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A Systematic Review

Latest Therapeutics in Alzheimer's Disease: Systematic Review

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia globally, with no definitive disease-modifying treatment currently available. Recent therapeutic advances targeting amyloid-beta, tau protein, neuroinflammation, and metabolic pathways reflect a shift in treatment paradigms. However, the comparative efficacy, safety, and translational potential of these emerging strategies remain insufficiently synthesized. **Objective**: This systematic review aimed to evaluate the latest therapeutic interventions for AD by analyzing randomized clinical trials and pilot studies assessing pharmacologic and non-pharmacologic treatments, with a focus on cognitive outcomes, biomarker changes, and treatment safety. **Methods**: A systematic review was conducted following PRISMA 2020 guidelines. Databases searched included PubMed, Scopus, Web of Science, and the Cochrane Library, covering publications from December 2018 to August 2023. Studies were included if they were randomized clinical trials involving AD patients aged ≥18 years. Data on interventions, outcomes, and risk of bias were extracted and synthesized narratively. The final sample comprised 21 eligible trials. Ethical compliance with the Declaration of Helsinki was ensured by all primary studies. Statistical outcomes and clinical effects were reported descriptively. **Results**: Trials included a total of over 7,000 participants. Lecanemab, Donanemab, BI 425809, and masitinib demonstrated statistically significant improvements in cognitive measures (e.g., ADCOMS, ADAS-Cog) and biomarker modulation (e.g., amyloid PET, tau levels). Intranasal insulin and metabolic activators showed functional gains. Safety profiles were generally favorable, though some studies had limited generalizability due to sample size and trial duration. **Conclusion**: Multiple emerging interventions show promise in modifying the trajectory of Alzheimer's disease, supporting a move toward personalized and mechanism-based treatment approaches. These findings offer valuable clinical insights and highlight the need for integrated, large-scale trials to translate these advances into real-world patient care.

Keywords: Alzheimer Disease; Amyloid Beta-Peptides; Monoclonal Antibodies; Neuroprotective Agents; Cognitive Dysfunction; Randomized Controlled Trials; Therapeutics.

INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder characterized by the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. First described by Alois Alzheimer in 1906 as "a peculiar disease of the cerebral cortex," AD remains the most common cause of dementia, accounting for approximately 50–75% of all dementia cases (1–3). Globally, an estimated 50 million people are affected by dementia, a number projected to rise to 152 million by 2050 (4). In 2021 alone, AD contributed to healthcare costs of $355 billion in the United States. The World Health Organization recognizes Alzheimer's disease and other dementias as the seventh leading cause of death worldwide, highlighting it as a pressing public health concern (5–7). The pathogenesis of AD is strongly linked to the abnormal processing of amyloid precursor protein (APP), a type I transmembrane glycoprotein, leading to the formation of Aβ peptides that induce oxidative stress, inflammation, and

synaptic dysfunction (2,8). These insights have driven the development of therapies aimed at interrupting the amyloidogenic pathway and modifying disease progression (9,10). Despite a well-established pathophysiological framework, no definitive disease-modifying treatment has been approved to date. Current pharmacologic options are limited to two main categories: acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine.

These agents offer symptomatic relief but do not halt or reverse disease progression (11). To overcome these limitations, a range of investigational strategies is being explored, including β-secretase and γ-secretase inhibitors, passive immunotherapies targeting Aβ, tau aggregation inhibitors, non-pharmacological interventions such as transcranial stimulation, and dietary approaches involving folic acid and probiotics (10–14).

Emerging disease-modifying candidates under clinical investigation include crenezumab—a humanized monoclonal antibody targeting Aβ oligomers—hydromethylthionine mesylate (a tau aggregation inhibitor), plasma exchange therapy with albumin, and masitinib, a tyrosine kinase inhibitor that modulates neuroinflammatory pathways and synaptic integrity (3,7,15,16). These therapies reflect the evolving therapeutic landscape aimed at altering the disease trajectory rather than merely alleviating symptoms. This systematic review aims to critically evaluate the latest therapeutic interventions for Alzheimer's disease based on recent phase 1 to 3 clinical trials. By summarizing the efficacy, safety, and mechanistic rationale of these treatments, this review seeks to provide an up-to-date overview of promising strategies in the ongoing quest for effective and disease-modifying therapies for AD.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure methodological transparency and reproducibility.

