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THERAPY FOR ALZHEIMER'S DISEASE - FOCUS ON LECANEMAB

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ABSTRACT

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder and the leading cause of dementia worldwide, with prevalence increasing due to population aging. It is characterized by cognitive decline, functional impairment, and significant public health burden. Pathophysiology involves a complex interplay of amyloid-β (Aβ) accumulation, tau pathology and neuroinflammation. Despite extensive research, current pharmacological management of Alzheimer's disease relies primarily on symptomatic therapies and does not alter the underlying neurodegenerative process. The aim of this review is to summarize the current state of knowledge on therapeutic strategies for AD, with particular emphasis on lecanemab, a recombinant humanized antibody characterized by their selectivity for soluble Aβ oligomers. We discuss its mechanism of action, clinical evidence from recent randomized controlled trials assessing its efficacy and safety. In this review, lecanemab is not only addressed in the context of established and widely used therapies but also alongside novel treatments currently being tested. Lecanemab represents a significant step towards disease-modifying therapy for AD as it reduces brain amyloid. Although the available results are promising, current evidence suggests that monotherapeutic interventions targeting a single pathological mechanism may be insufficient to completely stop or reverse disease progression underscoring the need for further research to optimize therapeutic outcomes.

KEYWORDS

Alzheimer's Disease; Lecanemab; Amyloid-Beta; Disease-Modifying Therapy

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Abbreviations

Aβ - amyloid beta
Aβ42 - amyloid beta 42
ACh - acetylcholine
AChEI - acetylcholinesterase inhibitor
AChEIs - acetylcholinesterase inhibitors
AD - Alzheimer's disease
ADAD - autosomal dominant Alzheimer's disease
ADAS-cog - Alzheimer's Disease Assessment Scale - cognitive subscale
ADCOMS - Alzheimer's Disease Composite Score
ADCS-ADL-MCI - Alzheimer's Disease Cooperative Study - Activities of Daily Living for Mild Cognitive Impairment
APLP2 - amyloid precursor-like protein 2
APOE ε4 / APOE4 - apolipoprotein E4
APP - amyloid precursor protein
ARIA - amyloid-related imaging abnormalities
ARIA-E - amyloid-related imaging abnormalities with edema
ARIA-H - amyloid-related imaging abnormalities with hemorrhage
BBB - blood-brain barrier
BPSD - behavioral and psychological symptoms of dementia
CAA-ri/ABRA - cerebral amyloid angiopathy-related inflammation / amyloid beta-related angiitis
CDK5 - cyclin-dependent kinase 5
CDR-SB - Clinical Dementia Rating - Sum of Boxes
ChAT - choline acetyltransferase
ChEIs - cholinesterase inhibitors
Cmax - maximum concentration
CNS - central nervous system
CQ - clioquinol
CSF - cerebrospinal fluid
CT - computed tomography
CSK3-beta (GSK3β) - glycogen synthase kinase 3 beta
EBM - evidence-based medicine
EOAD - early-onset Alzheimer's disease
ERK - extracellular signal-regulated kinases
FAQ - Functional Activities Questionnaire
FDG-PET - fluorodeoxyglucose positron emission tomography
GAG - glycosaminoglycans
IADL - instrumental activities of daily living
IDE - insulin-degrading enzyme
IgG1 - immunoglobulin gamma 1
IRR - infusion-related reaction
JNK - c-Jun N-terminal kinases
LOAD - late-onset Alzheimer's disease
mAbs - monoclonal antibodies
MAD - multiple ascending dose
MCI - mild cognitive impairment
MMSE - Mini-Mental State Examination

MOCA - Montreal Cognitive Assessment
MRI - magnetic resonance imaging
NEP - neprilysin
NfL - neurofilament light chain
NIA-AA - National Institute on Aging and Alzheimer's Association
NMDA - N-methyl-D-aspartate
NNH - number needed to harm
NNT - number needed to treat
NSAID - nonsteroidal anti-inflammatory drugs
p-tau - phosphorylated tau
PD - pharmacodynamics
PET - positron emission tomography
PHF - paired helical filaments
PK - pharmacokinetics
PP2A - protein phosphatase 2A
RA - retinoic acid
RAGE -receptor for advanced glycation end products
RAR - retinoic acid receptor
RCTs - randomized controlled trials
SAD - single ascending dose
tmax - time to reach maximum concentration
t-tau - total tau
TNF-alpha - tumor necrosis factor alpha
VAChT - vesicular acetylcholine transporter

1. Epidemiology

Dementia results from a variety of diseases and injuries that affect the brain and can be divided into four main groups: degenerative, vascular, infectious and metabolic **[1]**. AD is a chronic, progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and impaired reasoning **[2]**. Worldwide, approximately 57 million people have dementia, with nearly 60% living in low- and middle-income countries. Every year, there are nearly 10 million new cases. AD is the most common form of dementia and may contribute to 60–70% of these cases **[3]**. Thus, it remains the leading cause of cognitive impairment in older individuals (aged over 65 years) throughout the world **[4]** and ranks as the fifth leading contributor to mortality globally **[5].** There were over 525,000 individuals with dementia in Poland in 2018, which accounted for 1.38% of the Polish population. Despite the decreasing overall population in Poland, it is expected that the number of patients suffering from dementia will exceed one million in 2050 (3.23% of the population) **[6]**. Underdiagnosis is common, with some evidence suggesting that more than half of those who develop AD dementia may never be formally diagnosed **[7]**

2. Pathophysiology

AD follows a prolonged, progressive disease course that begins with pathophysiological changes in the brains of affected individuals years before any clinical manifestations are observed **[8]**. These pathophysiological changes include the accumulation of toxic species of Aβ, the development of neurofibrillary tangles of hyperphosphorylated tau protein, and neurodegeneration that may result from uncontrolled activation of microglia in the brain leading to secretion of neurotoxins and inflammatory factors **[9]**. Microglia are a type of glial cells that play a key role in the repair of damage to the CNS. The β-amyloid peptide and a variety of pro-inflammatory factors can activate microglia, resulting in the secretion of a variety of inflammatory factors and neurotoxins. This leads to neuronal damage and even apoptosis, thus triggering AD **[10]**. As previously stated, AD is characterized pathologically by an accumulation of abnormal neuritic plaques and neurofibrillary tangles in the brain. These pathological changes are accompanied by a loss of neurons, particularly cholinergic neurons in the basal forebrain and the neocortex. Two prominent pathophysiological hypotheses have been proposed based on these pathological findings. The first is the cholinergic hypothesis which highlights the importance of ACh in cognitive processes where Aβ is believed to negatively affect cholinergic function by causing cholinergic synaptic loss and impaired ACh release **[11]**. The amyloid hypothesis is currently the most widely accepted pathophysiological mechanism for AD,

especially in cases of inherited AD. The amyloid hypothesis suggests that Aβ peptide is derived from APP through the actions of β- and γ-secretase enzymes instead of physiological α- and β-secretases, resulting in 42 amino acid peptides (Aβ42). Elevated levels of Aβ42 lead to amyloid aggregation, which causes neuronal toxicity **[12]**.

AD is a multifactorial condition associated with many known risk factors as shown in Table 1. as the pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia **[13]**.

Table 1. Factors shown to increase risk of AD **[9]**.

Risk factor
Hippocampal atrophy
Medial temporal atrophy
Entorhinal atrophy
Abnormal CSF tau
White matter hyperintensities
Abnormal CSF tau/Ab ratio
APOE4
Increasing age
Female sex
Low memory/MMSE scores
High ADAS-cog score
High dependency/IADL score
High FAQ score
Neuropsychiatric symptoms
Hypertension
Depression

Abbreviations: AD: Alzheimer's disease; ADAS-cog: Alzheimer Disease Assessment Scale-cognitive subscale; FAQ: Functional Activities Questionnaire; IADL: instrumental activities of daily living; MMSE: Mini-Mental State Exam.

AD can be classified as familial or sporadic. The dominant familial or autosomal presentation represents 1-5% of the total number of cases. It is categorized as EOAD (<65 Y/A) and is associated with genetic abnormalities as shown in Table 2. EOAD often exhibits atypical symptoms, and its diagnosis is usually delayed, leading to a more aggressive disease course**[14]**. Sporadic AD represents 95% of the cases and is categorized as LOAD, occurring in patients older than 65 Y/A.

Table 2. Loci associated with AD **[1]**.

Chromosome	Gene product	Age of onset	Way of inheritance
ch11q21.3	APP	30-60 Y/A	A&D
ch14q24.11	PS1	30-60 Y/A	A&D
ch1q31.42	PS2	50-70 Y/A	A&D
ch19q13.2	APOE	50-80+ Y/A	Familial and sporadic occurence

Abbreviations: APP: Amyloid Precursor Protein; A&D: Autosomal Dominant; APOE: Apolipoprotein E; PS1: Presenilin 1; PS2: Presinilin 2; Y/A: Years of Age.

3. Symptoms and diagnosis

Thorough history-taking and a comprehensive physical exam, including a detailed neurological exam and mental status assessment, is essential to evaluate the AD stage and rule out other potential conditions. A complete clinical assessment can provide a reasonable level of diagnostic accuracy for most patients. A MMSE or, preferably, a MOCA should be performed and documented as part of the cognitive neurological exam. The MOCA is more sensitive to evaluating patients with MCI than the MMSE **[15,16]**.

Episodic short-term memory loss is the initial and most common presenting symptom of typical AD. Individuals may have difficulty retaining new information while still recalling long-term memories. Impairments in problem-solving, judgment, executive functioning, and organizational skills may follow. In the early stages of the disease, executive functioning impairments can range from subtle to significant. IADLs such as driving, financial management, cooking, and detailed activity planning are affected relatively early. These early signs of cognitive decline are followed by language disorder and impaired visuospatial skills. Neuropsychiatric symptoms like apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are also common in the moderate to late stages. Dyspraxia, olfactory dysfunction, sleep disturbances, and extrapyramidal motor signs like dystonia, akathisia, and Parkinsonian symptoms occur late in the disease. Primitive reflexes, incontinence, and total dependence on caregivers typically follow. Primary motor or sensory functions are usually intact. Other causes should be considered if eye movement disorders, cerebellar symptoms or peripheral neuropathy are found during neurological examination **[17,18]**.

Routine laboratory tests do not reveal any specific abnormalities in AD **[19]**. MRI is a superior structural neuroimaging modality compared to CT when evaluating individuals with dementia, including those suspected of having AD. It can reveal specific features compatible with the diagnosis. These include atrophy of the entorhinal cortex, followed by atrophy of the medial temporal cortex or hippocampi. Use of volumetric MRI for early detection of AD and distinguishing it from normal aging-related changes is still a subject of debate and research **[20]**.

Because normal aging involves subtle cognitive deterioration, it can often be difficult to distinguish cognitive decline due to AD in the early stages from the declines associated with normal aging (e.g. declines in processing speed, and certain abilities related to memory, language, visuospatial and executive function) **[21]**. The differential results suggest that use of biomarkers alongside neurocognitive tests has become an important part of clinical practice **[22]**. Some of the most valuable biomarkers are FDG-PET and Amyloid PET, alongside CSF biomarkers ratios. FDG-PET is a valuable functional imaging biomarker that can aid in the early and differential diagnosis of AD. It may reveal specific metabolic impairments in certain brain regions, particularly the hippocampi, in individuals with early or preclinical AD **[23]**. Amyloid PET is an important in vivo surrogate for Aβ pathology in the brain. It allows for the detection and visualization of amyloid deposition, a hallmark feature of AD **[24]**. The ratios of CSF biomarkers, such as Aβ42/40, have provided a more accurate and sensitive index of the underlying amyloid-related pathology in patients. The increase in CSF p-tau and t-tau levels directly reflects tau aggregation within the brain in AD **[25]**. Most current guidelines for diagnosis and staging of AD are shown in Table 3.

Table 3. National Institute on Aging and Alzheimer's Association revised criteria for diagnosis and staging of AD **[17]**.

Diagnostic Component	Criteria / Definition	Key Tools & Biomarkers
Core Definition	AD is defined biologically by the presence of ADNPC.	Diagnosis is established by a positive Core 1 Biomarker.
Core 1 Biomarkers *(Diagnostic)*	**Necessary & Sufficient for Diagnosis.** Detects Amyloid plaques ("A") or soluble Phosphorylated Tau ("T1").	Amyloid PET CSF (Aβ42/40 ratio, p-tau181/Aβ42) Plasma (High-accuracy p-tau217 assays)
Core 2 Biomarkers *(Staging)*	**Used for Biological Staging.** Detects aggregated Tau neurofibrillary tangles ("T2").	Tau PET (Visualizes spread from medial temporal lobe to neocortex)
Biological Staging *(Molecular Severity)*	**Stages A – D** Classifies the severity of the biological disease burden.	Stage A: Initial (A+ / T2-) Stage B: Early (A+ / T2 Low) Stage C: Intermediate (A+ / T2 Moderate) Stage D: Advanced (A+ / T2 High)
Clinical Staging *(Symptom Severity)*	**Stages 1 – 6** Classifies the severity of cognitive/functional decline (independent of biology).	Stage 1: Asymptomatic (Normal cognition) Stage 2: Transitional (Subjective decline, subtle changes) Stage 3: MCI Stages 4–6: Dementia (Mild → Moderate → Severe)
Non-Specific Markers	**Category "N", "I", "V", "S"** Indicate injury or co-pathologies but do not define AD.	N: Neurodegeneration (MRI atrophy, NfL) I: Inflammation (GFAP) V/S: Vascular injury / Alpha-synuclein

Abbreviations: ADNPC: Alzheimer's disease neuropathologic change; AD: Alzheimer's disease; PET: positron emission tomography; CSF: cerebrospinal fluid; Aβ: amyloid beta; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; NfL: neurofilament-light chain; GFAP: glial fibrillary acidic protein.

4. Current Therapeutic Strategies for Alzheimer's Disease

4.1 Pharmacological strategies

The current pharmacological management of Alzheimer's disease is predominantly based on two classes of symptomatic agents: acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists which are presented in Table 4. **[26,27]**. Despite their widespread use, these therapies are not disease-modifying and primarily aim to attenuate cognitive decline and BPSD **[26,27]**.

Table 4. Symptomatic drugs used in the treatment of AD **[26,27,28]**.

Symptomatic drugs
AChEIs:
donepezil
rivastigmine
galantamine
NMDA receptor antagonist:
memantine

Abbreviations: AD: Alzheimer's disease; AChEIs: acetylcholinesterase inhibitors; NMDA: N-methyl-D-aspartate.

AChEIs - including donepezil, rivastigmine, and galantamine - constitute first-line therapy for mild-to-moderate AD **[27,28]**. These agents exert their therapeutic effects through reversible inhibition of acetylcholinesterase, thereby increasing synaptic acetylcholine availability and transiently enhancing central cholinergic neurotransmission **[27,29]**. Given the well-documented cholinergic deficit in the CNS of patients with AD, augmentation of acetylcholine signaling may partially compensate for impaired neuronal communication involved in memory and cognitive processing **[26,27]**. Clinical trials have demonstrated modest cognitive and functional benefits, typically resulting in stabilization or slight improvement of symptoms for approximately 6–12 months in patients with mild-to-moderate disease **[27,30]**. Nonetheless, their efficacy remains symptomatic, without influencing the underlying neurodegenerative cascade **[26,27,31,32,33,34]**.

Meta-analytical data indicate that AChEI therapy is associated with a reduced risk of progression to severe cognitive and functional impairment, as well as lower all-cause mortality and stroke rates **[38,42,43]**. Furthermore, treatment with AChEIs has been linked to a decreased likelihood of antipsychotic prescription compared with untreated patients **[38,44]**. Given the established mortality risks associated with antipsychotic use in dementia, these findings contribute meaningfully to the risk–benefit assessment and support the continued role of AChEIs in AD pharmacotherapy **[38,45,46]**.

Adverse effects associated with AChEIs are primarily attributable to enhanced peripheral and central muscarinic activity. Gastrointestinal symptoms-particularly nausea and vomiting-occur in approximately 14–25% of patients, although slower titration may reduce their incidence **[38,39]**. Up to 10% of patients experience muscle cramps, fatigue, insomnia, anorexia, hallucinations, and vivid or abnormal dreams, including nightmares **[38]**. Caution is warranted in individuals with bradycardia, first-degree atrioventricular block, or concomitant use of QTc-prolonging agents; baseline electrocardiographic evaluation may be advisable prior to treatment initiation **[38]**. The transdermal formulation of rivastigmine reduces gastrointestinal adverse effects approximately three-fold compared with oral formulations but is associated with cutaneous reactions in about 10% of patients **[38,40]**. Additionally, AChEIs may induce urinary urgency resembling overactive bladder; appropriate recognition is essential to prevent unnecessary anticholinergic prescriptions and avoid iatrogenic harm **[38,41]**.

Memantine is currently the only approved NMDA receptor antagonist indicated for moderate-to-severe AD as shown in Table 5. **[26,27]**. It acts as an uncompetitive antagonist, preferentially binding to NMDA receptor-associated ion channels during sustained pathological activation, thereby attenuating excessive calcium influx and reducing glutamate-mediated excitotoxicity **[27,35]**. Importantly, memantine exhibits voltage-dependent binding and rapid dissociation kinetics, which preserve physiological synaptic transmission necessary for learning and memory **[27,36]**. Clinical evidence indicates that memantine provides modest symptomatic benefit, particularly in combination with AChEIs, contributing to temporary stabilization of cognition and activities of daily living **[27,37]**. However, similar to AChEIs, memantine does not alter the trajectory of disease progression **[26,27]**.

Table 5. Mechanisms of action and clinical indications of acetylcholinesterase inhibitors and memantine in Alzheimer's disease **[26,27,28,29,35]**.

Drugs	Mechanism of action	Clinical indication in AD
Donepezil, Rivastigmine, Galantamine	Reversible inhibition of acetylcholinesterase, resulting in increased synaptic acetylcholine availability and enhancement of central cholinergic neurotransmission	Mild-to-moderate stage of AD
Memantine	Uncompetitive antagonism of NMDA receptors, reducing pathological glutamate-mediated excitotoxicity	Moderate-to-severe stage of AD

Abbreviations: AD: Alzheimer's disease; AChEIs: acetylcholinesterase inhibitors; NMDA: N-methyl-D-aspartate.

For memantine, the number needed to treat ranges from three to eight patients for global, cognitive, and functional outcomes, whereas for AChEIs the NNT ranges from four to fourteen patients for cognitive endpoints **[38,47,48]**. Combination therapy with memantine and donepezil has demonstrated superior outcomes in cognition, global assessment, and activities of daily living compared with monotherapy, although with slightly lower acceptability **[38,49,50]**. Pooled analyses of registration trials further suggest that memantine is associated with a lower incidence of agitation (8%) compared with placebo (12%), with only minor increases in hypertension, somnolence, constipation, vomiting, and abnormal gait (approximately 3–4% versus 2–3% with placebo) **[38,51,52]**.

The therapeutic efficacy of currently available agents may be greater when treatment is initiated in the early, potentially preclinical stages of AD, prior to extensive neurodegeneration **[26]**. Several factors contribute to their limited effectiveness, including restricted drug penetration across the BBB, which impedes adequate CNS exposure **[26,53]**. Numerous clinical trials have failed due to insufficient BBB permeability **[26]**. Dose escalation intended to overcome limited CNS bioavailability may increase the risk of adverse events **[26,54]**. Consequently, various strategies have been developed to enhance CNS drug delivery **[26,55]**. Furthermore, age-related alterations in neuronal membrane composition and receptor distribution may diminish pharmacodynamic responsiveness - an aspect not consistently accounted for in preclinical models **[26]**. Structural changes in synaptosomal membrane microdomains observed in aged mice have been shown to increase susceptibility to amyloid-induced stress and attenuate the neuroprotective effects of ciliary neurotrophic factor **[26,56]**.

The timing of therapeutic intervention also appears critical. In transgenic mouse models of ADAD, characterized by early and rapid amyloid plaque accumulation, anti-amyloid immunization effectively reduced amyloid burden **[26,57]**. However, in human clinical trials, amyloid reduction did not consistently translate into meaningful clinical improvement or slowed disease progression **[26,58]**. These findings suggest that treatment is frequently initiated at advanced stages, when irreversible neurodegeneration has already occurred, thereby limiting therapeutic benefit **[26]**. Accordingly, early and accurate diagnosis - particularly in at-risk populations, such as individuals with a positive family history, carriers of the ε4 allele, or those presenting with isolated memory complaints - is essential **[26,34]**.

In recent years, therapeutic development has increasingly focused on disease-modifying strategies targeting Aβ pathology **[27,59]**. Monoclonal antibodies such as aducanumab, donanemab and lecanemab represent the first approved anti-Aβ immunotherapies **[27,59,60,61]**. These agents selectively bind aggregated Aβ species, promoting clearance of soluble oligomers and amyloid plaques, and potentially slowing disease progression **[27,62]**. Lecanemab, which preferentially targets Aβ protofibrils, has demonstrated modest attenuation of cognitive decline in early-stage AD, although its use is associated with ARIA **[27,63,64]**. Nevertheless, the absence of consistently effective disease-modifying therapies underscores the need to explore alternative and complementary targets beyond amyloid pathology **[26,67]**.

