adaptive platform trials, and expanded real-world evidence programs to refine risk stratification and monitoring. These trajectories are already reflected in evolving labels, MRI schedules, and payer-registry infrastructures for anti-amyloid agents (30–38).

Key research gaps. Stronger surrogate–clinical correlations (plaque/tau PET and plasma p-tau vs. meaningful cognitive/functional outcomes); validated tau efficacy endpoints; long-term safety (including hemorrhage risk in ε4/ε4 and anticoagulated patients); and predictive biomarkers to select responders/non-responders—and to tailor monitoring intensity—remain top priorities (30–32,39–41).

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