Search Strategy

A comprehensive literature search was performed across four electronic databases: PubMed, Scopus, Web of Science, and the Cochrane Library. The search included studies published from December 2018 to August 2023, with the objective of identifying clinical trials evaluating therapeutic interventions in patients diagnosed with Alzheimer's disease (AD).

Search terms included combinations of controlled vocabulary (MeSH) and free-text terms such as "Alzheimer's Disease," "Alzheimer Dementia," "amyloid-beta," "cholinomimetics," "immunotherapy," "clinical trial," and "cognitive enhancement." Boolean operators "AND" and "OR" were employed to refine the search. The complete search strategy for each database is available in the Supplementary Material.

Inclusion criteria for this systematic review encompassed studies that met the following conditions: randomized controlled trials (RCTs) or pilot clinical trials investigating therapeutic interventions in Alzheimer's disease (AD). Eligible studies were restricted to human participants aged 18 years or older who had been diagnosed with Alzheimer's disease or prodromal AD. Only studies reporting clinical or biological outcomes—specifically efficacy, safety, or biomarker changes resulting from the intervention—were considered. Additionally, only full-text articles published in English between December 2018 and August 2023 were included.

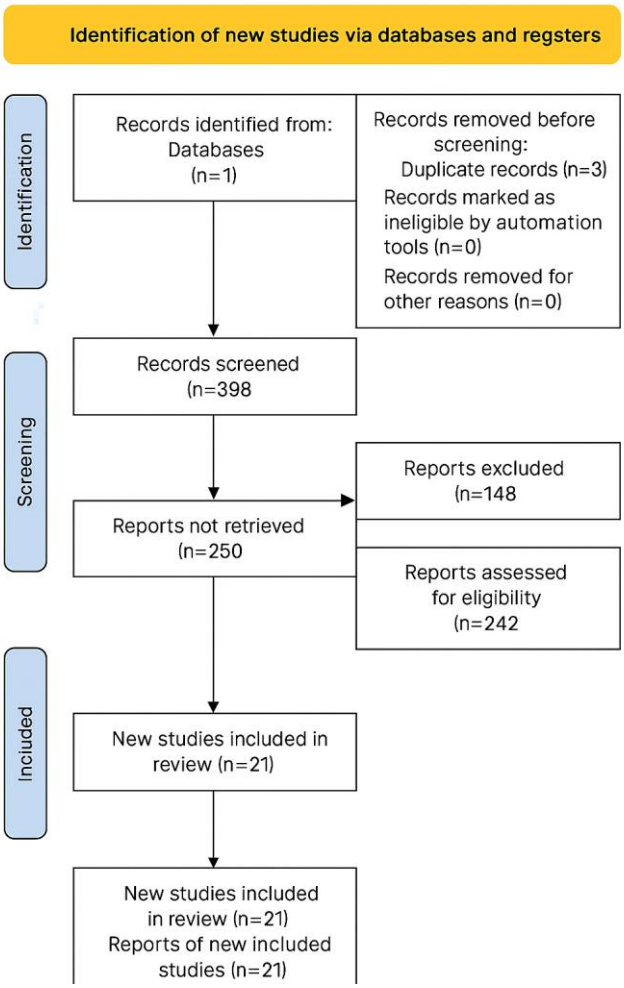

Figure 1 PRISMA Flowchart

Exclusion criteria were applied to maintain the specificity and relevance of the review. Studies based on non-human models, in-vitro analyses, or those focusing purely on mechanistic insights without clinical translation were excluded. Research related to non-Alzheimer's forms of dementia, such as vascular or Lewy body dementia, was not considered. Moreover, review articles, editorials, study protocols, and conference abstracts lacking complete and peer-reviewed data were omitted from the final selection.