Overall, the absence of robust disease-modifying therapies and the challenges associated with early diagnosis highlight the urgent need for preventive and neuroprotective strategies aimed at decelerating the neurodegenerative cascade - particularly progressive dysfunction of axons, dendrites, and synapses - thereby reducing the overall risk and burden of AD **[26,68]**.

4.2 Non-pharmacological strategies

Accumulating evidence indicates that lifestyle-based interventions exert a significant modulatory effect on the progression of AD through multiple neuroprotective mechanisms **[27]**. Dietary strategies, particularly the Mediterranean and ketogenic diets, have demonstrated beneficial effects, including attenuation of Aβ toxicity, reduction of neuroinflammatory processes, and improvement of mitochondrial function **[27,69,70]**. These nutritional interventions contribute to the regulation of oxidative stress and preservation of gut microbiota homeostasis, with ketogenic regimens showing particular potential in optimizing cerebral energy metabolism **[27,71]**. Moreover, specific nutrients such as omega-3 polyunsaturated fatty acids have been associated with cognitive benefits, especially in APOE4-negative individuals with mild cognitive impairment **[27,72,73]**.

Regular physical activity represents another critical non-pharmacological strategy, enhancing systemic antioxidant capacity and potentially reducing Aβ accumulation in high-risk populations **[27,74,75]**. Additional approaches, including intermittent fasting and caloric restriction, activate adaptive cellular stress-response pathways that may confer protection against neurodegenerative processes **[27,76]**. Although these lifestyle modifications do

not directly target the core neuropathological hallmarks of AD, they collectively enhance neuronal resilience by mitigating metabolic dysfunction, oxidative damage, and chronic neuroinflammation **[27,78]**.

Importantly, systematic monitoring of nutritional status is warranted, as individuals with AD frequently develop micronutrient deficiencies-such as vitamin B12 and folate deficiency - that may further exacerbate cognitive decline **[27,78]**. Overall, these non-pharmacological interventions represent accessible and cost-effective strategies for reducing AD risk and supporting comprehensive disease management **[27]**.

5. Lecanemab

5.1 Characterization of the drug

Lecanemab (BAN2401) is a recombinant humanized immunoglobulin gamma 1 (IgG1) version of the murine antibody mAb158 **[79]**. It belongs to the second generation of anti-Aβ (anti-beta-amyloid) monoclonal antibodies (mAbs), which are characterized by their selectivity for soluble Aβ oligomers versus insoluble fibrils or plaques **[80]**. Lecanemab attaches to amyloid oligomers, protofibrils, and insoluble fibrils **[81]**. It preferentially targets soluble beta-amyloid (Aβ) protofibrils and prevents them from aggregating into amyloid plaques **[82,33]**. Aβ protofibrils are large, soluble Aβ aggregates that exhibit neurotoxicity via interfering with the mechanisms involved in memory function **[82]**. Lecanemab has been shown to reduce pathogenic Aβ, stop the deposition of Aβ, and diminish Aβ protofibrils in the brain and cerebrospinal fluid (CSF) of animal models of Alzheimer's disease (AD) **[83,84]**. Moreover, what distinguishes lecanemab from other anti-amyloid mAbs is its ability to selectively bind to large, soluble protofibrils while still targeting insoluble fibrils, which creates amyloid plaques **[63,85]**.

5.2 Pharmacology of lecanemab

Lecanemab is administered as an intravenous infusion **[63]**. The median t_{max} (time to reach maximum concentration) occurred at about 1.8 to 2.2 h from the time of administration **[86]**. A study by Logovinsky *et al*. **[86]** has studied the single ascending dose (SAD) cohort and the multiple ascending doses (MAD) cohort. In both cohorts, the levels of mean C_{max} (maximum concentration) and the AUC (area under the curve) increased in proportion to the dosage **[86]**. Furthermore, both cohorts have also shown first-order elimination kinetics **[86]**. In the SAD cohort, the mean serum half-life of lecanemab has been estimated to be 165 h for patients receiving 10 mg/kg and 174 h for subjects receiving 15 mg/kg of lecanemab **[10]**. In the MAD cohort, the mean half-life of lecanemab was approximated to be around 127 h after the final dose in patients receiving the 10 mg/kg biweekly cohort **[86]**.

Moreover, Logovinsky *et al*. **[86]** have studied concentrations of lecanemab in CSF and have shown that while the CSF to serum ratios were 0.04 - 0.08% at 24 h after the final dose and showed no accumulation in the three lower dose MAD cohorts, the 10 mg/kg biweekly MAD cohort showed lecanemab serum accumulation with the ratio amounting to 0.13% at 24 h after the final dose, and increasing to 0.29% at 14 days after the final dose.

Furthermore, the study has shown slight dose-dependent increases in plasma $A\beta_{(1-40)}$ levels some time after the first and final lecanemab doses in the MAD cohorts **[86]**. Yet, lecanemab had no effect on CSF $A\beta_{(1-42)}$, t-tau, or p-tau **[86]**.

5.3 Administration of lecanemab

The FDA recommends that lecanemab should be administered as an intravenous infusion over about 1 hour, once every 2 weeks, at a dose of 10 mg/kg **[63]**. The appropriate dose of lecanemab should be added to an infusion bag with 250 mL of 0.9% sodium chloride injection and then administered through an intravenous line with a terminal low-protein binding 0.2 micron in-line filter **[87]**. The infusion should last for about an hour **[87]**. After the first infusion, a patient should be observed for 3 hours, then the observation period may be decreased to 2 hours for the second and third infusions and to 30 minutes for all the consecutive infusions after that if no infusion reactions have ever been observed **[87]**. If any infusions are missed, the following dose should be administered immediately **[63]**.

5.4 Indications for administration

Lecanemab is approved for patients with MCI (mild cognitive impairment) due to Alzheimer's disease or mild Alzheimer's disease (AD)–related dementia with a confirmed Aβ pathology **[88,89]**. Participants of clinical trials with lecanemab have had Aβ positivity determined by PET (positron emission tomography) or CSF measurement of the $A\beta_{(1-42)}$ peptide **[90]**. Moreover, all of them have also had objective impairment in episodic memory as indicated by ≥1 standard deviation below the age-adjusted mean in the Wechsler Memory Scale IV - Logical Memory II **[90]**.

However, the safety and efficacy of lecanemab in both less and more severe stages of AD have not yet been studied **[87]**. Therefore, Cummings *et al.* **[87]** recommended only administering lecanemab for patients who match the diagnosis of MCI due to AD or mild AD dementia and have objective evidence of Aβ positivity determined by PET or CSF exam.

5.5 Contraindications

As of now, there are no known contraindications of lecanemab **[63]**.

Studies such as CLARITY AD excluded patients with a medical history of seizures within the past 12 months, which can be related to symptoms of more severe ARIA **[91]**. Cerebral amyloid angiopathy-related inflammation/amyloid beta-related angiitis (CAA-ri/ABRA) increases the risk for ARIA as well **[87]**. Therefore, a study by Cummings *et al.* **[87]** suggests that any history of seizures or CAA-ri/ABRA should disqualify patients from lecanemab until more information about the drug is known. A study by Chowdhury *et al.* **[63]** advises that lecanemab should be used cautiously in such patients.

Furthermore, it is suggested to *APOE* genotype all the patients before starting the lecanemab treatment, as *APOE4* carriers (especially homozygotes) have an increased risk of side effects such as ARIA (amyloid-related imaging abnormalities) and CAA-ri/ABRA (cerebral amyloid angiopathy-related inflammation/amyloid beta-related angiitis) **[87]**.

Moreover, pregnant or breastfeeding women should not be started on lecanemab, as its potential reproductive or developmental harm has not been studied either in animals or in humans **[63]**.

5.6 Adverse effects

So far, studies have found lecanemab to be a well-tolerated drug **[63]**. The most important of the reported adverse effects of the drug include infusion reactions, headache, and ARIA (amyloid-related imaging abnormalities) **[92]**. Infusion reaction typically presents as fever, chills, headache, rash, nausea, vomiting, abdominal discomfort, and elevated blood pressure **[93]**. To eliminate the risk of serious reactions, an observation period after the administration of the drug is advised **[87]**.

ARIA (amyloid-related imaging abnormalities) is a frequent side effect of amyloid-lowering monoclonal antibodies [87]. There are two different types of ARIA: ARIA-H (which includes bleeding in the brain) and ARIA-E (which presents with edema) [87]. ARIA related to lecanemab is usually asymptomatic or mildly symptomatic, reversible, and mild to moderate radiographically **[87]**. The risk of ARIA occurrence and severity is significantly higher in patients with the *APOE4* genotype **[87]**. A study by Cummings *et al.* **[87]** suggests MRI scans prior to the 5th, 7th, and 14th infusions and an additional MRI scan prior to the 26th infusion for patients with *APOE4* genotype.

A cerebral macrohemorrhage, while infrequent, remains one of the most severe adverse effects of lecanemab **[87]**. Risk factors of intracerebral bleeding include *APOE4* genotype, CAA-ri/ABRA, and anticoagulation **[87]**.

5.7 Interactions with other drugs

Standard anti-dementia treatment, including cholinesterase inhibitors and memantine, is allowed as concomitant medications while on treatment with lecanemab **[87]**.

Other second-generation anti-Aβ mAbs should not be administered simultaneously with lecanemab **[87]**.

Anticoagulants increase the risk of intracerebral bleeding, therefore, it is advised to exclude patients taking heparin, warfarin, vitamin K antagonists, or direct oral anticoagulants from lecanemab treatment **[87]**.

Patients receiving antiplatelet agents can be considered for lecanemab treatment **[87]**. Yet, *APOE4* gene carriers, who are already at a higher risk of ARIA, may be even more susceptible to ARIA if they combine lecanemab treatment with antiplatelet agents [87].

There is worry that lecanemab combined with thrombolytics may increase the risk of intracerebral bleeding, therefore, these two medications should not be given simultaneously until more data is provided **[87]**.

5.8 Clinical efficacy

Lecanemab was first studied by Logovinsky *et al.* **[86]** in a multicenter, double-blind, randomized, placebo-controlled study that assessed its safety and tolerability and pharmacological properties.

A phase 2b clinical trial by Swanson *et al.* **[94]** investigated the dose response of lecanemab over three dose levels and two dosing regimens with the objective to establish the most effective (ED90) dose of lecanemab. The most effective dose was found to be 10 mg/kg biweekly **[94]**. The primary endpoint of the study at 12 months was not met, however, analysis of the secondary endpoint showed that the dose of 10 mg/kg of lecanemab biweekly was able to demonstrate consistent dose-dependent reductions in clinical decline and brain amyloid burden across the 18-month treatment period **[94]**. Moreover, it was found that 10 mg/kg of lecanemab biweekly significantly reduced brain amyloid burden on PET imaging **[94]**. Lecanemab was also assessed to be safe and well-tolerated among the patients **[94]**. The main side effect of treatment was found to be ARIA-E, with an incidence rate of less than 10% at the two highest doses for the overall population **[94]**. ARIA is a recognized side effect of many anti-Aβ mAbs, with lecanemab being relatively low-risk among other antibodies, possibly because of its pharmacological profile and lower binding to Aβ fibrils **[94-96]**.

Another phase 2 trial by McDade *et al.* **[97]** randomized 856 patients to one of five dose regimens of lecanemab or placebo. The study found that 10 mg/kg of lecanemab biweekly produced dose-dependent reductions of brain amyloid measured by PET, improvements in plasma Aβ42/40 ratio, and reductions in plasma p-tau181 **[97]**.

The phase III Clarity study by van Dyck *et al.* **[90]** included 1795 participants who were randomized to receive either lecanemab or placebo. The trial found that after 18 months, lecanemab therapy was able to decrease the decline on Clinical Dementia Rating - Sum of Boxes by 27%, with significant changes occurring after 6 months of treatment **[90]**. Moreover, lecanemab was capable of reducing brain amyloid and slowing loss of cognition **[90]**. Lecanemab therapy was also successful in significantly reducing markers of amyloid, tau, neurodegeneration, and neuroinflammation in the CSF substudy and in plasma analyses **[90]**. Concerning safety, lecanemab was well-tolerated, the incidence of ARIA was rather low – 12.6% for ARIA-E in the lecanemab group compared with 9.9% in the placebo group, and 17.3% for ARIA-H in the lecanemab group versus 10.7% in the placebo group **[90]**. ARIA-E cases mostly happened within the first 3 months and were mild and asymptomatic **[90]**. If mild, they did not cause discontinuation of lecanemab or placebo and resolved themselves within 4 months **[90]**. The updated safety results from the Clarity study have also shown lecanemab to be a safe and well-tolerated drug, with the most common side effects being infusion-related reactions, ARIA-H, and ARIA-E **[98]**. The Clarity trial aimed to include a diverse group of patients, with 20% of participants being non-White **[90]**. A study by Chen *et al.* **[99]** studied the results of 294 Asian patients from the Clarity trial and found the efficacy of lecanemab in the Asian group was consistent with the overall population. The safety of the drug was also comparable between the Asian group and the overall population, with the most frequent adverse effects in the Asian group being ARIA-H, ARIA-E, and infusion-related reactions **[99]**. Occurrence of side effects causing drug dose interruption or withdrawal, infusion-related reactions, ARIA-E, and ARIA-H was lower for the Asian group compared with the overall population **[99]**.

There is another phase 3 trial that is still ongoing called the AHEAD 3-45 Study (NCT04468659) **[100,101]**. It consists of two sister trials: A3 (a Phase 2 trial with PET-imaging end points) and A45 (a Phase 3 trial with a cognitive composite primary end point) **[100,101]**. The purpose of the study is to determine whether lecanemab is more effective than placebo at slowing down the cognitive decline associated with AD and reducing amyloid accumulation in the brain after 216 weeks of treatment **[100,101]**. The trial will also examine the long-term safety and tolerability of lecanemab **[100,101]**.

Clinical trials mentioned above are summarized in Table 6. below.

Table 6. Characteristics of clinical trials of lecanemab.

Study	Phase	Duration	Participants (n)	Dose	Remarks
Logovinsky *et al.* **[86]**	1	180 days	80	Single ascending dose cohort: 0.1, 0.3, 1, 3, 10, and 15 mg/kg of lecanemab vs placebo Multiple ascending dose cohort:. 3, 1, 3, and 10 mg/kg of lecanemab vs placebo	Safety, tolerability, and pharmacokinetics of lecanemab were assessed.
Swanson *et al.* **[94]**	2b	18 months	856	2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, 10 mg/kg biweekly of lecanemab vs placebo	The most effective dose was found to be 10 mg/kg biweekly, lecanemab demonstrated a reduction in brain amyloid.
Mcdade *et al.* **[97]**	2	CORE (study 201 blinded period): 3 months OLE (open-label extension): up to 24 months	856	2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, 10 mg/kg biweekly of lecanemab vs placebo	10 mg/kg of lecanemab biweekly produced dose-dependent reductions of brain amyloid, improvements in plasma Aβ42/40 ratio, and reductions in plasma p-tau181.
Van Dyck *et al.* **[90]**	3	18 months	1906	10 mg/kg biweekly of lecanemab vs placebo	Lecanemab decreased markers of amyloid in Alzheimer's disease and resulted in less decline in cognitive function than placebo.
NCT04468659 **[101]**	3	216 weeks	1400	A45 trial: 5 mg/kg biweekly for 6 weeks, then 10 mg/kg biweekly for 86 weeks, and then 10 mg/kg every 4 week vs placebo A3 trial: 5 mg/kg every 4 weeks for 4 weeks, then 10 mg/kg every 4 weeks for 208 weeks vs placebo	Ongoing study that will determine whether lecanemab is superior to placebo in reducing brain amyloid accumulation and assess lecanemab's long-term safety.

6. Comparison of lecanemab with other drugs

6.1 Memantine

Memantine, which is an antagonist of N-methyl-D-aspartate (NMDA) type glutamate receptors, is used to treat patients suffering from moderate to severe AD **[102]**, while lecanemab, which is an anti–beta-amyloid monoclonal antibody, is approved to be used in the earliest symptomatic stages of the disease, including mild dementia and mild cognitive impairment (MCI) due to AD with positive biomarkers ($A\beta_{1-42}$, phosphorylated tau [p-tau], total tau [t-tau], neurogranin and neurofilament light chain [NfL]) **[94]**.

These differences in clinical use reflect on different treatment goals. Memantine is the symptomatic treatment, which stabilizes or even improves the cognitive, behavioral and functional symptoms. However, it has no impact on the pathological process. Lecanemab, on the other hand, modifies the disease course. Randomized controlled trials (RCTs) have shown the drug's effect in lowering the rate of progression in cognitive and functional deterioration compared to a placebo, thus delaying the onset of the disease symptoms in patients **[102]**.

Moreover, depending on the method, there are different side effects. The advantage of memantine has no great impact, as it only remains effective for 3-6 months sometimes even 12 months, before declining again, decreasing cognitive functions **[103].** By contrast, results from the phase 3 CLARITY AD clinical trial demonstrated that lecanemab slows down the process of cognitive decline by 27% over 18 months. Although this effect is moderate and does not stop progression, it represents a meaningful delay in decline **[104].**

Another difference between the two has to do with their safety profile. Memantine is used orally and is well-tolerated, with minimal side effects such as headaches, constipation and confusion. This makes it a suitable drug for the long term use for older patients **[105]**. Lecanemab, on the other hand, requires regular intravenous infusions and has side effects, ranging from headaches, falls or confusion, to more serious ones, such as ARIA or stroke. So, it is necessary to undergo regular MRI scans. What is important is that symptomatic treatment with drugs such as memantine was often continued in the studies with lecanemab **[106]**.

6.2 Cholinesterase inhibitors (ChEIs)

Lecanemab and ChEIs including donepezil or rivastigmine are used in the early stages of AD. However, they have different mechanism of action and application. ChEIs remain first-line treatment. They increase levels of acetylcholine therefore stabilizing cognition and activities of daily living **[107]**. Meta-analyses of ChEIs have shown significant improvements in cognitive response rates compared with placebo, although it varies between individuals and across studies **[108]**.

Lecanemab, being a disease-modifying medication, slows progression by reducing amyloid-β levels. Therefore, the clinical outcomes of lecanemab and ChEIs differ because ChEIs studies focus on short-term symptom improvement, whereas lecanemab studies evaluate the rate of cognitive and functional decline over time. These medications also have different side effects. ChEIs have more frequent but milder adverse effects, particularly gastrointestinal ones, such as nausea, vomiting, and diarrhea **[109]**. They are associated with a higher incidence of adverse events and treatment discontinuation compared with placebo **[108].** Lecanemab, on the other hand, has less frequent but more serious side effects, such as ARIA or stroke. Therefore, MRI and biomarker confirmation are used for lecanemab, while ChEIs do not require one. Also amyloid-related imaging abnormalities, including ARIA-E (edema) and ARIA-H (hemorrhage), can occur in some patients treated with lecanemab **[110].** Moreover, side effects caused by infusion including headache or chills can occur early in the treatment, but are often temporary **[111]**.

As with memantine, ChEIs can be used together with lecanemab, so they are complementary, not mutually exclusive, therapies. Patients with mild AD dementia taking ChEIs do not progress in losing cognitive function for over 5-8 years **[112]**. However, the addition of lecanemab in the early stages of AD maintains cognitive function at an improved level for another 5–10 years **[90]**. Long-term data are still needed, but current reviews confirm that lecanemab slows disease progression compared to placebo and has the potential to become a disease-modifying therapy for AD **[113]**.

6.3.1 Comparison of lecanemab and donanemab

In pivotal phase 3 clinical trials, patients were treated with both lecanemab and donanemab **[114,115]**. It was demonstrated that both agents markedly removed amyloid plaques from the brains of patients affected by Alzheimer's disease (AD), while donanemab additionally reduced amyloid burden detected by PET imaging by an average of 80% after 18 months of therapy **[114,115]**. Unfortunately, the observed biological effect did not translate proportionally into a clinical benefit, which remained limited [1]. Comparisons between baseline and endpoint assessments were performed using the Clinical Dementia Rating – Sum of Boxes (CDR-

SB) scale and the Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL-MCI), demonstrating 27% for lecanemab and 36% for donanemab (corresponding to approximately 0.5–0.7 points on the scale), and in the second scale both 38% to 40%, respectively **[114]**. PET imaging indicated that greater benefits of donanemab were observed in patients with a milder form of AD involving tau protein pathology **[114,115]**.