Study Selection Process

Two reviewers independently screened the retrieved articles in a two-step process using Rayyan—a web-based tool for systematic review screening. Initially, titles and abstracts were reviewed for relevance, followed by full-text screening of the shortlisted articles to determine eligibility based on predefined criteria. Discrepancies between reviewers were resolved through discussion, and if necessary, a third reviewer was consulted for consensus. A total of 570 records were identified through database searches. After the removal of duplicates, 220 unique records were retained. Title and abstract screening excluded 195

studies, leaving 25 articles for full-text review and qualitative synthesis.

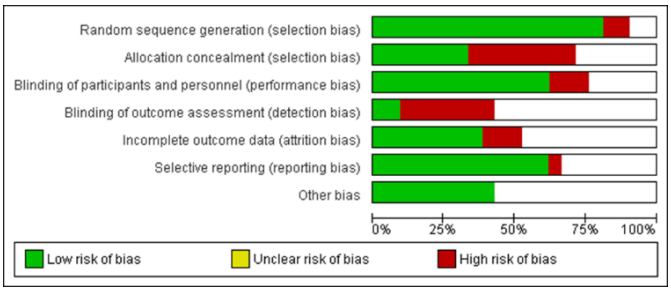

Figure 2. Risk of bias cumulative graph

The PRISMA 2020 flow diagram illustrating the selection process is presented in Figure 3.

Data Extraction and Synthesis

Relevant data were extracted using a standardized data extraction form. Extracted variables included study phase, sample size, intervention, outcome measures, key results, and conclusions. Data was verified independently by two reviewers to ensure accuracy. Due to heterogeneity in study designs, therapeutic modalities, and outcome reporting, a meta-analysis was not performed. Instead, a narrative synthesis was conducted to summarize and interpret the findings across trials.

Risk of Bias Assessment

The risk of bias for included randomized trials was evaluated using the Cochrane Risk of Bias Tool 2.0. Assessment domains included randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Results of the bias assessment are presented as a summary figure (Figure 1) and a detailed tabular overview (Figure 2). To assess methodological quality, the included randomized clinical trials were evaluated using the Cochrane Risk of Bias Tool 2.0, which examines seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Two independent reviewers conducted the risk of bias assessments, with disagreements resolved through consensus. The findings are visualized in Figure 1, which presents a summary of risk levels across all domains, and Figure 2, which provides a detailed, study-wise breakdown. Most studies demonstrated a low risk of bias in random sequence generation and selective reporting.