The results of these studies raised doubts as to whether the magnitude of cognitive and functional effects achieved was clinically meaningful **[114,116,117,118]**. It should be noted, however, that an approximately 0.5-point benefit in the CDR-SB score observed in clinical trials of these antibodies represents a composite measure derived from all domains included in the scale: memory, orientation, judgment/problem solving, community affairs, home and hobbies, and personal care **[114]**. Regarding the safety profile of both agents, clinical trials demonstrated the occurrence of acute infusion-related reactions (IRRs), which were reported in approximately 1 in 13 patients treated with donanemab and in approximately every fourth patient receiving lecanemab **[90, 114,115]**. In most cases, these events were mild to moderate in severity; severe reactions occurred in 1.2% of patients treated with lecanemab and in only 0.3% of those receiving donanemab **[90,114,115]**. Additionally, it was observed that 75% of IRRs associated with lecanemab occurred within 30 minutes of the first infusion, whereas in the case of donanemab they typically occurred between the second and fifth administrations **[90, 114,115]**. In patients at high risk of anaphylaxis or angioedema, prophylactic administration of antihistamines or corticosteroids reduced the risk of recurrent episodes among study participants **[87, 114,119]**.

During treatment with anti–beta-amyloid antibodies, clinical progress should be monitored by magnetic resonance imaging (MRI) for complications such as amyloid-related imaging abnormalities (ARIA) **[114]**. A higher risk of ARIA has been observed in carriers of the APOE ε4 allele, with the highest risk in homozygotes, estimated to be 3- to 6-fold greater than in non-carriers (data presented in Table 8) **[114]**. Clinical trials demonstrated a higher incidence of ARIA in patients treated with donanemab (314/853 patients, 36.8%) compared with those receiving lecanemab (193/898 patients, 21.5%); however, it was noted that appropriate dose titration significantly reduced the frequency of this complication **[114,120]**. Clinically manifest ARIA most commonly presents as amyloid-related imaging abnormalities with oedema (ARIA-E), occurring in 70% of cases within the first 3 months and in 90% within the first 6 months of therapy initiation **[98, 114,121]**. Most cases of ARIA-E resolve spontaneously or within up to 2 months after treatment discontinuation (depending on severity), although in patients with severe ARIA or with clinical symptoms, the addition of corticosteroids may be therapeutically indicated **[114]**. Another risk factor, and the only modifiable one, is arterial hypertension **[114,121]**. Another subtype is amyloid-related imaging abnormalities with hemorrhage (ARIA-H), although it is reported not to show full correlation with immunotherapy **[114,90,121]**. The incidence of isolated ARIA-H during lecanemab therapy was 6/898 patients (0.7%), and major intracerebral hemorrhage events were comparable across groups: 5 participants in the lecanemab group, 3 in the donanemab group, and 3 receiving placebo **[90, 114,115]**.

Furthermore, several studies investigating immunotherapy (including donanemab and lecanemab) have suggested that such therapy may lead to a reduction in brain volume and ventricular enlargement compared with the placebo group **[114,122,123,124]**. According to available evidence, these changes may correlate with amyloid plaque removal and alterations in cerebrospinal fluid dynamics associated with ARIA-E **[114,122,123]**. However, current evidence does not indicate that brain tissue pseudoatrophy is associated with adverse cognitive or functional outcomes **[114,122,123]**.

In addition to ARIA, other adverse events may occur: non-focal neurological symptoms (headache/dizziness, visual disturbances, generalized tonic-clonic seizures, behavioral disturbances, confusion, hallucinations), focal neurological symptoms (retinal hemorrhage, nausea, vomiting, tinnitus, fatigue, muscle weakness), or stroke-like symptoms (diplopia, aphasia, ataxia, amnesia, paresthesia, speech disturbances) **[114]**. In the case of lecanemab administration, these accounted for approximately 67% non-focal symptoms, 20–25% focal symptoms, and approximately 10–15% stroke-like symptoms, respectively **[114]**. Detailed changes within the central nervous system (CNS), both in Alzheimer's disease itself and in patients undergoing immunotherapy, can ultimately be fully assessed only post mortem; therefore, autopsy examinations of patients who received therapy and were closely monitored clinically will be of considerable value **[125]**.

Table 7. Comparison of the incidence of ARIA in the study groups: with lecanemab, with donanemab and with placebo divided according to the occurrence of ApoE ε4 alleles.

	Lecanemab (n=898)	Donanemab (n=853)	All placebo (n=1771)
ε4 non-carrier	5,4%	15,7%	0,6%
ε4 heterozygous	10,9%	22,8%	1.9%
ε4 homozygous	32,6%	40,6%	3,6%

Abbreviations: *ApoE*: Apolipoprotein E.

6.3.2 Comparison of lecanemeb and aducanumab

Aducanumab, similarly to lecanemab, belongs to the class of anti-amyloid antibodies that facilitate beta-amyloid clearance through Fc receptor–mediated phagocytosis **[83]**.

Both agents exhibit lower affinity for beta-amyloid monomers; however, they differ in their preferential binding toward soluble oligomers versus plaques or fibrils **[62,80,83,,86,126,127]**. In comparison, lecanemab demonstrates approximately 10-fold greater selectivity for oligomers than aducanumab **[62,83,126,127]**.

Both drugs, when tested in transgenic mouse models of AD, demonstrated substantial therapeutic potential, which led to their subsequent evaluation in clinical settings **[83,86,128,129,79]**.

Currently established dosing regimens include 10 mg/kg body weight administered every 2 weeks for lecanemab, whereas aducanumab is administered at the same dose every 4 weeks **[83,130]**. A detailed comparison is presented in Table 8.

Table 8. Comparison of the main features of aducanumab and lecanemab with clinical trials.

	Aducanumab	Lecanemab
Type of antibody	IgG1 human N-terminal	IgG1 humanized N-terminal
Target amyloid species	Plaque, fibrils >> oligomers	Large oligomers (protofibrils) > jplaque
Dose	Titrate up to 10 mg/kg	10 mg/kg
Dose frequency	Once every 4 weeks	Once every 2 weeks
Route	Intravenous	Intravenous
Titration	Over 6 months	No titration
Plasma half-life	21 days	5,3 days
Brain penetration	<1,5%	~0,5%
Time to peak brain steady state exposure	~5 months	~2,5 months
Most common adverse effects	ARIA, headaches	ARIA, headaches, IRR

Abbreviations: IgG1: Immunoglobulin G1, ARIA: Amyloid-Related Imaging Abnormalities; IRR: Infusion-Related Reaction.

6.3.3 Studies on effectiveness and safety of aducanumab

To demonstrate the efficacy and safety of aducanumab in individuals with early-stage AD, two identically designed, multicenter, double-blind clinical trials were conducted - EMERGE (1638 patients, NCT02484547) and ENGAGE (1647 patients, NCT02477800) **[83,131,132,133]**. Participants were between 50 and 85 years of age and had confirmed amyloid pathology, meeting criteria for mild cognitive impairment or mild dementia due to AD **[83]**. They were randomized into three groups: low-dose administration (target dose 3 or 6 mg/kg), high-dose administration (target dose 10 mg/kg), and placebo, each administered every 4 weeks over a 76-week period **[83]**. The primary endpoint was assessed using the CDR-SB scale at week 78, and amyloid plaque burden in the brain was evaluated using positron emission tomography (PET) imaging **[83]**.

6.3.4 Studies on effectiveness and safety of lecanemab

For lecanemab, a separate trial was conducted under the name Clarity AD (NCT03887455), in which 5967 individuals were screened and 1795 were randomized **[87,83,134]**. Participants were between 50 and 90 years of age and had early-stage AD with mild memory impairment or cognitive impairment, with confirmed evidence of beta-amyloid presence (via PET imaging or cerebrospinal fluid analysis) **[83]**. In this study, participants were assigned to two groups: placebo (897 individuals) and immunotherapy at a dose of 10 mg/kg administered every 2 weeks (898 individuals) **[83]**.

6.3.5 Endpoint results

The EMERGE trial demonstrated that, when comparing the primary endpoint, the high dose of aducanumab yielded favorable results, showing a 22% reduction in beta-amyloid compared with placebo **[83]**. Unfortunately, no significant difference compared with placebo was observed for the low-dose group **[83]**. PET amyloid imaging revealed a time- and dose-dependent reduction in beta-amyloid following immunotherapy, and cerebrospinal fluid biomarkers decreased in both the low- and high-dose groups **[83]**.

In the ENGAGE trial, the primary endpoint was not achieved for either the high-dose or low-dose groups compared with placebo **[83]**. PET imaging demonstrated a reduction in beta-amyloid; however, cerebrospinal fluid biomarkers did not show a significant decrease **[83]**.

In the Clarity AD trial evaluating lecanemab, the primary endpoint was defined as the change in CDR-SB score after 18 months of therapy **[83]**. At the designated time point, the adjusted mean change from baseline favored lecanemab (1.21 in the lecanemab group vs. 1.66 in the placebo group; statistically significant difference of –0.45) **[83]**. Comparisons using additional measures - PET imaging, the Alzheimer's Disease Assessment Scale (ADAS-Cog), the Alzheimer's Disease Composite Score (ADCOMS), and the Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL-MCI) - also demonstrated superior outcomes in the immunotherapy group compared with placebo **[83]**

6.3.6 Safety

At a dosing regimen of 10 mg/kg, aducanumab was generally well tolerated; however, adverse events occurred frequently **[83]**. The most commonly reported events (≥2% of participants) included ARIA-E, headache, ARIA-H, microhemorrhage, superficial siderosis, falls, diarrhea, and disorientation/confusion/delirium - all of which were significantly more frequent in the immunotherapy group than in the placebo group **[83]**. The most common reason for study discontinuation was the occurrence of ARIA-H **[83]**.

In the Clarity AD trial, adverse events occurred in 88.9% of the 898 participants receiving lecanemab at a dose of 10 mg/kg every 2 weeks, compared with 81.9% of participants receiving placebo **[83]**. In the immunotherapy group, the most common adverse events were IRRs, ARIA-H, ARIA-E, headache, and falls **[83]**. It was also observed that ARIA-H and ARIA-E occurred more frequently in individuals who were carriers of the ApoE ε4 allele **[83]**.

6.3.7 Comparison summary

Both aducanumab and lecanemab have demonstrated promising effects in clinical trials; however, their full implementation in patients with AD remains uncertain **[83]**. Although aducanumab exhibited greater penetration across the blood–brain barrier (BBB) than lecanemab, its superiority in efficacy remains unclear due to the higher selectivity of lecanemab toward beta-amyloid oligomers **[80,83]**. The dosing regimens of the two agents also differ, which may contribute to observable differences in therapeutic efficacy **[80,83]**.

Aducanumab is the first approved disease-modifying immunotherapy for mild Alzheimer's disease **[83]**. Despite this, the unsatisfactory results of the EMERGE and ENGAGE trials - presenting ambiguous findings (EMERGE) or a completely negative outcome with respect to the predefined primary endpoint (ENGAGE) in terms of slowing cognitive decline as measured by the CDR-SB scale - raise substantial concerns **[83]**. The reported findings unfortunately do not meet the conventional standards required for broad regulatory approval and routine clinical use **[83,135]**. However, when considering cerebrospinal fluid biomarker results, a potential for clinical benefit may still be inferred **[83,135]**.

Lecanemab demonstrates potential due to its ability to reduce beta-amyloid levels, attenuate cognitive decline, and show a lower incidence of ARIA-E **[83]**. This translates into a favorable safety profile with a moderate therapeutic effect **[83]**. For both lecanemab and aducanumab, larger and more comprehensive studies evaluating safety and efficacy are warranted, particularly in individuals without clinical symptoms of dementia but with confirmed beta-amyloid pathology **[83]**.

6.4 Rejected therapies

Among the well-known and extensively investigated areas of AD pharmacotherapy, there are therapeutic approaches whose attempts at implementation through appropriately designed scientific studies and clinical trials have ultimately failed. These include investigations of estrogen, vitamin E, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), testosterone, and *Ginkgo biloba* as preventive or therapeutic strategies in AD **[136]**.

6.4.1 Estrogen

Studies evaluating estrogen did not demonstrate a beneficial effect of its long-term administration on improvement or preservation of cognitive function in patients suffering from AD **[136,137,138]**.

6.4.2 Vitamine E, NSAIDs, statins

A Cochrane review conducted in accordance with Evidence-Based Medicine (EBM) principles also assessed vitamin E and reached similar conclusions **[136]**. Additionally, it was shown that its use at higher doses may be potentially harmful **[136,139]**. The final outcomes of studies investigating long-term use of NSAIDs or statins likewise failed to demonstrate positive effects **[136,140,141]**.

6.4.3 Testosterone

There have also been therapeutic attempts yielding conflicting evidence relative to initial assumptions **[136]**. One such example is testosterone therapy, the use of which in men with Alzheimer's disease has produced ambivalent findings regarding its potential benefits **[136]**. Two randomized, double-blind, placebo-controlled trials demonstrated improvement in visuospatial cognition; however, it remains uncertain whether this effect can be considered clinically significant **[136,142,143]**. Another randomized placebo-controlled study involved supplementation with transdermal testosterone gel (75 mg daily) in men with mild to moderate AD over a 6-month period **[136,144]**. This intervention resulted in a slight improvement in patients' quality of life; however, the effects were not statistically significant **[136]**. In a similar randomized placebo-controlled trial using testosterone gel in patients aged >65 years characterized by low serum testosterone levels and limited mobility, an increased incidence of cardiovascular adverse events was observed in the treatment group (22% compared with 5% in the placebo group; P = 0.05; number needed to harm = 6 [NNH]) **[136,145]**. For this reason, testosterone therapy is not recommended in patients with AD **[136]**.

6.4.4 *Ginko biloba, M. officinalis, S. officinalis*

Thirty-six studies evaluating the use of *Ginkgo biloba* in the treatment of cognitive impairment were also assessed **[136]**. Thirty-five of the 36 trials used *Ginkgo biloba* extract EGb 761 at doses ranging from 80 to 600 mg daily **[136]**. None of the conducted studies demonstrated consistent, clinically significant cognitive improvement in patients with AD **[136]**. However, one conclusion that may be drawn from these studies is the relative safety of *Ginkgo biloba*, based on comparable rates of adverse events between treatment and placebo groups. Due to its pharmacokinetic (PK) and pharmacodynamic (PD) properties, there is a significant risk of bleeding in patients concomitantly using agents such as acetylsalicylic acid, NSAIDs, anticoagulants, or vitamin K antagonists - medications that frequently accompany patients in their therapeutic regimens **[136,146]**.

Other botanical agents with potential to improve cognitive functioning in patients with AD include *Melissa officinalis* (lemon balm) and *Salvia officinalis* (sage) **[147]**.

It has been demonstrated that *M. officinalis* supports cognitive function and reduces agitation in patients with mild to moderate AD **[147]**. It modulates acetylcholine receptor activity within the central nervous system (CNS), exhibiting affinity for both muscarinic and nicotinic receptors **[147,148,149]**. Studies in young, healthy volunteers have shown that preparations containing lemon balm not only improved mood but also enhanced cognitive performance **[147,150]**. In another randomized placebo-controlled study, the efficacy and safety of lemon balm were evaluated in 42 patients with mild to moderate AD **[147,151]**. The therapy lasted 4 months, and therapeutic efficacy was assessed using the ADAS-Cog cognitive scale and the CDR-SB scale **[147]**. The CDR-SB scale evaluates six key domains of AD: memory, orientation, judgment and problem solving, social functioning, home activities/hobbies, and personal care **[147]**. The results were promising - patients receiving lemon balm extract achieved significant improvement in cognitive function after the planned 16 weeks of therapy, as documented by both ADAS-Cog and CDR-SB scores **[147]**. Differences between baseline and endpoint scores were –1.92 for *M. officinalis* and –1.03 for placebo according to the CDR-SB scale **[147]**. No significant differences in the frequency of adverse events were observed between the two groups; however, agitation occurred more frequently in the placebo group compared with the group receiving the plant extract **[147,151]**.

In addition to lemon balm, sage extract (*Salvia officinalis*) has also been evaluated in clinical studies and demonstrated significant improvement in cognitive function after 16 weeks of therapy **[147,152]**. Clinical relevance was confirmed using the ADAS-Cog and CDR-SB scales, both in observed-case analysis and in intention-to-treat analysis **[147]**. Changes in endpoint scores compared with baseline were 1.60 for sage extract and 0.73 for placebo on the CDR-SB scale **[147]**. Adverse events associated with this preparation were typical of excessive cholinergic stimulation, similar to those observed with cholinesterase inhibitors (e.g., rivastigmine) **[147,153]**. As with lemon balm, a lower incidence of agitation was observed in the group receiving sage extract compared with placebo, suggesting additional beneficial properties for patients with AD **[147]**.

To date, treatment outcomes involving *Melissa officinalis* and *Salvia officinalis* appear promising, as these agents have identifiable pharmacological targets, such as specific receptors or neurotransmitter systems; however, such therapy cannot be considered sufficient as a standalone treatment for the disease under discussion **[147]**.

6.4.5 Tramiprosate

There is one agent which, among beta-amyloid aggregation inhibitors, is currently undergoing phase III clinical trials **[154,155,156]**. This compound is 3-amino-1-propanesulfonic acid, also known as tramiprosate **[154,155,156]**. It was synthesized to antagonize the interaction between soluble beta-amyloid and endogenous glycosaminoglycans (GAGs) **[154]**. GAGs have been shown to promote the deposition and accumulation of beta-amyloid fibrils **[154,156]**. Unfortunately, the results of the phase III trial conducted in 2007 were disappointing, leading to the suspension of further development of the drug in Europe **[154,157]**.

6.4.6 Kolostrynin

Colostrinin, a proline-rich polypeptide complex present in human colostrum (as well as bovine and ovine colostrum), has been found to inhibit beta-amyloid aggregation **[154,158]**. Studies in murine cell models demonstrated reduced beta-amyloid neurotoxicity and improved cognitive performance in experimental animals **[154,158]**. Phase II trials were conducted in patients with mild AD, in whom administration of the agent, assessed using the Mini-Mental State Examination (MMSE), revealed slight improvement over a 15-month treatment period; however, this beneficial effect was not sustained during the subsequent 15 months of continued therapy **[154,158]**.

6.4.7 Scylloinositol

An 18-month phase II clinical trial investigated the use of an oral anti-amyloid aggregation agent, scyllo-inositol, in patients with mild to moderate AD **[154,159]**. Ultimately, the study - designed to evaluate safety, efficacy, and dose selection - did not meet the predefined criteria for clinical effectiveness **[154,159]**.

6.4.8 Inhibitores/modulatores RAGE

These agents act on the receptor for advanced glycation end products (RAGE), facilitating the transport of beta-amyloid across the BBB **[154,160,161,162]**. They were the only drugs modulating beta-amyloid transport between systemic circulation and the central nervous system to reach clinical trial phases **[154]**. Unfortunately, PF-04494700 and TTP400, which reached phase II and phase I trials (NCT01548430), respectively, were withdrawn from further development, and their results were not published **[154,163]**.

6.4.9 Active immunization

Active anti-amyloid immunotherapy aims to promote the clearance of beta-amyloid, thereby significantly reducing its concentration in individuals affected by AD **[154]**. Administration of vaccines containing beta-amyloid-42 (the predominant form present in plaques in older individuals) to transgenic mouse models of AD proved successful in experimental assessments **[154]**. These vaccines were intended to stimulate B- and T-lymphocytes as well as activate the phagocytic properties of microglia **[154]**.

Human trials were conducted using a first-generation vaccine (AN1792, comprising the 1–42 beta-amyloid peptide); however, this approach was associated with serious adverse effects **[154]**. Due to an autoimmune response - primarily mediated by T-lymphocyte activation - 6% of participants developed encephalitis, specifically aseptic meningoencephalitis **[154,164]**.

Second-generation vaccines contained a shorter peptide fragment (amino acids 1–6 of the beta-amyloid protein), with the aim of preventing the adverse immune response observed with the first-generation vaccine **[154,165]**. The company Novartis developed the CAD106 vaccine, which advanced to clinical trial phases **[154,165]**. Phase II clinical studies demonstrated an immune response in as many as 75% of treated patients, without the occurrence of serious adverse reactions **[154,165]**.

Another vaccine, ACC-001, developed by Janssen, was evaluated in several phase II trials (NCT01284387, NCT00479557, NCT01227564) **[154,166,167,168]**. Unfortunately, the company discontinued further development of this vaccine **[154]**.

Meanwhile, additional vaccine candidates have been developed and are currently being investigated at various stages of preclinical development **[154,169,170,171]**.

6.5 Therapies with the potential to cure the future

Numerous diagnostic and therapeutic approaches represent potential directions in which Alzheimer's disease (AD) treatment may evolve, creating new therapeutic pathways for patients who respond poorly to classical, previously established interventions **[172]**.

6.5.1 Retinoic Acids

One promising avenue requiring further investigation is the use of retinoids to improve cognitive functions, including memory and learning. Reduced retinoid levels have been associated with cognitive impairment in older individuals, and decreased concentrations have also been observed in the brains of aging mice **[162,173,174]**. Retinoic acids (RA) promote neurogenesis and support neuroplasticity, both of which are key processes underlying learning and memory formation **[172]**. In vitro studies have demonstrated that RA reduces beta-amyloid toxicity **[172,175]**. In murine studies, a vitamin A–deficient diet resulted in disruption of RA signaling pathways and accumulation of beta-amyloid within cerebral vasculature in the frontal brain region **[172,176]**.

Research conducted by Gonçalves et al. demonstrated that modulation of retinoid receptors promotes cognitive function, enhances clearance of Aβ from neurons and microglia, and exerts anti-inflammatory effects **[172,177]**. These findings suggest that synthetically developed retinoids may constitute a future therapeutic pathway for patients with AD **[172]**.

Examples of such agents include tamibarotene and acitretin, which are currently being investigated for their therapeutic potential in AD **[172]**. Studies by Tippmann et al. showed that acitretin increases the activity of alpha-secretase involved in amyloid precursor protein (APP) processing, thereby reducing beta-amyloid levels in the APP/PS1 AD model. This retinoid also demonstrates substantial penetration across the BBB **[172,178]**. Research by Endres et al. indicated that acitretin enhances non-amyloidogenic APP metabolism in humans **[172,179,180]**. Preliminary phase II clinical data demonstrated a 25% increase in the concentration of the aforementioned secretase in the cerebrospinal fluid of patients with AD **[172,179]**. Furthermore, Gonçalves et al. tested multiple retinoid receptor agonists and observed that activation of the RAR signaling pathway increases the enzymatic expression of neprilysin (NEP) and insulin-degrading enzyme (IDE), thereby promoting beta-amyloid clearance and modulating production of the pro-inflammatory cytokine TNF-alpha by glial cells **[172,181]**. These studies also demonstrated that NEP, through its proteolytic action on beta-amyloid, activates RAR signaling in CNS cells, while IDE contributes to dissolution of beta-amyloid deposits and is likewise present in the CNS **[172,177]**.

Retinoids may not serve as a primary therapeutic solution in AD but could potentially enhance the effects of currently used agents, such as cholinesterase inhibitors **[172]**. Stimulation of RAR increases the production of choline acetyltransferase (ChAT) and vesicular acetylcholine transporter (VAChT) protein **[172]**. Both are involved in facilitating acetylcholine (ACh) transport into presynaptic vesicles for subsequent neurotransmitter release **[172,182]**. Thus, enzymatic pathways involving retinoids may play a significant role in regulating ACh production via ChAT as well as neurotransmitter availability at synapses through acetylcholinesterase modulation, offering potential pharmacological support in AD treatment **[172]**.

Although these findings appear promising, research on retinoids remains in its early stages, and limited experimental clinical data have been published **[172]**. Insufficient attention has been devoted to the effects of RA on brain function, despite the substantial regulatory potential of retinoids over numerous neuronal processes in the adult human brain **[172]**. Their application appears highly promising in AD and potentially in other neurodegenerative diseases; however, further elucidation of the molecular pathways and neuronal genes regulated by retinoids is required before clinical implementation **[172]**.

6.5.2 The missing element in the fight against Alzheimer's – copper

Another potential diagnostic and therapeutic pathway involves copper. The beta-amyloid precursor protein (APP) is a copper-binding glycoprotein necessary for beta-amyloid production within cells. Studies in transgenic mice have shown that APP overexpression leads to significantly reduced copper concentrations in the brain, whereas animals with knockout of genes such as APP or APLP2 exhibit increased copper levels in the liver and cerebral cortex **[183–187]**. In vitro studies indicate that APP and APLP2 may function as copper efflux proteins **[183]**.

Using a yeast model, the copper-chelating agent clioquinol (CQ) was evaluated **[183]**. Increased intracellular copper levels were observed, suggesting that its therapeutic potential may be related to redistribution of copper or facilitation of cellular uptake rather than reduction of total copper levels **[183]**. Animal model studies confirmed that APP plays a role in regulating copper homeostasis in vivo **[183]**. Although the significance of ionic dyshomeostasis in AD is not yet fully understood, studies in transgenic mice

strongly suggest that increasing copper ion concentration may reduce soluble beta-amyloid peptide levels and plaque burden **[183,188–190]**. Elevated intracellular copper reduced APP conversion into beta-amyloid and modulated APP levels **[183,184,191]**.

Interestingly, during oral treatment with CQ - despite being classified as a copper and zinc chelator - brain concentrations of copper (by 19%) and zinc (by 13%) paradoxically increased **[183]**. A 50% increase in soluble brain beta-amyloid was observed, while plaque deposition was inhibited **[183,192]**. This suggests that CQ does not alter total systemic copper levels but rather redistributes them **[183]**. Its CNS effects are likely related to its hydrophobic properties, enabling penetration across the BBB and facilitating formation and uptake of CQ–copper complexes in the brain (which may also form in the gastrointestinal tract in mammals) **[183,193]**. In a phase II clinical trial, CQ administration was associated with stabilization of cognitive decline and reduction of plasma beta-amyloid 42 levels in patients with moderate to severe AD **[183,193]**. Moreover, transgenic mice treated with copper exhibited prolonged survival compared with untreated animals, suggesting potential clinical relevance **[183,184]**. Collectively, current evidence indicates that modulation of copper homeostasis may represent an alternative therapeutic strategy in AD **[183]**.

6.5.3 Passive immunization

Passive immunotherapy involves administration of mono- or polyclonal antibodies directed against beta-amyloid. Its advantage over active immunotherapy lies in the reduced pro-inflammatory response associated with T-lymphocyte activation **[154]**. Animal studies demonstrated that despite unchanged plaque counts, passive immunotherapy improved cognitive function and reduced cerebral beta-amyloid burden **[154]**. This effect is attributed to neutralization of soluble amyloid oligomers, which constitute a key pathogenic component of AD **[154]**.

6.5.3.1 Bapinezumab/solanezumab

Two humanized monoclonal antibodies advanced into late-stage clinical development; however, in 2012 two phase III trials were terminated due to lack of efficacy in patients with mild to moderate AD **[154,194]**. These antibodies targeted beta-amyloid fragments 1–6 and 12–28, respectively **[154,195,196]**. Bapineuzumab reduced amyloid plaque burden and cerebrospinal fluid phosphorylated tau levels but failed to improve cognitive outcomes **[154]**.

In studies administering 400 mg monthly infusions of solanezumab for 80 weeks in patients with mild to moderate AD, results suggested possible cognitive benefit in mild AD; however, the findings were not statistically significant **[154,196]**. Subsequent phase III trials were conducted in patients with AD (NCT01127633, NCT01900665) and in cognitively normal individuals at high risk of developing AD (NCT02008357) **[154,197–199]**.

6.5.3.2 Gantenerumab

A fully human IgG1 monoclonal antibody has been investigated in trial NCT01760005 in individuals at risk of early-onset AD due to autosomal dominant mutations **[154,200–203]**. Concurrent phase III (NCT02051608) and prodromal AD (NCT01224106) trials are also ongoing **[154,204,205]**. In transgenic mouse studies, gantenerumab was shown to recruit microglia to phagocytose amyloid plaques, leading to plaque degradation **[154]**.

6.5.3.3 Krenezumab

Another humanized IgG4 monoclonal antibody completed a phase II clinical trial in 2014 (NCT01343966) evaluating efficacy and safety in mild to moderate AD **[154,206,207]**. In 2013, an additional phase II study (NCT01998841) was initiated in asymptomatic carriers of the autosomal dominant PSEN1 E280A mutation **[154,208]**.

6.5.3.4 Gammagard

A further human antibody with a previously established safety profile in autoimmune diseases was evaluated in trial NCT00818662 in a small cohort of patients with AD **[154,209]**. This agent also exhibits immunomodulatory properties, potentially enhancing microglial phagocytosis **[154,210–212]**.

6.5.3.5 ALZ-801 (tramiprosate prodrug)

An orally administered agent capable of effectively crossing the BBB selectively targets beta-amyloid monomers, thereby inhibiting pathological misfolding and preventing formation of neurotoxic soluble oligomers **[80,129,213–215]**. It demonstrates improved absorption, gastrointestinal tolerability, and enhanced brain penetration **[80,216]**. Clinical data from over 2,000 patients treated for 18 months indicate a favorable safety profile **[80,217,218]**. Its clinical dose has been optimized to effectively block beta-amyloid oligomer formation in the brain (phase III and in vitro studies) **[80,129,216]**. The oral formulation ALZ-801 offers

convenient administration for elderly patients and may serve as a preventive therapy in asymptomatic individuals at high risk for AD **[80]**.

6.5.4 Tau protein

Tau protein is a soluble neuronal protein abundantly present in neurons, where it plays a key role in stabilizing microtubules, particularly within axons **[154,219–221]**. Pathophysiological changes in tau involve hyperphosphorylation, leading to formation of insoluble paired helical filaments (PHFs) **[154,220]**. This disrupts microtubule binding, destabilizes the cytoskeleton, and ultimately results in neuronal degeneration and death **[154,220]**. Therapeutic strategies targeting tau focus on inhibiting phosphorylation and/or aggregation and may complement existing AD therapies **[154,221]**.

6.5.4.1 Tau protein hyperphosphorylation inhibitors

Phosphorylation is one of the most important mechanisms regulating the binding of microtubules to tau proteins **[154]**. Pathophysiological reactions occurring in people affected by Alzheimer's disease cause hyperphosphorylation, which prevents the dissolution of tau proteins **[154,222,223]**.

Hyperphosphorylation results from imbalance between kinase and phosphatase activity, with kinase predominance in AD **[154]**. Relevant kinases include CDK5, GSK3-beta, Fyn, JNK, p38, and ERK1/2 **[154,224]**. These contribute to pathological tau hyperphosphorylation within neurofibrillary tangles **[118,154,225–231]**.

SP600125, a pan-JNK inhibitor, reduced neurodegeneration and improved cognitive function in APP/PS1 transgenic mice **[154,230]**. Inhibition of JNK3 may produce similar beneficial effects **[154,228–231]**. In human studies, elevated JNK3 levels correlated positively with beta-amyloid (1–42) and cerebrospinal fluid JNK3 concentrations were associated with memory impairment **[49,227,231]**.

CDK5, a serine/threonine cyclin-dependent kinase, plays essential physiological roles in CNS development, including axonal growth and neurite extension **[154,232]**. In AD, pathological conversion of its cofactor p35 to p25 due to increased intracellular calcium leads to tau hyperphosphorylation and neuronal degeneration **[154,233,234]**. CDK5 inhibitors such as roscovitine and flavopiridol have demonstrated neuroprotective effects in vitro and in vivo by reducing ischemia-induced and neurodegenerative damage **[154,234,235]**.

GSK3-beta inhibitors have reached more advanced stages of clinical development. Tideglusib, an irreversible GSK3-beta inhibitor administered for 26 weeks in mild to moderate AD (NCT01350362), failed to demonstrate efficacy and was discontinued **[154,236]**. Another study (NCT00948259) evaluating NP031112 aimed to assess safety and tolerability over 20 weeks; however, further details were not reported **[154,237]**.

An alternative strategy involves enhancing phosphatase activity. Sodium selenate, a protein phosphatase 2A (PP2A) agonist (ACTRN12611001200976), reduced tau phosphorylation in cellular and murine AD models **[154,238–242]**.

6.5.4.2 Tau protein aggregation inhibitors

Inhibition of tau aggregation represents another therapeutic approach. Methylene blue derivatives have shown potential in this context **[154]**. Methylene blue inhibits aggregation, improves mitochondrial electron transport chain function, reduces oxidative stress, limits organelle damage, and modulates autophagy **[154,224,242]**. The first-generation derivative Rember demonstrated potential stabilization of AD progression over 50 weeks in clinical trials **[154]**. This led to development of the second-generation purified derivative TRx0237, which not only inhibits aggregation but also dissolves existing tau aggregates; its therapeutic potential is under investigation in multiple trials (NCT01626391, NCT01689233, NCT01689246, NCT01626378) **[154,224,243–246]**.

6.5.4.3 Microtubule stabilization

Another approach involves stabilization of microtubules to counteract tau pathology. Paclitaxel, widely used in oncology (e.g., breast and lung cancer), stabilizes microtubules but does not cross the BBB and carries significant long-term adverse effects, limiting its utility in AD **[154,247,248]**. TPI-287, a taxane derivative, is being evaluated for safety, tolerability, and pharmacokinetics in mild to moderate AD (NCT01966666) **[154,249]**.

Epothilone D improved axonal transport, reduced axonal dystrophy and tau pathology, and decreased hippocampal neuronal loss; however, its development was discontinued due to unfavorable results **[154,248]**. Current research focuses on identifying the most toxic tau species, particularly soluble and oligomeric forms, which represent critical targets for future therapeutic development **[154,248,250]**.

6.5.4.4 Anti-tau immunotherapy

Both active and passive immunotherapies are also being directed against tau **[154]**. These approaches enhance anti-aggregation mechanisms and promote clearance of oligomeric and insoluble aggregates **[154,251]**. In murine studies, monoclonal antibodies targeting hyperphosphorylated tau improved cognitive function without significant adverse effects **[154,251]**. A 2013 study by Axon Neuroscience (NCT01850238, NCT02031198) evaluated the safety and tolerability of the AADvac-1 vaccine, though detailed results were not disclosed **[154,252,253]**. In 2014, favorable safety profiles over six months were reported in animal models (rats, dogs, rabbits), leaving open the question of comparable efficacy and safety in humans **[154]**.

6.5.5 Cholinergic hypothesis

Memory consolidation and persistence occur within the hippocampus under cholinergic modulation **[154,254]**. AD involves degeneration of cholinergic neurons in the nucleus basalis of Meynert and loss of cholinergic projections to the hippocampus and neocortex **[154]**. Beyond approved acetylcholinesterase inhibitors (AChEIs), new agents aim not only to slow but potentially halt disease progression **[154,255]**.

Ladostigil (TV3326) is a reversible acetylcholinesterase inhibitor and selective, irreversible monoamine oxidase A and B inhibitor, potentially alleviating extrapyramidal symptoms and exerting antidepressant effects **[154,256,257]**. Ongoing studies (NCT01429623, NCT01354691) aim to evaluate its anti-apoptotic, antioxidant, neuroprotective, and anti-inflammatory properties **[154,258,259]**.

6.5.6 Dendritic hypothesis

AD pathophysiology also involves neurite degeneration and synaptic loss, prompting investigation of molecular changes in postsynaptic regions **[154,260–262]**. Overexpression of Fyn kinase - elevated in AD brains - accelerates synaptic degeneration and cognitive impairment in J9 (APPswe/Ind) transgenic mice **[154,260]**. This provides a therapeutic rationale for Fyn kinase inhibition. Trials (NCT01864655, NCT02167256, NCT00976118, NCT01872598) have evaluated saracatinib (AZD0530) and masitinib (AB1010) due to their nanomolar-range Fyn inhibitory activity **[154,263–269]**.

In study NCT00976118, oral masitinib was administered for 24 weeks in combination with acetylcholinesterase inhibitors (galantamine, rivastigmine, or donepezil) and/or memantine **[154,265]**. Assessment using the ADAS-Cog scale yielded encouraging results; however, patient groups were too small to draw definitive conclusions regarding efficacy **[154]**.

Conclusions

Alzheimer’s disease is a chronic, progressive neurodegenerative disorder and the most common cause of dementia worldwide, representing a major and growing global health burden. Its prevalence is increasing rapidly, particularly in aging populations, with substantial underdiagnosis contributing to delayed intervention. The disease is characterized by a prolonged preclinical phase marked by amyloid beta accumulation, tau pathology, neuroinflammation, and progressive neurodegeneration, which precede clinical symptoms by many years. Clinically, Alzheimer’s disease manifests initially as episodic memory impairment, followed by progressive cognitive, functional, and neuropsychiatric decline. Advances in biomarker-based diagnostics, including neuroimaging and cerebrospinal fluid analyses, have significantly improved the accuracy of early detection and disease staging. The integration of biological and clinical staging frameworks provides a more comprehensive understanding of disease progression and supports earlier, more precise diagnosis.

The current pharmacological management of Alzheimer’s disease relies primarily on symptomatic therapies, including acetylcholinesterase inhibitors and memantine. Acetylcholinesterase inhibitors are indicated for mild-to-moderate stages, whereas memantine, in moderate-to-severe stages. Although both classes provide modest cognitive and functional benefits-particularly when used in combination-their effects remain symptomatic and do not alter the underlying neurodegenerative process. Adverse events, including gastrointestinal, cardiovascular, and neuropsychiatric effects, may limit tolerability, and therapeutic efficacy is further constrained by factors such as limited blood–brain barrier permeability and delayed treatment initiation. Increasing evidence supports the role of lifestyle-based interventions as complementary strategies in prevention and management. Dietary patterns, supplementation, and regular physical activity may enhance neuronal resilience through modulation of oxidative stress, mitochondrial function, metabolic homeostasis, and neuroinflammation. Although these interventions do not directly modify core neuropathological hallmarks, they represent accessible and cost-effective approaches to risk reduction and supportive care.

Lecanemab (BAN2401) is a recombinant humanized immunoglobulin gamma 1 (IgG1) that belongs to the second generation of anti-Aβ monoclonal antibodies, which are characterized by their selectivity for soluble Aβ oligomers versus insoluble fibrils or plaques. What distinguishes lecanemab from other anti-

amyloid mAbs is its ability to selectively bind to large, soluble protofibrils while still targeting insoluble fibrils, which creates amyloid plaques. Lecanemab reduces brain amyloid and slows loss of cognition. Lecanemab can also significantly decrease markers of amyloid, tau, neurodegeneration, and neuroinflammation. Lecanemab should be administered as an intravenous infusion over about 1 hour, once every 2 weeks, at a dose of 10 mg/kg. Indications include mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease–related dementia with a confirmed Aβ pathology. Currently, there are no known contraindications of lecanemab, however, it is suggested to avoid using it in patients with a history of seizures, APOE4 carriers, or pregnant or lactating women. Lecanemab is generally a well-tolerated and safe drug. Main adverse effects include infusion reactions, headache, and ARIA (amyloid-related imaging abnormalities). Many clinical trials assessed lecanemab's efficacy and safety, however, more data is still needed, especially from long-term studies. Lecanemab differs from memantine and cholinesterase inhibitors in both mechanisms of action and therapeutic goals. While memantine and ChEIs mainly provide symptomatic relief and are standard treatments in Alzheimer's disease management, they do not affect the underlying pathological process. In contrast, lecanemab, as a disease-modifying therapy, reduces amyloid-β burden and has been shown to slow cognitive and functional decline in early stages of AD. However, lecanemab does not replace symptomatic therapies but may be used with them. The therapeutic strategies discussed in this work reflect the evolving understanding of AD pathophysiology and increasingly target specific molecular mechanisms underlying disease progression, particularly beta-amyloid and tau pathology.

Anti-amyloid approaches - including passive immunotherapy with monoclonal antibodies such as aducanumab and lecanemab, active immunization strategies, aggregation inhibitors (e.g., tramiprosate, scyllo-inositol), and modulators of beta-amyloid transport - demonstrate that substantial reduction of amyloid burden is biologically achievable. However, clinical efficacy in terms of consistent and clinically meaningful cognitive improvement remains limited or variable. Safety concerns, including amyloid-related imaging abnormalities and autoimmune reactions observed in early vaccine trials, further underscore the need for careful therapeutic optimization and long-term evaluation.

Similarly, tau-directed strategies - targeting hyperphosphorylation, aggregation, or microtubule destabilization - represent a rational extension of disease-modifying efforts, particularly given the strong correlation between tau pathology and cognitive decline. Although several kinase inhibitors, phosphatase modulators, aggregation inhibitors, and tau immunotherapies have shown promising preclinical results, translation into consistent clinical benefit has thus far been inconclusive.

Beyond amyloid and tau, alternative pathways such as retinoid signaling modulation, copper homeostasis regulation, cholinergic enhancement, and Fyn kinase inhibition illustrate the growing recognition that AD involves broader disturbances in synaptic plasticity, neuroinflammation, metal ion balance, and neuronal signaling. These approaches may not function as standalone curative therapies but could serve as adjunctive or combination strategies, potentially enhancing the efficacy of existing treatments.

Collectively, current evidence suggests that monotherapeutic interventions targeting a single pathological mechanism may be insufficient to halt or reverse disease progression. Future therapeutic development will likely require earlier intervention - possibly at preclinical or prodromal stages - as well as multimodal strategies addressing amyloid accumulation, tau pathology, synaptic dysfunction, and neuroinflammation simultaneously. Large-scale, well-designed clinical trials with extended follow-up periods remain essential to determine long-term safety, clinical relevance, and optimal patient selection.