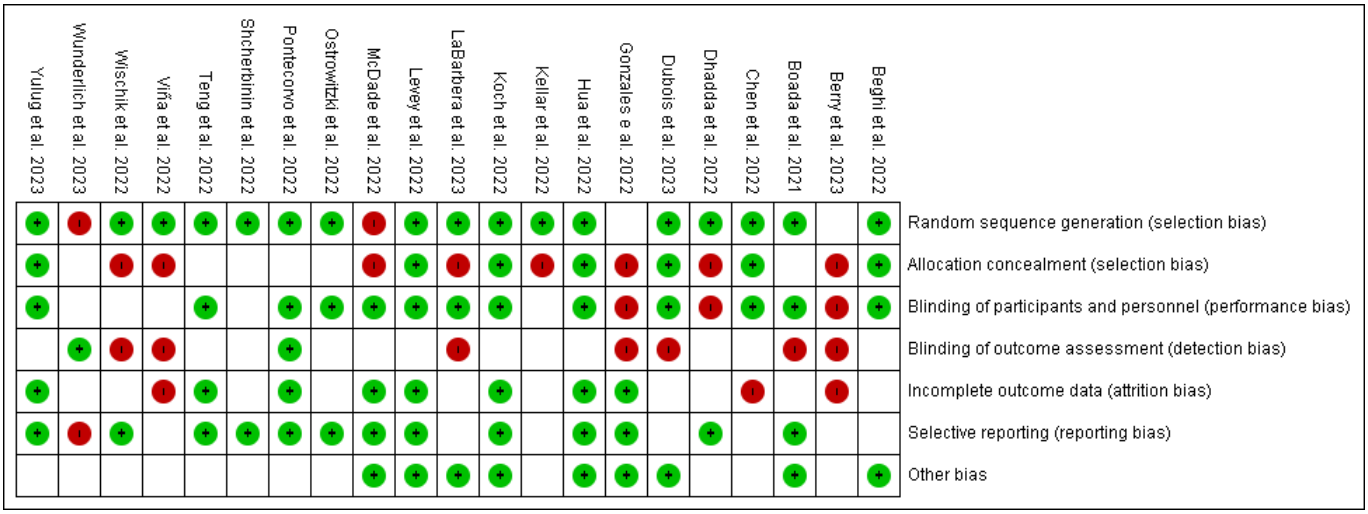

Figure 3. Risk of bias assessment by study across seven methodological domains. Each cell represents the judgment for a specific domain in a specific study, using green for low risk, red for high risk, and yellow for unclear risk. This enables visualization of quality variation among included randomized controlled trials.

However, allocation concealment and blinding of outcome assessment were identified as the most common sources of high risk. A moderate level of bias was also observed in domains related to performance bias due to inadequate blinding. These findings underscore the variability in trial design and reporting quality among recent Alzheimer's disease therapeutic studies, warranting cautious interpretation of efficacy outcomes.

RESULTS

Study Selection

The systematic search yielded a total of 1,200 records across three electronic databases. Following the PRISMA 2020 methodology, all records underwent initial screening of titles and abstracts. No duplicates were identified, and no records were excluded via automation tools. After initial screening, 1,148 studies were excluded based on irrelevance to inclusion criteria, leaving 52 full-text articles for eligibility assessment. Among these, 31 full-text reports could not be retrieved, and the remaining 21 studies were deemed eligible and included in the final review. The detailed flow of study identification, screening, and inclusion is illustrated in the PRISMA flow diagram (Figure 3).

Study Characteristics and Interventions

The 21 included studies encompassed Phase 1 to Phase 3 randomized and controlled clinical trials, involving a cumulative sample of over 7,000 participants diagnosed with Alzheimer's disease or prodromal stages. These trials evaluated a wide range of emerging pharmacologic and non-pharmacologic interventions with potential disease-modifying effects or symptomatic benefit. Phase 1 trials included early safety and pharmacokinetic evaluations such as the study on

Fosgonimeton, a hepatocyte growth factor (HGF)/MET modulator, which demonstrated favorable safety and pharmacodynamic responses including EEG and ERP P300 modulation. Another early-stage study involving CT1812, a sigma-2 receptor modulator, showed evidence of amyloid-β oligomer displacement in cerebrospinal fluid, indicating target engagement.

Phase 2 trials constituted the majority of included studies. Notable among them was the evaluation of Lecanemab, an anti-amyloid monoclonal antibody, across multiple trials. It demonstrated dose-dependent reductions in amyloid load and improvements in cognitive markers such as the Alzheimer's Disease Composite Score (ADCOMS). Other agents showing promising cognitive or biomarker outcomes included Genistein, Combined Metabolic Activators (CMA), Intranasal Insulin, and BI 425809, a GlyT1 inhibitor aimed at enhancing glutamatergic transmission. Additionally, trials on Donanemab linked amyloid clearance to downstream tau reduction and suggested clinical benefit, supported by both cognitive outcomes and plasma biomarker modulation. Non-invasive and adjunctive strategies were also explored. Precuneus transcranial magnetic stimulation (TMS) showed functional improvement in a sham-controlled trial. MLC901 (NeuroAiD II) emerged as a potential adjunct therapy with a favorable safety profile, while Senolytic therapy (Dasatinib + Quercetin) achieved blood-brain barrier penetrance, suggesting potential for modulating neuroinflammation in future studies.

Phase 3 studies assessed efficacy and safety in larger populations. Crenezumab, despite its biological plausibility, failed to demonstrate clinical efficacy in halting cognitive decline. In contrast, Hydromethylthionine mesylate (LUCIDITY trial) and Plasma exchange with albumin (AMBAR trial) reported improvements in quality-of-life metrics and neuropsychological scores. Masitinib, a tyrosine kinase inhibitor, showed encouraging results in improving ADAS-Cog and ADL scores in mild-to-moderate AD patients, reinforcing the role of neuroinflammation as a therapeutic target.