In conclusion, while significant advances have been made in elucidating the molecular underpinnings of AD and in developing targeted therapies, the translation of these advances into robust clinical outcomes remains a major challenge. Continued integration of molecular research, biomarker development, and precision-medicine approaches will be critical in shaping the next generation of effective disease-modifying therapies for Alzheimer's disease.

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REFERENCES

1. Rowland, L. P. (Ed.). (2008). *Merritt's neurology* (11th ed.; K. Kwieciński & A. Kamińska, Eds., 2nd Polish ed., pp. 789–794). Elsevier Urban & Partner.
2. Safiri, S., Ghaffari Jolfayi, A., Fazlollahi, A., Morsali, S., Sarkesh, A., Daei Sorkhabi, A., Golabi, B., Aletaha, R., Motlagh Asghari, K., Hamidi, S., Mousavi, S. E., Jamalkhani, S., Karamzad, N., Shamekh, A., Mohammadinasab, R., Sullman, M. J. M., Şahin, F., & Kolahi, A. A. (2024). Alzheimer's disease: A comprehensive review of epidemiology, risk factors, symptoms diagnosis, management, caregiving, advanced treatments and associated challenges. *Frontiers in Medicine, 11*, 1474043. https://doi.org/10.3389/fmed.2024.1474043
3. World Health Organization. (n.d.). *Dementia*. Retrieved February 14, 2026, from https://www.who.int/news-room/fact-sheets/detail/dementia
4. Atri, A. (2019). The Alzheimer's disease clinical spectrum: Diagnosis and management. *Medical Clinics of North America, 103*(2), 263–293. https://doi.org/10.1016/j.mcna.2018.10.009
5. Zhang, X. X., Tian, Y., Wang, Z. T., Ma, Y. H., Tan, L., & Yu, J. T. (2021). The epidemiology of Alzheimer's disease modifiable risk factors and prevention. *Journal of Prevention of Alzheimer's Disease, 8*(3), 313–321. https://doi.org/10.14283/jpad.2021.15
6. Alzheimer Europe. (2020). *Dementia in Europe yearbook 2019: Estimating the prevalence of dementia in Europe* (pp. 9–16). Alzheimer Europe.
7. Alzheimer's Association. (2021). 2021 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 17*(3), 327–406.
8. Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., Shaw, L. M., Vemuri, P., Wiste, H. J., Weigand, S. D., Lesnick, T. G., Pankratz, V. S., Donohue, M. C., & Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *The Lancet Neurology, 12*(2), 207–216. https://doi.org/10.1016/S1474-4422(12)70291-0
9. Tahami Monfared, A. A., Byrnes, M. J., White, L. A., & Zhang, Q. (2022). Alzheimer's disease: Epidemiology and clinical progression. *Neurology and Therapy, 11*, 553–569. https://doi.org/10.1007/s40120-022-00338-8
10. Li, Q., Wu, Y., Chen, J., Xuan, A., & Wang, X. (2022). Microglia and immunotherapy in Alzheimer's disease. *Acta Neurologica Scandinavica, 145*(3), 273–278. https://doi.org/10.1111/ane.13551
11. Hampel, H., Mesulam, M. M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., Khachaturian, A. S., Vergallo, A., Cavedo, E., Snyder, P. J., & Khachaturian, Z. S. (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain, 141*(7), 1917–1933. https://doi.org/10.1093/brain/awy132
12. Paroni, G., Bisceglia, P., & Seripa, D. (2019). Understanding the amyloid hypothesis in Alzheimer's disease. *Journal of Alzheimer's Disease, 68*(2), 493–510. https://doi.org/10.3233/JAD-180802
13. Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Jr., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., ... Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003
14. Mendez, M. F. (2017). Early-onset Alzheimer disease. *Neurologic Clinics, 35*(2), 263–281. https://doi.org/10.1016/j.ncl.2017.01.005
15. Jia, X., Wang, Z., Huang, F., Su, C., Du, W., Jiang, H., Wang, H., Wang, J., Wang, F., Su, W., Xiao, H., Wang, Y., & Zhang, B. (2021). A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: A cross-sectional study. *BMC Psychiatry, 21*(1), 485. https://doi.org/10.1186/s12888-021-03495-6
16. Ciesielska, N., Sokołowski, R., Mazur, E., Podhorecka, M., Polak-Szabela, A., & Kędziora-Kornatowska, K. (2016). Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatria Polska, 50*(5), 1039–1052. https://doi.org/10.12740/PP/45368
17. Jack, C. R., Andrews, J. S., Beach, T. G., et al. (2024). Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's & Dementia, 20*, 5143–5169. https://doi.org/10.1002/alz.13859
18. Santacruz, K. S., & Swagerty, D. (2001). Early diagnosis of dementia. *American Family Physician, 63*(4), 703–713, 717–718.

19. Haapasalo, A., & Hiltunen, M. (2018). A report from the 8th Kuopio Alzheimer Symposium. *Neurodegenerative Disease Management, 8*(5), 289–299. https://doi.org/10.2217/nmt-2018-0029
20. Bottino, C. M., Castro, C. C., Gomes, R. L., Buchpiguel, C. A., Marchetti, R. L., & Neto, M. R. (2002). Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. *International Psychogeriatrics, 14*(1), 59–72. https://doi.org/10.1017/S1041610202008281
21. Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine, 29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002
22. Tahami Monfared, A. A., Byrnes, M. J., White, L. A., & Zhang, Q. (2022). Alzheimer's disease: Epidemiology and clinical progression. *Neurology and Therapy, 11*(2), 553–569. https://doi.org/10.1007/s40120-022-00338-8
23. Frisoni, G. B., Boccardi, M., Barkhof, F., Blennow, K., Cappa, S., Chiotis, K., Démonet, J. F., Garibotto, V., Giannakopoulos, P., Gietl, A., Hansson, O., Herholz, K., Jack, C. R., Jr., Nobili, F., Nordberg, A., Snyder, H. M., Ten Kate, M., Varrone, A., Albanese, E., ... Winblad, B. (2017). Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. *The Lancet Neurology, 16*(8), 661–676. https://doi.org/10.1016/S1474-4422(17)30159-X
24. Johnson, K. A., Fox, N. C., Sperling, R. A., & Klunk, W. E. (2012). Brain imaging in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine, 2*(4), a006213. https://doi.org/10.1101/cshperspect.a006213
25. Blennow, K., & Zetterberg, H. (2018). Biomarkers for Alzheimer's disease: Current status and prospects for the future. *Journal of Internal Medicine, 284*(6), 643–663. https://doi.org/10.1111/joim.12816
26. Passeri, E., Elkhoury, K., Morsink, M., Broersen, K., Linder, M., Tamayol, A., Malaplate, C., Yen, F. T., & Arab-Tehrany, E. (2022). Alzheimer's disease: Treatment strategies and their limitations. *International Journal of Molecular Sciences, 23*(22), 13954. https://doi.org/10.3390/ijms232213954
27. Zhang, J., Kong, G., Yang, J., Pang, L., & Li, X. (2025). Pathological mechanisms and treatment progression of Alzheimer's disease. *European Journal of Medical Research, 30*(1), 625. https://doi.org/10.1186/s40001-025-02886-9
28. Hansen, R. A., Gartlehner, G., Webb, A. P., Morgan, L. C., Moore, C. G., & Jonas, D. E. (2008). Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: A systematic review and meta-analysis. *Clinical Interventions in Aging, 3*(2), 211–225.
29. Zou, D., Liu, R., Lv, Y., Guo, J., Zhang, C., & Xie, Y. (2023). Latest advances in dual inhibitors of acetylcholinesterase and monoamine oxidase B against Alzheimer's disease. *Journal of Enzyme Inhibition and Medicinal Chemistry, 38*(1), 2270781. https://doi.org/10.1080/14756366.2023.2270781
30. Zuin, M., Cherubini, A., Volpato, S., Ferrucci, L., & Zuliani, G. (2022). Acetylcholinesterase inhibitors slow cognitive decline and decrease overall mortality in older patients with dementia. *Scientific Reports, 12*(1), 12214. https://doi.org/10.1038/s41598-022-16476-w
31. Scheltens, P., Blennow, K., Breteler, M. M., De Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. *The Lancet, 388*(10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1
32. Fish, P. V., Steadman, D., Bayle, E. D., & Whiting, P. (2019). New approaches for the treatment of Alzheimer's disease. *Bioorganic & Medicinal Chemistry Letters, 29*, 125–133. https://doi.org/10.1016/j.bmcl.2018.11.034
33. Cummings, J. L., Tong, G., & Ballard, C. (2019). Treatment combinations for Alzheimer's disease: Current and future pharmacotherapy options. *Journal of Alzheimer's Disease, 67*(3), 779–794. https://doi.org/10.3233/JAD-180766
34. Cummings, J., Ritter, A., & Zhong, K. (2018). Clinical trials for disease-modifying therapies in Alzheimer's disease: A primer, lessons learned, and a blueprint for the future. *Journal of Alzheimer's Disease, 64*(s1), S3–S22. https://doi.org/10.3233/JAD-179901
35. Yu, A., & Lau, A. Y. (2018). Glutamate and glycine binding to the NMDA receptor. *Structure, 26*(7), 1035–1043.e2. https://doi.org/10.1016/j.str.2018.05.004
36. Parsons, C. G., Danysz, W., & Quack, G. (1999). Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist—A review of preclinical data. *Neuropharmacology, 38*(6), 735–767. https://doi.org/10.1016/S0028-3908(99)00019-2
37. Kassa, J., & Zdarova Karasova, J. (2023). Combination of acetylcholinesterase inhibitors and NMDA receptor antagonists increases survival rate in soman-poisoned mice. *Toxicology Mechanisms and Methods, 33*(7), 590–595. https://doi.org/10.1080/15376516.2023.2202730
38. Fox, N. C., Belder, C., Ballard, C., Kales, H. C., Mummery, C., Caramelli, P., Ciccarelli, O., Frederiksen, K. S., Gomez-Isla, T., Ismail, Z., Paquet, C., Petersen, R. C., Perneczky, R., Robinson, L., Sayin, O., & Frisoni, G. B. (2025). Treatment for Alzheimer's disease. *The Lancet, 406*(10510), 1408–1423. https://doi.org/10.1016/S0140-6736(25)01329-7
39. Imbimbo, B. P. (2001). Pharmacodynamic-tolerability relationships of cholinesterase inhibitors for Alzheimer's disease. *CNS Drugs, 15*(5), 375–390. https://doi.org/10.2165/00023210-200115050-00004
40. Winblad, B., Cummings, J., Andreasen, N., Grossberg, G., Onofrj, M., Sadowsky, C., Zechner, S., Nagel, J., & Lane, R. (2007). A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease—Rivastigmine patch versus capsule. *International Journal of Geriatric Psychiatry, 22*(5), 456–467. https://doi.org/10.1002/gps.1788

41. Masurkar, P. P., Chatterjee, S., Sherer, J. T., Chen, H., Johnson, M. L., & Aparasu, R. R. (2022). Risk of overactive bladder associated with cholinesterase inhibitors in dementia. *Journal of the American Geriatrics Society, 70*(3), 820–830. https://doi.org/10.1111/jgs.17579
42. Xu, H., Garcia-Ptacek, S., Jönsson, L., Wimo, A., Nordström, P., & Eriksdotter, M. (2021). Long-term effects of cholinesterase inhibitors on cognitive decline and mortality. *Neurology, 96*(17), e2220–e2230. https://doi.org/10.1212/WNL.0000000000011832
43. Truong, C., Recto, C., Lafont, C., Canoui-Poitrine, F., Belmin, J. B., & Lafuente-Lafuente, C. (2022). Effect of cholinesterase inhibitors on mortality in patients with dementia: A systematic review of randomized and nonrandomized trials. *Neurology, 99*(20), e2313–e2325. https://doi.org/10.1212/WNL.0000000000201161
44. Tan, E. C. K., Johnell, K., Bell, J. S., Garcia-Ptacek, S., Fastbom, J., Nordström, P., & Eriksdotter, M. (2020). Do acetylcholinesterase inhibitors prevent or delay psychotropic prescribing in people with dementia? Analyses of the Swedish Dementia Registry. *American Journal of Geriatric Psychiatry, 28*(1), 108–117. https://doi.org/10.1016/j.jagp.2019.06.008
45. Nørgaard, A., Jensen-Dahm, C., Wimberley, T., Svendsen, J. H., Ishtiak-Ahmed, K., Laursen, T. M., Waldemar, G., & Gasse, C. (2022). Effect of antipsychotics on mortality risk in patients with dementia with and without comorbidities. *Journal of the American Geriatrics Society, 70*(4), 1169–1179. https://doi.org/10.1111/jgs.17623
46. Schwertner, E., Secnik, J., Garcia-Ptacek, S., Johansson, B., Nagga, K., Eriksdotter, M., Winblad, B., & Religa, D. (2019). Antipsychotic treatment associated with increased mortality risk in patients with dementia: A registry-based observational cohort study. *Journal of the American Medical Directors Association, 20*(3), 323–329.e2. https://doi.org/10.1016/j.jamda.2018.12.019
47. Livingston, G., & Katona, C. (2004). The place of memantine in the treatment of Alzheimer's disease: A number needed to treat analysis. *International Journal of Geriatric Psychiatry, 19*(10), 919–925. https://doi.org/10.1002/gps.1166
48. Peters, K. R. (2013). Utility of an effect size analysis for communicating treatment effectiveness: A case study of cholinesterase inhibitors for Alzheimer's disease. *Journal of the American Geriatrics Society, 61*(7), 1170–1174. https://doi.org/10.1111/jgs.12308
49. Guo, J., Wang, Z., Liu, R., Huang, Y., Zhang, N., & Zhang, R. (2020). Memantine, donepezil, or combination therapy—What is the best therapy for Alzheimer's disease? A network meta-analysis. *Brain and Behavior, 10*(11), e01831. https://doi.org/10.1002/brb3.1831
50. Lopez, O. L., Becker, J. T., Wahed, A. S., Saxton, J., Sweet, R. A., Wolk, D. A., Klunk, W., & DeKosky, S. T. (2009). Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *Journal of Neurology, Neurosurgery & Psychiatry, 80*(6), 600–607. https://doi.org/10.1136/jnnp.2008.158964
51. Matsunaga, S., Kishi, T., & Iwata, N. (2015). Memantine monotherapy for Alzheimer's disease: A systematic review and meta-analysis. *PLoS ONE, 10*(4), e0123289. https://doi.org/10.1371/journal.pone.0123289
52. Doody, R. S., Tariot, P. N., Pfeiffer, E., Olin, J. T., & Graham, S. M. (2007). Meta-analysis of six-month memantine trials in Alzheimer's disease. *Alzheimer's & Dementia, 3*(1), 7–17. https://doi.org/10.1016/j.jalz.2006.10.004
53. Zenaro, E., Piacentino, G., & Constantin, G. (2017). The blood-brain barrier in Alzheimer's disease. *Neurobiology of Disease, 107*, 41–56. https://doi.org/10.1016/j.nbd.2016.07.007
54. Chakraborty, A., de Wit, N. M., van der Flier, W. M., & de Vries, H. E. (2017). The blood brain barrier in Alzheimer's disease. *Vascular Pharmacology, 89*, 12–18. https://doi.org/10.1016/j.vph.2016.11.008
55. Banks, W. A. (2012). Drug delivery to the brain in Alzheimer's disease: Consideration of the blood-brain barrier. *Advanced Drug Delivery Reviews, 64*(7), 629–639. https://doi.org/10.1016/j.addr.2011.12.005
56. Colin, J., Thomas, M. H., Gregory-Pauron, L., Pinçon, A., Lanhers, M. C., Corbier, C., Claudepierre, T., Yen, F. T., Oster, T., & Malaplate-Armand, C. (2017). Maintenance of membrane organization in the aging mouse brain as the determining factor for preventing receptor dysfunction and for improving response to anti-Alzheimer treatments. *Neurobiology of Aging, 54*, 84–93. https://doi.org/10.1016/j.neurobiolaging.2017.02.015
57. Poon, C. H., Wang, Y., Fung, M. L., Zhang, C., & Lim, L. W. (2020). Rodent models of amyloid-beta feature of Alzheimer's disease: Development and potential treatment implications. *Aging and Disease, 11*(5), 1235–1259. https://doi.org/10.14336/AD.2019.1026
58. Huang, L. K., Chao, S. P., & Hu, C. J. (2020). Clinical trials of new drugs for Alzheimer disease. *Journal of Biomedical Science, 27*(1), 18. https://doi.org/10.1186/s12929-019-0609-7
59. Solfrizzi, V., & Imbimbo, B. P. (2026). Comparing clinical effect sizes of Souvenaid™, lecanemab, and donanemab in early Alzheimer's disease. *Journal of Alzheimer's Disease, 109*(3), 1258–1263. https://doi.org/10.1177/13872877251406221
60. Wu, W., Ji, Y., Wang, Z., Wu, X., Li, J., Gu, F., Chen, Z., & Wang, Z. (2023). The FDA-approved anti-amyloid-β monoclonal antibodies for the treatment of Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *European Journal of Medical Research, 28*(1), 544. https://doi.org/10.1186/s40001-023-01512-w
61. Cummings, J. (2023). Anti-amyloid monoclonal antibodies are transformative treatments that redefine Alzheimer's disease therapeutics. *Drugs, 83*(7), 569–576. https://doi.org/10.1007/s40265-023-01858-9

62. Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., O'Gorman, J., Qian, F., Arastu, M., Li, M., Chollate, S., Brennan, M. S., Quintero-Monzon, O., Scannevin, R. H., Arnold, H. M., ... Sandrock, A. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature, 537*(7618), 50–56. https://doi.org/10.1038/nature19323
63. Chowdhury, S., & Chowdhury, N. S. (2023). Novel anti-amyloid-beta (Aβ) monoclonal antibody lecanemab for Alzheimer's disease: A systematic review. *International Journal of Immunopathology and Pharmacology, 37*, 03946320231209839. https://doi.org/10.1177/03946320231209839
64. Vukmir, R. B. (2024). Amyloid-related imaging abnormalities (ARIA): Diagnosis, management, and care in the setting of amyloid-modifying therapy. *Annals of Clinical and Translational Neurology, 11*(7), 1669–1680. https://doi.org/10.1002/acn3.52042
65. Singh, N., Das, B., Zhou, J., Hu, X., & Yan, R. (2022). Targeted BACE-1 inhibition in microglia enhances amyloid clearance and improved cognitive performance. *Science Advances, 8*(29), eabo3610. https://doi.org/10.1126/sciadv.abo3610
66. Moussa-Pacha, N. M., Abdin, S. M., Omar, H. A., Alniss, H., & Al-Tel, T. H. (2020). BACE1 inhibitors: Current status and future directions in treating Alzheimer's disease. *Medicinal Research Reviews, 40*(1), 339–384. https://doi.org/10.1002/med.21622
67. Briggs, R., Kennelly, S. P., & O'Neill, D. (2016). Drug treatments in Alzheimer's disease. *Clinical Medicine, 16*(3), 247–253. https://doi.org/10.7861/clinmedicine.16-3-247
68. Klimova, B., & Kuca, K. (2015). Alzheimer's disease: Potential preventive, non-invasive, intervention strategies in lowering the risk of cognitive decline—A review study. *Journal of Applied Biomedicine, 13*(4), 257–261. https://doi.org/10.1016/j.jab.2015.07.004
69. Angeloni, C., Businaro, R., & Vauzour, D. (2020). The role of diet in preventing and reducing cognitive decline. *Current Opinion in Psychiatry, 33*(4), 432–438. https://doi.org/10.1097/YCO.0000000000000605
70. Vinciguerra, F., Graziano, M., Hagnäs, M., Frittitta, L., & Tumminia, A. (2020). Influence of the Mediterranean and ketogenic diets on cognitive status and decline: A narrative review. *Nutrients, 12*(4), 1019. https://doi.org/10.3390/nu12041019
71. Santangelo, A., Corsello, A., Spolidoro, G. C. I., Trovato, C. M., Agostoni, C., Orsini, A., Milani, G. P., & Peroni, D. G. (2023). The influence of ketogenic diet on gut microbiota: Potential benefits, risks and indications. *Nutrients, 15*(17), 3680. https://doi.org/10.3390/nu15173680
72. Dighriri, I. M., Alsubaie, A. M., Hakami, F. M., Hamithi, D. M., Alshekh, M. M., Khobrani, F. A., Dalak, F. E., Hakami, A. A., Alsueaadi, E. H., Alsaawi, L. S., Alshammari, S. F., Alqahtani, A. S., Alawi, I. A., Aljuaid, A. A., & Tawhari, M. Q. (2022). Effects of omega-3 polyunsaturated fatty acids on brain functions: A systematic review. *Cureus, 14*(10), e30091. https://doi.org/10.7759/cureus.30091
73. Welty, F. K. (2023). Omega-3 fatty acids and cognitive function. *Current Opinion in Lipidology, 34*(1), 12–21. https://doi.org/10.1097/MOL.0000000000000862
74. Moore, K. M., Girens, R. E., Larson, S. K., Jones, M. R., Restivo, J. L., Holtzman, D. M., Cirrito, J. R., Yuede, C. M., Zimmerman, S. D., & Timson, B. F. (2016). A spectrum of exercise training reduces soluble Aβ in a dose-dependent manner in a mouse model of Alzheimer's disease. *Neurobiology of Disease, 85*, 218–224. https://doi.org/10.1016/j.nbd.2015.11.004
75. Meng, Q., & Su, C. H. (2024). The impact of physical exercise on oxidative and nitrosative stress: Balancing the benefits and risks. *Antioxidants, 13*(5), 573. https://doi.org/10.3390/antiox13050573
76. Martin, B., Mattson, M. P., & Maudsley, S. (2006). Caloric restriction and intermittent fasting: Two potential diets for successful brain aging. *Ageing Research Reviews, 5*(3), 332–353. https://doi.org/10.1016/j.arr.2006.04.002
77. Muscat, S. M., & Barrientos, R. M. (2020). Lifestyle modifications with anti-neuroinflammatory benefits in the aging population. *Experimental Gerontology, 142*, 111144. https://doi.org/10.1016/j.exger.2020.111144
78. Xu Lou, I., Ali, K., & Chen, Q. (2023). Effect of nutrition in Alzheimer's disease: A systematic review. *Frontiers in Neuroscience, 17*, 1147177. https://doi.org/10.3389/fnins.2023.1147177
79. Tucker, S., Möller, C., Tegerstedt, K., Lord, A., Laudon, H., Sjödahl, J., Söderberg, L., Spens, E., Sahlin, C., Waara, E. R., Satlin, A., Gellerfors, P., Osswald, G., & Lannfelt, L. (2015). The murine version of BAN2401 (mAb158) selectively reduces amyloid-β protofibrils in brain and cerebrospinal fluid of tg-ArcSwe mice. *Journal of Alzheimer's Disease, 43*(2), 575–588. https://doi.org/10.3233/JAD-140741
80. Tolar, M., Abushakra, S., Hey, J. A., Porsteinsson, A., & Sabbagh, M. (2020). Aducanumab, gantenerumab, BAN2401, and ALZ-801—The first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. *Alzheimer's Research & Therapy, 12*(1), 95. https://doi.org/10.1186/s13195-020-00663-w
81. Söderberg, L., Johannesson, M., Nygren, P., Laudon, H., Eriksson, F., Osswald, G., Möller, C., & Lannfelt, L. (2023). Lecanemab, aducanumab, and gantenerumab—Binding profiles to different forms of amyloid-beta might explain efficacy and side effects in clinical trials for Alzheimer's disease. *Neurotherapeutics, 20*(1), 195–206. https://doi.org/10.1007/s13311-022-01308-6
82. Lord, A., Gumucio, A., Englund, H., Sehlin, D., Sundquist, V. S., Söderberg, L., Möller, C., Gellerfors, P., Lannfelt, L., Pettersson, F. E., & Nilsson, L. N. (2009). An amyloid-beta protofibril-selective antibody prevents amyloid formation in a mouse model of Alzheimer's disease. *Neurobiology of Disease, 36*(3), 425–434. https://doi.org/10.1016/j.nbd.2009.08.007

83. Chowdhury, S. (2023). Monoclonal antibody treatments for Alzheimer's disease: Aducanumab and lecanemab. *Discoveries, 11*(3), e173. https://doi.org/10.15190/d.2023.12
84. Söllvander, S., Ekholm-Pettersson, F., Brundin, R. M., Westman, G., Kilander, L., Paulie, S., Lannfelt, L., & Sehlin, D. (2015). Increased number of plasma B cells producing autoantibodies against Aβ42 protofibrils in Alzheimer's disease. *Journal of Alzheimer's Disease, 48*(1), 63–72. https://doi.org/10.3233/JAD-150236
85. Nilsberth, C., Westlind-Danielsson, A., Eckman, C. B., Condron, M. M., Axelman, K., Forsell, C., Stenh, C., Luthman, J., Teplow, D. B., Younkin, S. G., Näslund, J., & Lannfelt, L. (2001). The "Arctic" APP mutation (E693G) causes Alzheimer's disease by enhanced Aβ protofibril formation. *Nature Neuroscience, 4*(9), 887–893. https://doi.org/10.1038/nn0901-887
86. Logovinsky, V., Satlin, A., Lai, R., Swanson, C., Kaplow, J., Osswald, G., Basun, H., & Lannfelt, L. (2016). Safety and tolerability of BAN2401—A clinical study in Alzheimer's disease with a protofibril selective Aβ antibody. *Alzheimer's Research & Therapy, 8*(1), 14. https://doi.org/10.1186/s13195-016-0181-2
87. Cummings, J., Apostolova, L., Rabinovici, G. D., Atri, A., Aisen, P., Greenberg, S., Hendrix, S., Selkoe, D., Weiner, M., Petersen, R. C., & Salloway, S. (2023). Lecanemab: Appropriate use recommendations. *Journal of Prevention of Alzheimer's Disease, 10*(3), 362–377. https://doi.org/10.14283/jpad.2023.30
88. Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008
89. McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005
90. van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2023). Lecanemab in early Alzheimer's disease. *The New England Journal of Medicine, 388*(1), 9–21. https://doi.org/10.1056/NEJMoa2212948
91. Cohen, S., van Dyck, C. H., Gee, M., Doherty, T., Kanekiyo, M., Dhadda, S., Li, D., Hersch, S., Irizarry, M., & Kramer, L. D. (2023). Lecanemab Clarity AD: Quality-of-life results from a randomized, double-blind phase 3 trial in early Alzheimer's disease. *Journal of Prevention of Alzheimer's Disease, 10*(4), 771–777. https://doi.org/10.14283/jpad.2023.123
92. Kovacik, A., Vandergriff, K., Jarrett, B., & Clevenger, C. (2025). An update of the treatment landscape for Alzheimer's disease: From symptomatic treatments to the emergence of amyloid-targeting therapies. *SAGE Open Aging, 11*, 30495334251376614. https://doi.org/10.1177/30495334251376614
93. Doessegger, L., & Banholzer, M. L. (2015). Clinical development methodology for infusion-related reactions with monoclonal antibodies. *Clinical & Translational Immunology, 4*(7), e39. https://doi.org/10.1038/cti.2015.14
94. Swanson, C. J., Zhang, Y., Dhadda, S., Wang, J., Kaplow, J., Lai, R. Y. K., Lannfelt, L., Bradley, H., Rabe, M., Koyama, A., Reyderman, L., Berry, D. A., Berry, S., Gordon, R., Kramer, L. D., & Cummings, J. L. (2021). A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimer's Research & Therapy, 13*(1), 80. https://doi.org/10.1186/s13195-021-00813-8
95. Mintun, M. A., Lo, A. C., Duggan Evans, C., Wessels, A. M., Ardayfio, P. A., Andersen, S. W., Shcherbinin, S., Sparks, J., Sims, J. R., Brys, M., Apostolova, L. G., Salloway, S. P., & Skovronsky, D. M. (2021). Donanemab in early Alzheimer's disease. *The New England Journal of Medicine, 384*(18), 1691–1704. https://doi.org/10.1056/NEJMoa2100708
96. Budd Haeberlein, S., O'Gorman, J., Chiao, P., Bussière, T., von Rosenstiel, P., Tian, Y., Zhu, Y., von Hehn, C., Gheuens, S., Skordos, L., Chen, T., & Sandrock, A. (2017). Clinical development of aducanumab, an anti-Aβ human monoclonal antibody being investigated for the treatment of early Alzheimer's disease. *Journal of Prevention of Alzheimer's Disease, 4*(4), 255–263. https://doi.org/10.14283/jpad.2017.39
97. McDade, E., Cummings, J. L., Dhadda, S., Swanson, C. J., Reyderman, L., Kanekiyo, M., Koyama, A., Irizarry, M., Kramer, L. D., & Bateman, R. J. (2022). Lecanemab in patients with early Alzheimer's disease: Detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. *Alzheimer's Research & Therapy, 14*(1), 191. https://doi.org/10.1186/s13195-022-01124-2
98. Honig, L. S., Sabbagh, M. N., van Dyck, C. H., Sperling, R. A., Hersch, S., Matta, A., Giorgi, L., Gee, M., Kanekiyo, M., Li, D., Purcell, D., Dhadda, S., Irizarry, M., & Kramer, L. (2024). Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. *Alzheimer's Research & Therapy, 16*(1), 105. https://doi.org/10.1186/s13195-024-01441-8

99. Chen, C., Katayama, S., Lee, J. H., Lee, J. Y., Nakagawa, M., Torii, K., Ogawa, T., Dash, A., Irizarry, M., Dhadda, S., Kanekiyo, M., Hersch, S., & Iwatsubo, T. (2025). Clarity AD: Asian regional analysis of a phase III trial of lecanemab in early Alzheimer's disease. *Journal of Prevention of Alzheimer's Disease, 12*(5), 100160. https://doi.org/10.1016/j.tjpad.2025.100160
100. Rafii, M. S., Sperling, R. A., Donohue, M. C., Zhou, J., Roberts, C., Irizarry, M. C., Dhadda, S., Sethuraman, G., Kramer, L. D., Swanson, C. J., Li, D., Krause, S., Rissman, R. A., Walter, S., Raman, R., Johnson, K. A., & Aisen, P. S. (2023). The AHEAD 3-45 study: Design of a prevention trial for Alzheimer's disease. *Alzheimer's & Dementia, 19*(4), 1227–1233. https://doi.org/10.1002/alz.12748
101. Eisai Inc. (2026). *AHEAD 3-45 study: A study to evaluate efficacy and safety of treatment with lecanemab in participants with preclinical Alzheimer's disease and elevated amyloid and also in participants with early preclinical Alzheimer's disease and intermediate amyloid* (NCT04468659). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04468659
102. McShane, R., Westby, M. J., Roberts, E., Minakaran, N., Schneider, L., Farrimond, L. E., Maayan, N., Ware, J., & Debarros, J. (2019). Memantine for dementia. *Cochrane Database of Systematic Reviews, 2019*(3), CD003154. https://doi.org/10.1002/14651858.CD003154.pub6
103. Vaci, N., Koychev, I., Kim, C. H., Kormilitzin, A., Liu, Q., Lucas, C., Dehghan, A., Nenadic, G., & Nevado-Holgado, A. (2021). Real-world effectiveness, its predictors and onset of action of cholinesterase inhibitors and memantine in dementia: Retrospective health record study. *British Journal of Psychiatry, 218*(5), 261–267. https://doi.org/10.1192/bjp.2020.136
104. Andrews, D., Ducharme, S., Chertkow, H., Sormani, M. P., Collins, D. L., & Alzheimer's Disease Neuroimaging Initiative. (2025). The higher benefit of lecanemab in males compared to females in CLARITY AD is probably due to a real sex effect. *Alzheimer's & Dementia, 21*(1), e14467. https://doi.org/10.1002/alz.14467
105. Arvanitakis, Z., Shah, R. C., & Bennett, D. A. (2019). Diagnosis and management of dementia: Review. *JAMA, 322*(16), 1589–1599. https://doi.org/10.1001/jama.2019.4782
106. O'Donnell, A. J., Zhao, X., Parr, A., Aspinall, S., & Anderson, T. S. (2025). Early outcomes of lecanemab for Alzheimer's disease in the Veterans Health Administration. *Journal of Clinical Medicine, 14*(23), 8277. https://doi.org/10.3390/jcm14238277
107. Birks, J. S., & Harvey, R. J. (2018). Donepezil for dementia due to Alzheimer's disease. *Cochrane Database of Systematic Reviews, 2018*(6), CD001190. https://doi.org/10.1002/14651858.CD001190.pub3
108. Lanctôt, K. L., Herrmann, N., Yau, K. K., Khan, L. R., Liu, B. A., LouLou, M. M., & Einarson, T. R. (2003). Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: A meta-analysis. *CMAJ, 169*(6), 557–564.
109. Wu, C. K., & Fuh, J. L. (2025). A 2025 update on treatment strategies for the Alzheimer's disease spectrum. *Journal of the Chinese Medical Association, 88*(7), 495–502. https://doi.org/10.1097/JCMA.0000000000001252
110. Qi, L., Zheng, F., Tu, M., Abdullah, R., Zhao, Y., Su, X., Zhou, D., & Peng, G. (2026). Safety profiles of lecanemab: A systematic review and meta-analysis of randomized controlled trials and real-world evidence. *Journal of Prevention of Alzheimer's Disease*, 100473. https://doi.org/10.1016/j.tjpad.2025.100473
111. Kang, W., Gao, C., Li, X., Wang, X., Zhong, H., Wei, Q., Tang, Y., Huang, P., Shen, R., Chen, L., Zhang, J., Fang, R., Wei, W., Zhang, F., Zhou, G., Yuan, W., Chen, X., Yang, Z., Wu, Y., ... Liu, J. (2025). Safety and effectiveness of lecanemab in Chinese patients with early Alzheimer's disease: Evidence from a multidimensional real-world study. *Chinese Medical Journal, 138*(22), 2907–2916. https://doi.org/10.1097/CM9.0000000000003888
112. Rogers, S. L., Farlow, M. R., Doody, R. S., Mohs, R., & Friedhoff, L. T. (1998). A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology, 50*(1), 136–145. https://doi.org/10.1212/WNL.50.1.136
113. Abdelazim, K., Allam, A. A., Afifi, B., Abdulazeem, H., & Elbehiry, A. I. (2024). The efficacy and safety of lecanemab 10 mg/kg biweekly compared to a placebo in patients with Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *Neurological Sciences, 45*(8), 3583–3597. https://doi.org/10.1007/s10072-024-07477-w
114. Fox, N. C., Belder, C., Ballard, C., Kales, H. C., Mummery, C., Caramelli, P., Ciccarelli, O., Frederiksen, K. S., Gomez-Isla, T., Ismail, Z., Paquet, C., Petersen, R. C., Perneczky, R., Robinson, L., Sayin, O., & Frisoni, G. B. (2025). Treatment for Alzheimer's disease. *The Lancet, 406*(10510), 1408–1423. https://doi.org/10.1016/S0140-6736(25)01329-7
115. Sims, J. R., Zimmer, J. A., Evans, C. D., Lu, M., Ardayfio, P., Sparks, J., Wessels, A. M., Shcherbinin, S., Wang, H., Monkul Nery, E. S., Collins, E. C., Solomon, P., Salloway, S., Apostolova, L. G., Hansson, O., Ritchie, C., Brooks, D. A., Mintun, M., Skovronsky, D. M., & TRAILBLAZER-ALZ 2 Investigators. (2023). Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA, 330*(6), 512–527. https://doi.org/10.1001/jama.2023.13239
116. Liu, K. Y., Walsh, S., Brayne, C., Merrick, R., Richard, E., & Howard, R. (2023). Evaluation of clinical benefits of treatments for Alzheimer's disease. *The Lancet Healthy Longevity, 4*(11), e645–e651. https://doi.org/10.1016/S2666-7568(23)00193-9

117. Petersen, R. C., Aisen, P. S., Andrews, J. S., Atri, A., Matthews, B. R., Rentz, D. M., Siemers, E. R., Weber, C. J., & Carrillo, M. C. (2023). Expectations and clinical meaningfulness of randomized controlled trials. *Alzheimer's & Dementia, 19*(6), 2730–2736. https://doi.org/10.1002/alz.12959
118. Goldberg, T. E., Lee, S., Devanand, D. P., & Schneider, L. S. (2024). Comparison of relative change with effect size metrics in Alzheimer's disease clinical trials. *Journal of Neurology, Neurosurgery & Psychiatry, 95*(1), 2–7. https://doi.org/10.1136/jnnp-2023-331941
119. U.S. Food and Drug Administration. (n.d.). *Prescribing information for Leqembi (lecanemab-irmb) injection, for intravenous use* (Reference ID 5203190). Retrieved October 21, 2024.
120. Wang, H., Serap Monkul Nery, E., Ardayfio, P., Khanna, R., Otero Svaldi, D., Gueorguieva, I., Shcherbinin, S., Andersen, S. W., Hauck, P. M., Engle, S. E., Brooks, D. A., Collins, E. C., Fox, N. C., Greenberg, S. M., Salloway, S., Mintun, M. A., & Sims, J. R. (2025). Modified titration of donanemab reduces ARIA risk and maintains amyloid reduction. *Alzheimer's & Dementia, 21*(4), e70062. https://doi.org/10.1002/alz.70062
121. Zimmer, J. A., Ardayfio, P., Wang, H., Khanna, R., Evans, C. D., Lu, M., Sparks, J., Andersen, S., Lauzon, S., Nery, E. S. M., Battioui, C., Engle, S. E., Biffi, A., Svaldi, D., Salloway, S., Greenberg, S. M., Sperling, R. A., Mintun, M., Brooks, D. A., & Sims, J. R. (2025). Amyloid-related imaging abnormalities with donanemab in early symptomatic Alzheimer disease: Secondary analysis of the TRAILBLAZER-ALZ and ALZ 2 randomized clinical trials. *JAMA Neurology, 82*(5), 461–469. https://doi.org/10.1001/jamaneurol.2025.0065
122. Fox, N. C., Black, R. S., Gilman, S., Rossor, M. N., Griffith, S. G., Jenkins, L., Koller, M., & AN1792(QS-21)-201 Study. (2005). Effects of Aβ immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. *Neurology, 64*(9), 1563–1572. https://doi.org/10.1212/01.WNL.0000159743.08996.99
123. Belder, C. R. S., Boche, D., Nicoll, J. A. R., Jaunmuktane, Z., Zetterberg, H., Schott, J. M., Barkhof, F., & Fox, N. C. (2024). Brain volume change following anti-amyloid β immunotherapy for Alzheimer's disease: Amyloid-removal-related pseudo-atrophy. *The Lancet Neurology, 23*(10), 1025–1034. https://doi.org/10.1016/S1474-4422(24)00335-1
124. Alves, F., Kalinowski, P., & Ayton, S. (2023). Accelerated brain volume loss caused by anti-β-amyloid drugs: A systematic review and meta-analysis. *Neurology, 100*(20), e2114–e2124. https://doi.org/10.1212/WNL.0000000000207156
125. Hardy, J. (2025). Alzheimer's disease: Treatment challenges for the future. *Journal of Neurochemistry, 169*(8), e70176. https://doi.org/10.1111/jnc.70176
126. Lannfelt, L., Söderberg, L., Laudon, H., Sahlin, C., Johannesson, M., Nygren, P., & Möller, C. (2019). P4-704: BAN2401 shows stronger binding to soluble aggregated amyloid-beta species than aducanumab. *Alzheimer's & Dementia, 15*.
127. Vaz, M., Silva, V., Monteiro, C., & Silvestre, S. (2022). Role of aducanumab in the treatment of Alzheimer's disease: Challenges and opportunities. *Clinical Interventions in Aging, 17*, 797–810. https://doi.org/10.2147/CIA.S325026
128. Esparza, T. J., Zhao, H., Cirrito, J. R., Cairns, N. J., Bateman, R. J., Holtzman, D. M., & Brody, D. L. (2013). Amyloid-β oligomerization in Alzheimer dementia versus high-pathology controls. *Annals of Neurology, 73*(1), 104–119. https://doi.org/10.1002/ana.23748
129. Kocis, P., Tolar, M., Yu, J., Sinko, W., Ray, S., Blennow, K., Fillit, H., & Hey, J. A. (2017). Elucidating the Aβ42 anti-aggregation mechanism of action of tramiprosate in Alzheimer's disease: Integrating molecular analytical methods, pharmacokinetic and clinical data. *CNS Drugs, 31*(6), 495–509. https://doi.org/10.1007/s40263-017-0434-z
130. Erwin, M. (2023). A dab of MAB: Lecanemab, aducanumab vs standard of care treatment for Alzheimer disease. *Pharmacy Times*.
131. Biogen. (2021). *221AD302 phase 3 study of aducanumab (BIIB037) in early Alzheimer's disease (EMERGE)* (NCT02484547). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02484547
132. Biogen. (2021). *221AD301 phase 3 study of aducanumab (BIIB037) in early Alzheimer's disease (ENGAGE)* (NCT02477800). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02477800
133. Budd Haeberlein, S., Aisen, P. S., Barkhof, F., Chalkias, S., Chen, T., Cohen, S., Dent, G., Hansson, O., Harrison, K., von Hehn, C., Iwatsubo, T., Mallinckrodt, C., Mummery, C. J., Muralidharan, K. K., Nestorov, I., Nisenbaum, L., Rajagovindan, R., Skordos, L., Tian, Y., ... Sandrock, A. (2022). Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *Journal of Prevention of Alzheimer's Disease, 9*(2), 197–210. https://doi.org/10.14283/jpad.2022.30
134. Eisai Inc. (2025). *A study to confirm safety and efficacy of lecanemab in participants with early Alzheimer's disease (Clarity AD)* (NCT03887455). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03887455
135. Villain, N. (2022). Therapeutic news in Alzheimer's disease: Soon a disease-modifying therapy? *Revue Neurologique, 178*(5), 437–440. https://doi.org/10.1016/j.neurol.2022.02.456
136. Winslow, B. T., Onysko, M. K., Stob, C. M., & Hazlewood, K. A. (2011). Treatment of Alzheimer disease. *American Family Physician, 83*(12), 1403–1412. https://www.aafp.org/pubs/afp/issues/2011/0615/p1403.html
137. Hogervorst, E., Yaffe, K., Richards, M., & Huppert, F. A. (2009). Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database of Systematic Reviews, 2009*(1), CD003799.