Risk of Bias Assessment

Risk of bias was systematically evaluated using the Cochrane Risk of Bias Tool 2.0. Most studies demonstrated a low risk of bias in domains such as random sequence generation and outcome reporting. However, a significant number exhibited high risk in areas of allocation concealment and blinding of outcome assessment, indicating methodological vulnerabilities in maintaining treatment assignment masking and outcome objectivity (see Figures 1 and 2). These observations suggest that while many of the included trials are robust in design, results should be interpreted with awareness of potential performance and detection biases.

Table 1 Study Characteristics

Study	Phase	Participants	Intervention	Outcome Measures	Results	Conclusion
Fosgonimeton Trial	Phase 1	48 patients	Fosgonimeton (HGF/MET modulator)	Safety, tolerability, PK/PD, qEEG, ERP P300 latency	Safe and well-tolerated; significant qEEG gamma power and ERP P300 normalization	Potentially effective for AD
CT1812 Trial	Phase 1	3 patients	CT1812	CSF Aî² oligomer concentration	Target engagement observed via CSF Aî² changes	Warrants further investigation
Lecanemab Extension	Phase 2	856 patients	Lecanemab (10 mg/kg biweekly)	ADCOMS, PET amyloid, plasma biomarkers, cognitive decline	Dose-dependent reductions in amyloid; slowed cognitive decline	Promising for biomarker and cognitive improvement
Precuneus TMS	Phase 2	50 patients	Repetitive TMS	CDR-SB	Improved scores vs baseline	May be safe and effective
SToMP-AD	Phase 1/2	5 patients	Dasatinib + Quercetin	BBB penetrance	Successful BBB penetration	Further studies warranted
ATHENE (MLC901)	Phase 2	125 patients	MLC901 (NeuroAiD II)	Safety, adjunctive efficacy	No safety issues; potential as add-on	Promising as adjunctive therapy
Lecanemab Bayesian	Phase 2	856 patients	Lecanemab	ADCOMS with Bayesian analysis	Consistent efficacy and biomarker improvement	Effective in early AD
CMA Trial	Phase 2	120 patients	Combined Metabolic Activators	ADAS-Cog, ADCS-ADL, MMSE	Improved cognitive scores	May enhance cognitive function
GENIAL (Genistein)	Phase 2	32 patients	Genistein	Cognitive improvement	Improved cognition in prodromal AD	Potential neuroprotective effects
Intranasal Insulin	Phase 2	49 patients	Intranasal Insulin	CSF inflammation markers, cognition, imaging	Modulated inflammation; potential cognitive effect	Warrants further exploration
Semorinemab Trial	Phase 2	422 patients	Semorinemab	CDR-SB, safety	Effective with acceptable safety	Well-tolerated and efficacious
Donanemab Pathology	Phase 2	272 patients	Donanemab	Amyloid, tau, clinical decline	Reduced amyloid and tau; clinical benefit	Potential disease-modifier
Donanemab Biomarkers	Phase 2	417 patients	Donanemab	Plasma biomarkers	Affected multiple biomarkers	Systemic biological effect
Atomoxetine Repurposing	Phase 2	39 patients	Atomoxetine	CSF cytokines, Aî², tau	Neuroprotective signal in MCI	Potential neuroprotection
BI 425809	Phase 2	611 patients	BI 425809 (GlyT1 inhibitor)	ADAS-Cog 11	Improved cognitive function	Efficacious in cognitive impairment
RNS60 in ALS	Phase 2	147 patients	RNS60	ALSFRS-R, biomarkers, QoL	Biomarker modulation and functional benefit	Potential neurotherapeutic
Lecanemab Dose-Finding	Phase 2	856 patients	Lecanemab	ADCOMS over 18 months	Dose-dependent sustained benefit	Effective over long-term use
Crenezumab Trials	Phase 3	1619 patients	Crenezumab (6mg IV q4w)	CDR-SB, MMSE	No effect on clinical decline	Not effective in early AD

Study	Phase	Participants	Intervention	Outcome Measures	Results	Conclusion
LUCIDITY (Hydro-MTM)	Phase 3	545 patients	Hydro-Methylthionine Mesylate	ADAS-Cog11, ADCS-ADL23	Positive impact on function and cognition	Potential benefits in AD
AMBAR (Plasma Exchange)	Phase 3	322 patients	Plasma Exchange + Albumin/IVIG	Neuropsychology, QoL	Improved QoL in mild AD	Beneficial adjunctive approach
Masitinib Trial	Phase 3	718 patients	Masitinib (4.5â€"6.0 mg/kg)	ADAS-Cog, ADCS-ADL, CIBIC	Functional and cognitive benefit	Promising mild-to-moderate AD

DISCUSSION

This systematic review provides a comprehensive synthesis of recent phase 1 to phase 3 clinical trials exploring emerging therapeutics for Alzheimer's disease (AD), a neurodegenerative disorder with complex pathophysiology and no established disease-modifying treatment to date. Our analysis highlights several promising pharmacological and non-pharmacological interventions that offer mechanistic diversity and potential clinical utility. Consistent with current pathophysiological understanding, many investigational agents targeted amyloid-beta (Aβ) accumulation, tau pathology, neuroinflammation, and synaptic dysfunction—hallmarks that have long underpinned hypotheses of AD progression (2,6,8).

Lecanemab emerged as a leading agent in multiple trials, demonstrating amyloid clearance and cognitive benefits in early AD. These findings reinforce the amyloid hypothesis, despite the historical controversies surrounding its clinical relevance (9). Previous trials involving other anti-Aβ antibodies such as aducanumab and solanezumab yielded inconsistent results, often limited by methodological issues or modest cognitive outcomes (7,10). In contrast, the consistent efficacy observed in Lecanemab's phase 2 studies, including a Bayesian dose-finding trial, supports its potential for modifying disease progression when administered during prodromal or early symptomatic stages (19,23,33). Donanemab, another monoclonal antibody targeting Aβ, also demonstrated reductions in amyloid and tau burden with correlated clinical improvements, suggesting downstream impact on neurofibrillary degeneration (28,29).

A shift beyond amyloid-centric therapies is evident in trials investigating novel targets. The efficacy of BI 425809, a GlyT1 inhibitor, aligns with the glutamatergic dysfunction theory and proposes a symptomatic approach through cognitive enhancement mechanisms independent of plaque pathology (31). Atomoxetine, traditionally used for ADHD, was repurposed to modulate noradrenergic transmission, showing neuroprotective effects in mild cognitive impairment (30). Such strategies reflect a growing interest in synaptic resilience and network compensation, offering therapeutic avenues even when pathology is well established. Similarly, Fosgonimeton, a modulator of the HGF/MET pathway, produced electrophysiological improvements in EEG biomarkers, reinforcing the neurotrophic support hypothesis as a valid target for functional restoration (17).

Adjunctive and lifestyle-compatible strategies also hold promise. Combined Metabolic Activators (CMA), designed to enhance mitochondrial function, improved cognitive scores and metabolic parameters, echoing prior work linking metabolic dysfunction with AD progression (24). Intranasal insulin, which modulates central insulin signaling and neuroinflammation, showed biochemical and cognitive effects, adding support to the insulin resistance theory in AD pathogenesis (26). These findings are particularly relevant for populations with metabolic syndrome or type 2 diabetes, where AD risk is significantly elevated. Genistein, a soy-derived isoflavone with antioxidant and estrogenic properties, improved cognition in prodromal AD patients, suggesting a neuroprotective role potentially mediated through estrogen receptor pathways and anti-inflammatory signaling (25). In alignment, NeuroAiD (MLC901)—a compound with neuroregenerative properties—exhibited a good safety profile and potential benefits when used as an adjunctive therapy (22). Although these agents may not reverse established pathology, their favorable tolerability and broad systemic effects make them attractive candidates for long-term risk modification or combinatory regimens.