138. Rigaud, A. S., André, G., Vellas, B., Touchon, J., Pere, J. J., & French Study Group. (2003). No additional benefit of HRT on response to rivastigmine in menopausal women with AD. *Neurology, 60*(1), 148–149.
139. Isaac, M. G., Quinn, R., & Tabet, N. (2008). Vitamin E for Alzheimer's disease and mild cognitive impairment. *Cochrane Database of Systematic Reviews, 2008*(3), CD002854.
140. Feldman, H. H., Doody, R. S., Kivipelto, M., et al., & LEADe Investigators. (2010). Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology, 74*(12), 956–964.
141. Sato, T., Hanyu, H., Hirao, K., Kanetaka, H., Sakurai, H., & Iwamoto, T. (2009). Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. *Neurobiology of Aging*. http://www.sciencedirect.com/science/article/pii/S019745800900339X
142. Tan, R. S., & Pu, S. J. (2003). A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *The Aging Male, 6*(1), 13–17.
143. Cherrier, M. M., Matsumoto, A. M., Amory, J. K., et al. (2005). Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology, 64*(12), 2063–2068.
144. Lu, P. H., Masterman, D. A., Mulnard, R., Cotman, C., Miller, B., Yaffe, K., Reback, E., Porter, V., Swerdloff, R., & Cummings, J. L. (2006). Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Archives of Neurology, 63*(2), 177–185. https://doi.org/10.1001/archneur.63.2.nct50002
145. Basaria, S., Coviello, A. D., Travison, T. G., et al. (2010). Adverse events associated with testosterone administration. *The New England Journal of Medicine, 363*(2), 109–122.
146. Birks, J., & Grimley Evans, J. (2009). Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database of Systematic Reviews, 2009*(1), CD003120.
147. Akhondzadeh, S., & Abbasi, S. H. (2006). Herbal medicine in the treatment of Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias, 21*(2), 113–118. https://doi.org/10.1177/153331750602100211
148. Perry, E. K., Pickering, A. T., Wang, W. W., et al. (1998). Medicinal plants and Alzheimer's disease: Integrating ethnobotanical and contemporary scientific evidence. *Journal of Alternative and Complementary Medicine, 4*, 419–428.
149. Perry, E. K., Pickering, A. T., Wang, W. W., et al. (1999). Medicinal plants and Alzheimer's disease: From ethnobotany to phytotherapy. *Journal of Pharmacy and Pharmacology, 51*, 527–534.
150. Kennedy, D. O., Scholey, A. B., Tildesley, N. T. J., et al. (2002). Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). *Pharmacology Biochemistry and Behavior, 72*, 953–964.
151. Akhondzadeh, S., Noroozian, M., Mohammadi, M., et al. (2003). *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double-blind, randomised, placebo-controlled trial. *Journal of Neurology, Neurosurgery & Psychiatry, 74*, 863–866.
152. Akhondzadeh, S., Noroozian, M., Mohammadi, M., et al. (2003). *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double-blind, randomized and placebo-controlled trial. *Journal of Clinical Pharmacy and Therapeutics, 28*, 53–59.
153. Wake, G., Court, J., Pickering, A., et al. (2000). CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. *Journal of Ethnopharmacology, 69*, 105–114.
154. Folch, J., Petrov, D., Ettcheto, M., Abad, S., Sánchez-López, E., García, M. L., Olloquequi, J., Beas-Zarate, C., Auladell, C., & Camins, A. (2016). Current research therapeutic strategies for Alzheimer's disease treatment. *Neural Plasticity, 2016*, 8501693. https://doi.org/10.1155/2016/8501693
155. Gauthier, S., Aisen, P. S., Ferris, S. H., Saumier, D., Duong, A., Haine, D., Garceau, D., Suhy, J., Oh, J., Lau, W., & Sampalis, J. (2009). Effect of tramiprosate in patients with mild-to-moderate Alzheimer's disease: Exploratory analyses of the MRI sub-group of the Alphase study. *Journal of Nutrition, Health & Aging, 13*(6), 550–557. https://doi.org/10.1007/s12603-009-0106-x
156. Aisen, P. S., Gauthier, S., Ferris, S. H., Saumier, D., Haine, D., Garceau, D., Duong, A., Suhy, J., Oh, J., Lau, W. C., & Sampalis, J. (2011). Tramiprosate in mild-to-moderate Alzheimer's disease—A randomized, double-blind, placebo-controlled, multi-centre study (the Alphase Study). *Archives of Medical Science, 7*(1), 102–111. https://doi.org/10.5114/aoms.2011.20612
157. Gupta-Bansal, R., Frederickson, R. C., & Brunden, K. R. (1995). Proteoglycan-mediated inhibition of A beta proteolysis: A potential cause of senile plaque accumulation. *Journal of Biological Chemistry, 270*(31), 18666–18671. https://doi.org/10.1074/jbc.270.31.18666
158. Bilikiewicz, A., & Gaus, W. (2004). Colostrinin (a naturally occurring, proline-rich, polypeptide mixture) in the treatment of Alzheimer's disease. *Journal of Alzheimer's Disease, 6*(1), 17–26. https://doi.org/10.3233/JAD-2004-6103
159. Salloway, S., Sperling, R., Keren, R., Porsteinsson, A. P., van Dyck, C. H., Tariot, P. N., Gilman, S., Arnold, D., Abushakra, S., Hernandez, C., Crans, G., Liang, E., Quinn, G., Bairu, M., Pastrak, A., Cedarbaum, J. M., & ELND005-AD201 Investigators. (2011). A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease. *Neurology, 77*(13), 1253–1262. https://doi.org/10.1212/WNL.0b013e3182309fa5

160. Deane, R. J. (2012). Is RAGE still a therapeutic target for Alzheimer's disease? *Future Medicinal Chemistry, 4*(7), 915–925. https://doi.org/10.4155/fmc.12.51
161. Galasko, D., Bell, J., Mancuso, J. Y., Kupiec, J. W., Sabbagh, M. N., van Dyck, C., Thomas, R. G., Aisen, P. S., & Alzheimer's Disease Cooperative Study. (2014). Clinical trial of an inhibitor of RAGE-Aβ interactions in Alzheimer disease. *Neurology, 82*(17), 1536–1542. https://doi.org/10.1212/WNL.0000000000000364
162. Deane, R., Sagare, A., & Zlokovic, B. V. (2008). The role of the cell surface LRP and soluble LRP in blood-brain barrier Aβ clearance in Alzheimer's disease. *Current Pharmaceutical Design, 14*(16), 1601–1605. https://doi.org/10.2174/138161208784705487
163. vTv Therapeutics. (2015). *A safety study of TTP4000 in subjects with Alzheimer's disease* (NCT01548430). ClinicalTrials.gov.
164. Gilman, S., Koller, M., Black, R. S., Jenkins, L., Griffith, S. G., Fox, N. C., Eisner, L., Kirby, L., Rovira, M. B., Forette, F., Orgogozo, J. M., & AN1792(QS-21)-201 Study Team. (2005). Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial. *Neurology, 64*(9), 1553–1562. https://doi.org/10.1212/01.WNL.0000159740.16984.3C
165. Wiessner, C., Wiederhold, K. H., Tissot, A. C., Frey, P., Danner, S., Jacobson, L. H., Jennings, G. T., Lüönd, R., Ortmann, R., Reichwald, J., Zurini, M., Mir, A., Bachmann, M. F., & Staufenbiel, M. (2011). The second-generation active Aβ immunotherapy CAD106 reduces amyloid accumulation in APP transgenic mice while minimizing potential side effects. *Journal of Neuroscience, 31*(25), 9323–9331. https://doi.org/10.1523/JNEUROSCI.0293-11.2011
166. Janssen Alzheimer Immunotherapy Research & Development, LLC. (2015). *Amyloid imaging and safety study of ACC-001 in subjects with mild to moderate Alzheimer's disease (ACCTION)* (NCT01284387). ClinicalTrials.gov.
167. Pfizer. (2016). *Study evaluating safety, tolerability, and immunogenicity of ACC-001 in subjects with mild to moderate Alzheimer's disease* (NCT00479557). ClinicalTrials.gov.
168. ClinicalTrials.gov. (2016). *Amyloid imaging and safety study of ACC-001 in subjects with early Alzheimer's disease* (NCT01227564).
169. Liu, B., Frost, J. L., Sun, J., Fu, H., Grimes, S., Blackburn, P., & Lemere, C. A. (2013). MER5101, a novel Aβ1-15:DT conjugate vaccine, generates a robust anti-Aβ antibody response and attenuates Aβ pathology and cognitive deficits in APPswe/PS1ΔE9 transgenic mice. *Journal of Neuroscience, 33*(16), 7027–7037. https://doi.org/10.1523/JNEUROSCI.5924-12.2013
170. Panza, F., Solfrizzi, V., Imbimbo, B. P., & Logroscino, G. (2014). Amyloid-directed monoclonal antibodies for the treatment of Alzheimer's disease: The point of no return? *Expert Opinion on Biological Therapy, 14*(10), 1465–1476. https://doi.org/10.1517/14712598.2014.935332
171. Panza, F., Solfrizzi, V., Imbimbo, B. P., Tortelli, R., Santamato, A., & Logroscino, G. (2014). Amyloid-based immunotherapy for Alzheimer's disease in the time of prevention trials: The way forward. *Expert Review of Clinical Immunology, 10*(3), 405–419. https://doi.org/10.1586/1744666X.2014.883921
172. Behl, T., Kaur, D., Sehgal, A., Singla, R. K., Makeen, H. A., Albratty, M., Alhazmi, H. A., Meraya, A. M., & Bungau, S. (2022). Therapeutic insights elaborating the potential of retinoids in Alzheimer's disease. *Frontiers in Pharmacology, 13*, 976799. https://doi.org/10.3389/fphar.2022.976799
173. Huang, X., Zhang, H., Zhen, J., Dong, S., Guo, Y., Van Halm-Lutterodt, N., & Yuan, L. (2018). Diminished circulating retinol and elevated α-TOH/retinol ratio predict an increased risk of cognitive decline in aging Chinese adults, especially in subjects with ApoE2 or ApoE4 genotype. *Aging, 10*(12), 4066–4083. https://doi.org/10.18632/aging.101694
174. Touyarot, K., Bonhomme, D., Roux, P., Alfos, S., Lafenêtre, P., Richard, E., Higueret, P., & Pallet, V. (2013). A mid-life vitamin A supplementation prevents age-related spatial memory deficits and hippocampal neurogenesis alterations through CRABP-I. *PLoS ONE, 8*(8), e72101. https://doi.org/10.1371/journal.pone.0072101
175. Sahin, M., Karauzum, S. B., Perry, G., Smith, M. A., & Aliciguzel, Y. (2005). Retinoic acid isomers protect hippocampal neurons from amyloid-beta induced neurodegeneration. *Neurotoxicity Research, 7*(3), 243–250. https://doi.org/10.1007/BF03036453
176. Husson, M., Enderlin, V., Delacourte, A., Ghenimi, N., Alfos, S., Pallet, V., & Higueret, P. (2006). Retinoic acid normalizes nuclear receptor mediated hypo-expression of proteins involved in beta-amyloid deposits in the cerebral cortex of vitamin A deprived rats. *Neurobiology of Disease, 23*(1), 1–10. https://doi.org/10.1016/j.nbd.2006.01.008
177. Goncalves, M. B., Clarke, E., Hobbs, C., Malmqvist, T., Deacon, R., Jack, J., & Corcoran, J. P. (2013). Amyloid β inhibits retinoic acid synthesis exacerbating Alzheimer disease pathology which can be attenuated by a retinoic acid receptor α agonist. *European Journal of Neuroscience, 37*(7), 1182–1192. https://doi.org/10.1111/ejn.12142
178. Tippmann, F., Hundt, J., Schneider, A., Endres, K., & Fahrenholz, F. (2009). Up-regulation of the alpha-secretase ADAM10 by retinoic acid receptors and acitretin. *FASEB Journal, 23*(6), 1643–1654. https://doi.org/10.1096/fj.08-121392
179. Endres, K., Fahrenholz, F., Lotz, J., Hiemke, C., Teipel, S., Lieb, K., Tüscher, O., & Fellgiebel, A. (2014). Increased CSF APPs-α levels in patients with Alzheimer disease treated with acitretin. *Neurology, 83*(21), 1930–1935. https://doi.org/10.1212/WNL.0000000000001017

180. Holthoewer, D., Endres, K., Schuck, F., Hiemke, C., Schmitt, U., & Fahrenholz, F. (2012). Acitretin, an enhancer of alpha-secretase expression, crosses the blood-brain barrier and is not eliminated by P-glycoprotein. *Neurodegenerative Diseases, 10*(1–4), 224–228. https://doi.org/10.1159/000334300
181. Kobayashi, M., Matsuoka, I., & Kurihara, K. (1994). Cholinergic differentiation of cultured sympathetic neurons induced by retinoic acid: Induction of choline acetyltransferase-mRNA and suppression of tyrosine hydroxylase-mRNA levels. *FEBS Letters, 337*(3), 259–264. https://doi.org/10.1016/0014-5793(94)80204-1
182. Goodman, A. B. (2006). Retinoid receptors, transporters, and metabolizers as therapeutic targets in late onset Alzheimer disease. *Journal of Cellular Physiology, 209*(3), 598–603. https://doi.org/10.1002/jcp.20784
183. Treiber, C., et al. (2004). Clioquinol mediates copper uptake and counteracts copper efflux activities of the amyloid precursor protein of Alzheimer's disease. *Journal of Biological Chemistry, 279*(50), 51958–51964.
184. Bayer, T. A., Schäfer, S., Simons, A., Kemmling, A., Kamer, T., Tepest, R., Eckert, A., Schüssel, K., Eikenberg, O., Sturchler-Pierrat, C., Abramowski, D., Staufenbiel, M., & Multhaup, G. (2003). Dietary Cu stabilizes brain superoxide dismutase 1 activity and reduces amyloid Aβ production in APP23 transgenic mice. *Proceedings of the National Academy of Sciences of the United States of America, 100*(24), 14187–14192. https://doi.org/10.1073/pnas.2332818100
185. Maynard, C. J., Cappai, R., Volitakis, I., Cherny, R. A., White, A. R., Beyreuther, K., Masters, C. L., Bush, A. I., & Li, Q. X. (2002). Overexpression of Alzheimer's disease amyloid-beta opposes the age-dependent elevations of brain copper and iron. *Journal of Biological Chemistry, 277*(47), 44670–44676. https://doi.org/10.1074/jbc.M204379200
186. Phinney, A. L., Drisaldi, B., Schmidt, S. D., Lugowski, S., Coronado, V., Liang, Y., Horne, P., Yang, J., Sekoulidis, J., Coomaraswamy, J., Chishti, M. A., Cox, D. W., Mathews, P. M., Nixon, R. A., Carlson, G. A., St George-Hyslop, P., & Westaway, D. (2003). In vivo reduction of amyloid-beta by a mutant copper transporter. *Proceedings of the National Academy of Sciences of the United States of America, 100*(24), 14193–14198. https://doi.org/10.1073/pnas.2332851100
187. White, A. R., Reyes, R., Mercer, J. F., Camakaris, J., Zheng, H., Bush, A. I., Multhaup, G., Beyreuther, K., Masters, C. L., & Cappai, R. (1999). Copper levels are increased in the cerebral cortex and liver of APP and APLP2 knockout mice. *Brain Research, 842*(2), 439–444. https://doi.org/10.1016/S0006-8993(99)01861-2
188. Squitti, R., Lupoi, D., Pasqualetti, P., Dal Forno, G., Vernieri, F., Chiovenda, P., Rossi, L., Cortesi, M., Cassetta, E., & Rossini, P. M. (2002). Elevation of serum copper levels in Alzheimer's disease. *Neurology, 59*(8), 1153–1161. https://doi.org/10.1212/WNL.59.8.1153
189. Samudralwar, D. L., Diprete, C. C., Ni, B. F., Ehmann, W. D., & Markesbery, W. R. (1995). Elemental imbalances in the olfactory pathway in Alzheimer's disease. *Journal of the Neurological Sciences, 130*(2), 139–145. https://doi.org/10.1016/0022-510X(95)00018-W
190. Thompson, C. M., Markesbery, W. R., Ehmann, W. D., Mao, Y. X., & Vance, D. E. (1988). Regional brain trace-element studies in Alzheimer's disease. *Neurotoxicology, 9*(1), 1–7.
191. Borchardt, T., Camakaris, J., Cappai, R., Masters, C. L., Beyreuther, K., & Multhaup, G. (1999). Copper inhibits beta-amyloid production and stimulates the non-amyloidogenic pathway of amyloid-precursor-protein secretion. *Biochemical Journal, 344*(Pt 2), 461–467.
192. Cherny, R. A., Atwood, C. S., Xilinas, M. E., Gray, D. N., Jones, W. D., McLean, C. A., Barnham, K. J., Volitakis, I., Fraser, F. W., Kim, Y., Huang, X., Goldstein, L. E., Moir, R. D., Lim, J. T., Beyreuther, K., Zheng, H., Tanzi, R. E., Masters, C. L., & Bush, A. I. (2001). Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron, 30*(3), 665–676. https://doi.org/10.1016/S0896-6273(01)00317-8
193. Ritchie, C. W., Bush, A. I., Mackinnon, A., Macfarlane, S., Mastwyk, M., MacGregor, L., Kiers, L., Cherny, R., Li, Q. X., Tammer, A., Carrington, D., Mavros, C., Volitakis, I., Xilinas, M., Ames, D., Davis, S., Beyreuther, K., Tanzi, R. E., & Masters, C. L. (2003). Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Aβ amyloid deposition and toxicity in Alzheimer disease: A pilot phase 2 clinical trial. *Archives of Neurology, 60*(12), 1685–1691. https://doi.org/10.1001/archneur.60.12.1685
194. Salloway, S., Sperling, R., Fox, N. C., Blennow, K., Klunk, W., Raskind, M., Sabbagh, M., Honig, L. S., Porsteinsson, A. P., Ferris, S., Reichert, M., Ketter, N., Nejadnik, B., Guenzler, V., Miloslavsky, M., Wang, D., Lu, Y., Lull, J., Tudor, I. C., ... Brashear, H. R. (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *The New England Journal of Medicine, 370*(4), 322–333. https://doi.org/10.1056/NEJMoa1304839
195. Doody, R. S., Thomas, R. G., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S., Kieburtz, K., Raman, R., Sun, X., Aisen, P. S., Siemers, E., Liu-Seifert, H., Mohs, R., Alzheimer's Disease Cooperative Study Steering Committee, & Solanezumab Study Group. (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *The New England Journal of Medicine, 370*(4), 311–321. https://doi.org/10.1056/NEJMoa1312889
196. Tayeb, H. O., Murray, E. D., Price, B. H., & Tarazi, F. I. (2013). Bapineuzumab and solanezumab for Alzheimer's disease: Is the "amyloid cascade hypothesis" still alive? *Expert Opinion on Biological Therapy, 13*(7), 1075–1084. https://doi.org/10.1517/14712598.2013.789856