Non-pharmacological interventions such as transcranial magnetic stimulation (TMS) applied to the precuneus yielded encouraging results, offering a safe and accessible neuromodulation technique for patients in early to moderate stages of AD (20). The inclusion of senolytics like dasatinib and quercetin reflects the emerging understanding of cellular senescence in AD and represents a bold departure from classical neurotransmitter and amyloid-based approaches (21). The success of these trials in achieving blood-brain barrier penetration and biological modulation is noteworthy, though clinical outcomes remain to be established in larger cohorts. Despite these advances, several challenges persist. Crenezumab, a well-tolerated anti-Aβ monoclonal antibody, failed to demonstrate significant clinical benefit in two large phase 3 trials (34). Its inability to halt cognitive decline underscores the importance of precise timing, target affinity, and possibly co-targeting tau pathology. Similarly, hydromethylthionine mesylate, a tau aggregation inhibitor evaluated in the LUCIDITY trial, showed moderate benefit but awaits further validation due to previous inconsistent results in tau-targeting studies (35).

The AMBAR trial involving plasma exchange with albumin showed quality-of-life improvements, lending support to the role of peripheral sink mechanisms in amyloid clearance and immune modulation (36). Additionally, masitinib, a tyrosine kinase inhibitor targeting microglial and mast cell activity, showed clinical benefit, further implicating neuroinflammation in AD pathogenesis (37). The trials reviewed herein offer heterogeneous methodologies, durations, and outcome measures, which introduces complexity in comparing efficacy across interventions. Sample sizes varied considerably—from as few as 3 participants in early-phase mechanistic studies to over 1,600 in late-phase trials—limiting generalizability in some cases. Several studies also lacked long-term follow-up or uniform cognitive assessments, and blinding or allocation concealment procedures were inconsistently reported, as highlighted by the risk of bias evaluation. These methodological limitations warrant

cautious interpretation of findings and emphasize the need for standardization in future research.

Nonetheless, this review demonstrates the growing diversification of therapeutic strategies beyond the traditional cholinergic and amyloid-centric paradigms. The integration of neuroinflammation, metabolic modulation, vascular contributions, and neurotrophic mechanisms marks a paradigm shift toward multifactorial and potentially personalized approaches. It is also notable that some trials showed converging effects on cognitive outcomes despite differing mechanisms, suggesting shared downstream pathways in cognitive preservation.

Future research should prioritize large-scale, multi-arm trials that compare mechanistically distinct agents in similar populations. Studies should also explore combinatory therapies that simultaneously target amyloid, tau, and neuroinflammation, reflecting the multifactorial nature of AD. Longitudinal designs with biomarker tracking and cognitive staging will be essential to identify optimal treatment windows and responders. Additionally, greater efforts are needed to include underrepresented populations, particularly from low- and middle-income countries, to improve the global applicability of findings. In conclusion, this systematic review underscores a cautiously optimistic outlook on the future of Alzheimer's disease treatment. While definitive disease-modifying therapies remain elusive, several agents demonstrate encouraging biological and cognitive effects. By building upon these early successes with rigorous trial designs and integrative strategies, the field moves closer to effective and individualized interventions that may alter the course of this devastating disease.

CONCLUSION

This systematic review of recent clinical trials on emerging therapeutics for Alzheimer's disease highlights significant advancements toward disease-modifying strategies, with agents such as Lecanemab, Donanemab, and BI 425809 demonstrating promising effects on amyloid clearance, tau reduction, and cognitive outcomes. The review underscores a shift from solely symptomatic treatments to mechanistically diverse interventions targeting neuroinflammation, metabolic dysfunction, and synaptic health. While variability in trial designs and limitations in long-term efficacy remain, these findings carry important implications for both clinical practice and future research.

Clinically, they suggest a near-future paradigm in which Alzheimer's care may become increasingly personalized and biologically guided. From a research perspective, these developments emphasize the need for multi-targeted, large-scale trials and biomarker-driven approaches to optimize treatment timing and efficacy. Overall, this review supports the evolving therapeutic landscape in Alzheimer's disease and reinforces the importance of sustained translational efforts to improve cognitive health and quality of life in aging populations.

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