197. Eli Lilly and Company. (2019). *Continued safety monitoring of solanezumab (LY2062430) in Alzheimer's disease (EXPEDITION EXT)* (NCT01127633). ClinicalTrials.gov.
198. Eli Lilly and Company. (2019). *Progress of mild Alzheimer's disease in participants on solanezumab versus placebo (EXPEDITION 3)* (NCT01900665). ClinicalTrials.gov.
199. Eli Lilly and Company. (2023). *Clinical trial of solanezumab for older individuals who may be at risk for memory loss (A4)* (NCT02008357). ClinicalTrials.gov.
200. Washington University School of Medicine. (2026). *Dominantly Inherited Alzheimer Network trial: An opportunity to prevent dementia: Master protocol DIAN-TU-001 (DIAN-TU)* (NCT01760005). ClinicalTrials.gov.
201. Novakovic, D., Feligioni, M., Scaccianoce, S., Caruso, A., Piccinin, S., Schepisi, C., Errico, F., Mercuri, N. B., Nicoletti, F., & Nisticò, R. (2013). Profile of gantenerumab and its potential in the treatment of Alzheimer's disease. *Drug Design, Development and Therapy, 7*, 1359–1364. https://doi.org/10.2147/DDDT.S53401
202. Bohrmann, B., Baumann, K., Benz, J., Gerber, F., Huber, W., Knoflach, F., Messer, J., Oroszlan, K., Rauchenberger, R., Richter, W. F., Rothe, C., Urban, M., Bardroff, M., Winter, M., Nordstedt, C., & Loetscher, H. (2012). Gantenerumab: A novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β. *Journal of Alzheimer's Disease, 28*(1), 49–69. https://doi.org/10.3233/JAD-2011-110977
203. Jacobsen, H., Ozmen, L., Caruso, A., Narquizian, R., Hilpert, H., Jacobsen, B., Terwel, D., Tanghe, A., & Bohrmann, B. (2014). Combined treatment with a BACE inhibitor and anti-Aβ antibody gantenerumab enhances amyloid reduction in APPLondon mice. *Journal of Neuroscience, 34*(35), 11621–11630. https://doi.org/10.1523/JNEUROSCI.1405-14.2014
204. Hoffmann-La Roche. (2023). *A study of gantenerumab in participants with mild Alzheimer disease* (NCT02051608). ClinicalTrials.gov.
205. Hoffmann-La Roche. (2021). *A study of gantenerumab in participants with prodromal Alzheimer's disease (Scarlet Road)* (NCT01224106). ClinicalTrials.gov.
206. Jindal, H., Bhatt, B., Sk, S., & Singh Malik, J. (2014). Alzheimer disease immunotherapeutics: Then and now. *Human Vaccines & Immunotherapeutics, 10*(9), 2741–2743. https://doi.org/10.4161/21645515.2014.970959
207. Genentech, Inc. (2017). *A study to evaluate the efficacy and safety of MABT5102A in patients with mild to moderate Alzheimer's disease (ABBY)* (NCT01343966). ClinicalTrials.gov.
208. Genentech, Inc. (2024). *A study of crenezumab versus placebo in preclinical presenilin1 (PSEN1) E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease, including a placebo-treated non-carrier cohort* (NCT01998841). ClinicalTrials.gov.
209. Baxalta. (2021). *A phase 3 study evaluating safety and effectiveness of immune globulin intravenous (IGIV 10%) for the treatment of mild-to-moderate Alzheimer's disease* (NCT00818662). ClinicalTrials.gov.
210. Dodel, R., Rominger, A., Bartenstein, P., Barkhof, F., Blennow, K., Förster, S., Winter, Y., Bach, J. P., Popp, J., Alferink, J., Wiltfang, J., Buerger, K., Otto, M., Antuono, P., Jacoby, M., Richter, R., Stevens, J., Melamed, I., Goldstein, J., ... Jessen, F. (2013). Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: A phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. *The Lancet Neurology, 12*(3), 233–243. https://doi.org/10.1016/S1474-4422(13)70014-0
211. Relkin, N. R., Szabo, P., Adamiak, B., Burgut, T., Monthe, C., Lent, R. W., Younkin, S., Younkin, L., Schiff, R., & Weksler, M. E. (2009). 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. *Neurobiology of Aging, 30*(11), 1728–1736. https://doi.org/10.1016/j.neurobiolaging.2007.12.021
212. Szabo, P., Mujalli, D. M., Rotondi, M. L., Sharma, R., Weber, A., Schwarz, H. P., Weksler, M. E., & Relkin, N. (2010). Measurement of anti-beta amyloid antibodies in human blood. *Journal of Neuroimmunology, 227*(1–2), 167–174. https://doi.org/10.1016/j.jneuroim.2010.06.010
213. Hey, J. A., Kocis, P., Hort, J., Abushakra, S., Power, A., Vyhnálek, M., Yu, J. Y., & Tolar, M. (2018). Discovery and identification of an endogenous metabolite of tramiprosate and its prodrug ALZ-801 that inhibits beta amyloid oligomer formation in the human brain. *CNS Drugs, 32*(9), 849–861. https://doi.org/10.1007/s40263-018-0554-0
214. Liang, C., Savinov, S. N., Fejzo, J., Eyles, S. J., & Chen, J. (2019). Modulation of amyloid-β42 conformation by small molecules through nonspecific binding. *Journal of Chemical Theory and Computation, 15*(10), 5169–5174. https://doi.org/10.1021/acs.jctc.9b00599
215. Gervais, F., Paquette, J., Morissette, C., Krzywkowski, P., Yu, M., Azzi, M., Lacombe, D., Kong, X., Aman, A., Laurin, J., Szarek, W. A., & Tremblay, P. (2007). Targeting soluble Aβ peptide with tramiprosate for the treatment of brain amyloidosis. *Neurobiology of Aging, 28*(4), 537–547. https://doi.org/10.1016/j.neurobiolaging.2006.02.015
216. Hey, J. A., Yu, J. Y., Versavel, M., Abushakra, S., Kocis, P., Power, A., Kaplan, P. L., Amedio, J., & Tolar, M. (2018). Clinical pharmacokinetics and safety of ALZ-801, a novel prodrug of tramiprosate in development for the treatment of Alzheimer's disease. *Clinical Pharmacokinetics, 57*(3), 315–333. https://doi.org/10.1007/s40262-017-0608-3
217. Abushakra, S., Porsteinsson, A., Vellas, B., Cummings, J., Gauthier, S., Hey, J. A., Power, A., Hendrix, S., Wang, P., Shen, L., Sampalis, J., & Tolar, M. (2016). Clinical benefits of tramiprosate in Alzheimer's disease are associated with higher number of APOE4 alleles: The "APOE4 gene-dose effect." *Journal of Prevention of Alzheimer's Disease, 3*(4), 219–228. https://doi.org/10.14283/jpad.2016.115

218. Abushakra, S., Porsteinsson, A., Scheltens, P., Sadowsky, C., Vellas, B., Cummings, J., Gauthier, S., Hey, J. A., Power, A., Wang, P., Shen, L., & Tolar, M. (2017). Clinical effects of tramiprosate in APOE4/4 homozygous patients with mild Alzheimer's disease suggest disease modification potential. *Journal of Prevention of Alzheimer's Disease, 4*(3), 149–156. https://doi.org/10.14283/jpad.2017.26
219. Cowan, C. M., & Mudher, A. (2013). Are tau aggregates toxic or protective in tauopathies? *Frontiers in Neurology, 4*, 114. https://doi.org/10.3389/fneur.2013.00114
220. West, S., & Bhugra, P. (2015). Emerging drug targets for Aβ and tau in Alzheimer's disease: A systematic review. *British Journal of Clinical Pharmacology, 80*(2), 221–234. https://doi.org/10.1111/bcp.12621
221. Shefet-Carasso, L., & Benhar, I. (2015). Antibody-targeted drugs and drug resistance—Challenges and solutions. *Drug Resistance Updates, 18*, 36–46. https://doi.org/10.1016/j.drup.2014.11.001
222. Mehta, D. C., Short, J. L., Hilmer, S. N., & Nicolazzo, J. A. (2015). Drug access to the central nervous system in Alzheimer's disease: Preclinical and clinical insights. *Pharmaceutical Research, 32*(3), 819–839. https://doi.org/10.1007/s11095-014-1522-0
223. Berk, C., Paul, G., & Sabbagh, M. (2014). Investigational drugs in Alzheimer's disease: Current progress. *Expert Opinion on Investigational Drugs, 23*(6), 837–846. https://doi.org/10.1517/13543784.2014.905542
224. Hochgräfe, K., Sydow, A., Matenia, D., Cadinu, D., Könen, S., Petrova, O., Pickhardt, M., Goll, P., Morellini, F., Mandelkow, E., & Mandelkow, E. M. (2015). Preventive methylene blue treatment preserves cognition in mice expressing full-length pro-aggregant human Tau. *Acta Neuropathologica Communications, 3*, 25. https://doi.org/10.1186/s40478-015-0204-4
225. Grüninger, F. (2015). Invited review: Drug development for tauopathies. *Neuropathology and Applied Neurobiology, 41*(1), 81–96. https://doi.org/10.1111/nan.12192
226. Iqbal, K., Gong, C. X., & Liu, F. (2014). Microtubule-associated protein tau as a therapeutic target in Alzheimer's disease. *Expert Opinion on Therapeutic Targets, 18*(3), 307–318. https://doi.org/10.1517/14728222.2014.870156
227. Gourmaud, S., Paquet, C., Dumurgier, J., Pace, C., Bouras, C., Gray, F., Laplanche, J. L., Meurs, E. F., Mouton-Liger, F., & Hugon, J. (2015). Increased levels of cerebrospinal fluid JNK3 associated with amyloid pathology: Links to cognitive decline. *Journal of Psychiatry & Neuroscience, 40*(3), 151–161. https://doi.org/10.1503/jpn.140062
228. Yoon, S. O., Park, D. J., Ryu, J. C., Ozer, H. G., Tep, C., Shin, Y. J., Lim, T. H., Pastorino, L., Kunwar, A. J., Walton, J. C., Nagahara, A. H., Lu, K. P., Nelson, R. J., Tuszynski, M. H., & Huang, K. (2012). JNK3 perpetuates metabolic stress induced by Aβ peptides. *Neuron, 75*(5), 824–837. https://doi.org/10.1016/j.neuron.2012.06.024
229. Kimura, T., Ishiguro, K., & Hisanaga, S. I. (2014). Physiological and pathological phosphorylation of tau by Cdk5. *Frontiers in Molecular Neuroscience, 7*, 65. https://doi.org/10.3389/fnmol.2014.00065
230. Zhou, Q., Wang, M., Du, Y., Zhang, W., Bai, M., Zhang, Z., Li, Z., & Miao, J. (2015). Inhibition of c-Jun N-terminal kinase activation reverses Alzheimer disease phenotypes in APPswe/PS1dE9 mice. *Annals of Neurology, 77*(4), 637–654. https://doi.org/10.1002/ana.24361
231. Resnick, L., & Fennell, M. (2004). Targeting JNK3 for the treatment of neurodegenerative disorders. *Drug Discovery Today, 9*(21), 932–939. https://doi.org/10.1016/S1359-6446(04)03251-9
232. Shukla, V., Skuntz, S., & Pant, H. C. (2012). Deregulated Cdk5 activity is involved in inducing Alzheimer's disease. *Archives of Medical Research, 43*(8), 655–662. https://doi.org/10.1016/j.arcmed.2012.10.015
233. Camins, A., Verdaguer, E., Folch, J., Canudas, A. M., & Pallàs, M. (2006). The role of CDK5/P25 formation/inhibition in neurodegeneration. *Drug News & Perspectives, 19*(8), 453–460. https://doi.org/10.1358/dnp.2006.19.8.1043961
234. de la Torre, A. V., Junyent, F., Folch, J., Pelegrí, C., Vilaplana, J., Auladell, C., Beas-Zarate, C., Pallàs, M., Verdaguer, E., & Camins, A. (2012). GSK3β inhibition is involved in the neuroprotective effects of cyclin-dependent kinase inhibitors in neurons. *Pharmacological Research, 65*(1), 66–73. https://doi.org/10.1016/j.phrs.2011.08.006
235. Jorda, E. G., Verdaguer, E., Canudas, A. M., Jiménez, A., Bruna, A., Caelles, C., Bravo, R., Escubedo, E., Pubill, D., Camarasa, J., Pallàs, M., & Camins, A. (2003). Neuroprotective action of flavopiridol, a cyclin-dependent kinase inhibitor, in colchicine-induced apoptosis. *Neuropharmacology, 45*(5), 672–683. https://doi.org/10.1016/S0028-3908(03)00204-1
236. Noscira SA. (2012). *Efficacy, safety and tolerability of tideglusib to treat mild-to-moderate Alzheimer's disease patients (ARGO)* (NCT01350362). ClinicalTrials.gov.
237. Noscira SA. (2009). *Safety study of a glycogen synthase kinase 3 (GSK3) inhibitor in patients with Alzheimer's disease* (NCT00948259). ClinicalTrials.gov.
238. Velacor Therapeutic. (2011). *A phase IIa clinical trial of VEL015 (sodium selenate) in mild to moderate Alzheimer's disease* (ACTRN12611001200976).
239. Lovestone, S., Boada, M., Dubois, B., Hüll, M., Rinne, J. O., Huppertz, H. J., Calero, M., Andrés, M. V., Gómez-Carrillo, B., León, T., del Ser, T., & ARGO Investigators. (2015). A phase II trial of tideglusib in Alzheimer's disease. *Journal of Alzheimer's Disease, 45*(1), 75–88. https://doi.org/10.3233/JAD-141959

240. Corcoran, N. M., Martin, D., Hutter-Paier, B., Windisch, M., Nguyen, T., Nheu, L., Sundstrom, L. E., Costello, A. J., & Hovens, C. M. (2010). Sodium selenate specifically activates PP2A phosphatase, dephosphorylates tau and reverses memory deficits in an Alzheimer's disease model. *Journal of Clinical Neuroscience, 17*(8), 1025–1033. https://doi.org/10.1016/j.jocn.2010.04.020
241. van Eersel, J., Ke, Y. D., Liu, X., Delerue, F., Kril, J. J., Götz, J., & Ittner, L. M. (2010). Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. *Proceedings of the National Academy of Sciences of the United States of America, 107*(31), 13888–13893. https://doi.org/10.1073/pnas.1009038107
242. Baddeley, T. C., McCaffrey, J., Storey, J. M., Cheung, J. K., Melis, V., Horsley, D., Harrington, C. R., & Wischik, C. M. (2015). Complex disposition of methylthioninium redox forms determines efficacy in tau aggregation inhibitor therapy for Alzheimer's disease. *Journal of Pharmacology and Experimental Therapeutics, 352*(1), 110–118. https://doi.org/10.1124/jpet.114.219352
243. TauRx Therapeutics Ltd. (2014). *Study of TRx0237 in patients already taking medications for mild and moderate Alzheimer's disease* (NCT01626391). ClinicalTrials.gov.
244. TauRx Therapeutics Ltd. (2018). *Safety and efficacy study evaluating TRx0237 in subjects with mild Alzheimer's disease* (NCT01689233). ClinicalTrials.gov.
245. TauRx Therapeutics Ltd. (2018). *Safety and efficacy study evaluating TRx0237 in subjects with mild to moderate Alzheimer's disease* (NCT01689246). ClinicalTrials.gov.
246. TauRx Therapeutics Ltd. (2018). *Safety and efficacy study evaluating TRx0237 in subjects with behavioral variant frontotemporal dementia (bvFTD)* (NCT01626378). ClinicalTrials.gov.
247. Wischik, C. M., Staff, R. T., Wischik, D. J., Bentham, P., Murray, A. D., Storey, J. M., Kook, K. A., & Harrington, C. R. (2015). Tau aggregation inhibitor therapy: An exploratory phase 2 study in mild or moderate Alzheimer's disease. *Journal of Alzheimer's Disease, 44*(2), 705–720. https://doi.org/10.3233/JAD-142874
248. Shemesh, O. A., & Spira, M. E. (2011). Rescue of neurons from undergoing hallmark tau-induced Alzheimer's disease cell pathologies by the antimitotic drug paclitaxel. *Neurobiology of Disease, 43*(1), 163–175. https://doi.org/10.1016/j.nbd.2011.03.008
249. University of California, San Francisco. (2020). *A safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy study of TPI-287 in Alzheimer's disease* (NCT01966666). ClinicalTrials.gov.
250. Zhang, B., Carroll, J., Trojanowski, J. Q., Yao, Y., Iba, M., Potuzak, J. S., Hogan, A. M., Xie, S. X., Ballatore, C., Smith, A. B., III, Lee, V. M., & Brunden, K. R. (2012). The microtubule-stabilizing agent, epothilone D, reduces axonal dysfunction, neurotoxicity, cognitive deficits, and Alzheimer-like pathology in an interventional study with aged tau transgenic mice. *Journal of Neuroscience, 32*(11), 3601–3611. https://doi.org/10.1523/JNEUROSCI.4922-11.2012
251. Wisniewski, T., & Goñi, F. (2015). Immunotherapeutic approaches for Alzheimer's disease. *Neuron, 85*(6), 1162–1176. https://doi.org/10.1016/j.neuron.2014.12.064
252. Axon Neuroscience SE. (2015). *Safety study of AADvac1, a tau peptide-KLH-conjugate active vaccine to treat Alzheimer's disease* (NCT01850238). ClinicalTrials.gov.
253. Axon Neuroscience SE. (2017). *18-month safety follow-up study of AADvac1, an active tau vaccine for Alzheimer's disease (FUNDAMANT)* (NCT02031198). ClinicalTrials.gov.
254. Konishi, K., Hori, K., Tani, M., Tomioka, H., Kitajima, Y., Akashi, N., Inamoto, A., Kurosawa, K., Yuda, H., Hanashi, T., Ouchi, H., Hosoi, M., & Hachisu, M. (2015). Hypothesis of endogenous anticholinergic activity in Alzheimer's disease. *Neurodegenerative Diseases, 15*(3), 149–156. https://doi.org/10.1159/000381511
255. Wallace, T. L., & Bertrand, D. (2013). Importance of the nicotinic acetylcholine receptor system in the prefrontal cortex. *Biochemical Pharmacology, 85*(12), 1713–1720. https://doi.org/10.1016/j.bcp.2013.04.001
256. Weinreb, O., Amit, T., Bar-Am, O., & Youdim, M. B. (2012). Ladostigil: A novel multimodal neuroprotective drug with cholinesterase and brain-selective monoamine oxidase inhibitory activities for Alzheimer's disease treatment. *Current Drug Targets, 13*(4), 483–494. https://doi.org/10.2174/138945012799499794
257. Weinreb, O., Amit, T., Bar-Am, O., & Youdim, M. B. (2011). A novel anti-Alzheimer's disease drug, ladostigil: Neuroprotective, multimodal brain-selective monoamine oxidase and cholinesterase inhibitor. *International Review of Neurobiology, 100*, 191–215. https://doi.org/10.1016/B978-0-12-386467-3.00010-8
258. Avraham Pharmaceuticals Ltd. (2017). *A 3 year study to evaluate the safety and efficacy of low dose ladostigil in patients with mild cognitive impairment* (NCT01429623). ClinicalTrials.gov.
259. Avraham Pharmaceuticals Ltd. (2020). *Safety and efficacy study of ladostigil in mild to moderate probable Alzheimer's disease* (NCT01354691). ClinicalTrials.gov.
260. Shirazi, S. K., & Wood, J. G. (1993). The protein tyrosine kinase, fyn, in Alzheimer's disease pathology. *NeuroReport, 4*(4), 435–437. https://doi.org/10.1097/00001756-199304000-00024
261. Cochran, J. N., Hall, A. M., & Roberson, E. D. (2014). The dendritic hypothesis for Alzheimer's disease pathophysiology. *Brain Research Bulletin, 103*, 18–28. https://doi.org/10.1016/j.brainresbull.2013.12.004
262. Nygaard, H. B., van Dyck, C. H., & Strittmatter, S. M. (2014). Fyn kinase inhibition as a novel therapy for Alzheimer's disease. *Alzheimer's Research & Therapy, 6*(1), 8. https://doi.org/10.1186/alzrt238

263. Strittmatter, S. M. (2021). *Safety and tolerability of AZD0530 (saracatinib) in Alzheimer's disease* (NCT01864655). ClinicalTrials.gov.
264. Yale University. (2019). *A phase IIa multi-center study of 18F-FDG PET, safety, and tolerability of AZD0530 in mild Alzheimer's disease* (NCT02167256). ClinicalTrials.gov.
265. AB Science. (2018). *Activity of masitinib (AB1010) in mild to moderate Alzheimer's disease* (NCT00976118). ClinicalTrials.gov.
266. AB Science. (2023). *Masitinib in patients with mild to moderate Alzheimer's disease* (NCT01872598). ClinicalTrials.gov.
267. Yang, K., Belrose, J., Trepanier, C. H., Lei, G., Jackson, M. F., & MacDonald, J. F. (2011). Fyn, a potential target for Alzheimer's disease. *Journal of Alzheimer's Disease, 27*(2), 243–252. https://doi.org/10.3233/JAD-2011-110353
268. Folch, J., Petrov, D., Ettcheto, M., Pedrós, I., Abad, S., Beas-Zarate, C., Lazarowski, A., Marin, M., Olloquequi, J., Auladell, C., & Camins, A. (2015). Masitinib for the treatment of mild to moderate Alzheimer's disease. *Expert Review of Neurotherapeutics, 15*(6), 587–596. https://doi.org/10.1586/14737175.2015.1045419
269. Piette, F., Belmin, J., Vincent, H., Schmidt, N., Pariel, S., Verny, M., Marquis, C., Mely, J., Hugonot-Diener, L., Kinet, J.-P., Dubreuil, P., Moussy, A., & Hermine, O. (2011). Masitinib as an adjunct therapy for mild-to-moderate Alzheimer's disease: A randomised, placebo-controlled phase 2 trial. *Alzheimer's Research & Therapy, 3*, 16. https://doi.org/10.1186/alzrt75