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Current therapeutics for Alzheimer's disease and clinical trials

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Abstract

Alzheimer's disease (AD) is a major type of dementia and neurodegenerative disease, characterized by memory loss and cognitive decline. Over decades, significant efforts have been dedicated to finding its cause, pathogenic mechanisms, biomarkers for early detection, and clinical trials for its treatment. Earlier approved drugs mainly ameliorated the symptoms of AD, until recent years when two drugs targeting amyloid-beta (Aβ) protein were approved to slow down the progression of the disease. This review article encompasses the history of drug development in treating AD and clinical trials that failed and succeeded. Clinicaltrials.org website was systematically searched and screened for randomized controlled trials with results posted in the past 10 years. Among the 3,388 AD clinical trials, 211 interventional studies registered under AD have met eligibility. This review includes the interventional targets for drug discovery such as Aβ, tau, neurotransmitter receptors, neuroinflammation, multi-target studies, repurposing pharmacological agents, non-pharmacological interventions, and clinical therapy development for the neuropsychiatric symptoms of dementia. Current clinical trials are ongoing and no results are available as of yet. With the vast choices of drug targets that have been investigated, this review aims to present some insights into future AD drug design and trials and contribute to our ongoing efforts to find the cure.

Keywords

Clinical trials, Alzheimer's disease, amyloid-beta, tau protein, immunotherapies, multi-target drugs

Introduction

Alzheimer's disease (AD) has affected around 50 million people worldwide and is projected to reach 152 million by 2060 (for a review, see [1, 2]). AD and other dementias ranked among the top 10 leading causes of death globally [3]. Currently, there are about 24 million Alzheimer's patients worldwide [2]. It was suggested that gene changes can be a 70% risk factor for AD development [4, 5]. Three genes, also the main (high) risk factors for AD, are associated with early-onset AD. They are *APP* on 21q, *PSEN1* on 14q and

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PSEN2 on 1q [6]. The *apolipoprotein E* (*APOE*) gene is the strongest genetic (medium) risk factor for late-onset AD, located on chromosome 19q [7]. Among the *APOE* gene variants, *APOE4* is considered the strongest genetic risk factor for AD, and *APOE2* is neuroprotective [8].

FDA-approved immunotherapy drugs targeting amyloid-beta (Aβ) work best to slow the cognitive declining at the early stages of AD for some people, unlike earlier approved cholinergic drugs that provide symptomatic relief without altering the disease progression. The majority of clinical trials are targeting intervention with AD therapeutic agents at early/mild to moderate stages of AD, and its early detection. This review aims to provide an overview of the current treatments for relieving some AD symptoms by targeting cholinergic and N-methyl-D-aspartic acid (NMDA) receptors, and clinical trials in halting the progression of AD, targeting removing the toxic proteins typical of AD, Aβ proteins (extracellular plaques) and various forms of tau proteins (intracellular tangles) or other targets and multi-target drugs.

Approved treatments for Alzheimer's disease

Acetylcholinesterase inhibitors

The mainstay of current AD management targeting acetylcholinesterase is to make acetylcholine available for synaptic transmission [2, 9–11]. Five drugs (donepezil, rivastigmine, galantamine, memantine, and tacrine) are approved on the market with donepezil approved the earliest, in 1996. These drugs are used for all stages of AD, but inhibition of cholinesterase enzymes works best at the early stage of AD [9, 12].

Among them, a rivastigmine patch or oral capsule is the only acetylcholinesterase inhibitor (ACEI) that provides inhibition for both acetylcholinesterase and butyrylcholinesterase and shows efficacy and safety in helping to relieve the cognitive symptoms of AD (e.g., [13]).

NMDA receptor antagonist

Current therapeutics to ameliorate and control the cognitive and behavioral symptoms by targeting the NMDA receptor prevent Ca^{2+} induced excitotoxicity [2, 9–11], and memantine was approved for this purpose in 2003. Memantine is more effective in providing cognitive and behavioral benefits and approved for patients with moderate to severe AD as monotherapy or combination therapy with donepezil [9, 12]. Finally, memantine is both a non-competitive NMDA receptor antagonist and a dopamine agonist for moderate to severe AD [11].

Anti-amyloid monoclonal antibodies

The FDA has approved two drugs for mild cognitive impairment (MCI) to early, mild stages of AD after years of failed clinical trials. They are aducanemab, and lecanemab, among which aducanemab received accelerated approval [14, 15].

Clinical trials for Alzheimer's disease

As of May 2024, there are a total of 3,388 Alzheimer's disease clinical trials including all studies (clinicaltrials.gov). We chose to focus on the trials starting from 01/01/2015 and encompassing the past 10 years, including 2,030 studies. After excluding observational studies (with patient registries), and keeping all the interventional clinical trials, there are 1,596 studies registered under AD. After keeping the trials with results (excluding the ones without results), 211 studies remain with (early) phase 1 (n = 32), phase 2 (n = 78) trials on the safety and tolerability test, and phase 3 (n = 37) and phase 4 (n = 4) trials on slowing the cognitive decline. These trials were or are in the process of being carried out globally. This review includes the interventional targets for drug discovery such as neurotransmitter (receptors), Aβ, tau, neuroinflammation, growth factors, and hormones, including multi-target studies (Table 1, 2, 3); repurposing pharmacological agents already in use; non-pharmacological interventions such as environmental enrichment, combination therapy, and neurostimulation (devices); and clinical therapy development for the neuropsychiatric symptoms of dementia based on Common Alzheimer's and Related Dementias Research Ontology (CADRO). Anti-inflammatory therapy is intended to reduce the harmful

inflammatory response of microglia activation in the AD brain [16–18]. Moreover, there are other important approaches, for example, the exploration and efforts targeting oxidative stress linked to mitochondria dysfunction to screen neuroprotective antioxidant compounds in cells and mouse models of AD [16, 17, 19].

Table 1. Compounds target for cognitive improvement in AD and their combination treatments

Name	Target and rationale	Status on clinical trials (start date–end date)	AD stage	Results	Clinical trials identifier (NCT number)
CT1812	Antagonists for the sigma 2 and progesterone receptor membrane component 1 (PGRMC1) receptors	Phase 1–2 (2018–2020)	Mild to moderate	No alteration of synaptic density, insignificant changes in cognition memory task	03493282
Rasagiline (Azilect)	MAOB inhibitor, reducing reactive astrocytes	Phase 2 (2015–2019)	Mild to moderate	Glucose metabolism declining less showed benefit in quality of life only	02359552
Ladostigil	AchE inhibitor and MAO inhibitor, promoting cholinergic and serotonergic/dopaminergic neurotransmission	Phase1/2 (2019)	Mild	Failed to meet the primary endpoint	01429623
Idalopirdine	AchE inhibitor and 5-HT6 receptor, stimulating 5-HT and cholinergic receptor (as an adjunct therapy for AchE inhibitor)	Phase 1–3 (2014–2017)	Mild to moderate	Weak efficacy in phase 3, discontinued (2017)	02079246
Rivastigmine	Inhibitors of AchE and butyrylcholiesterase	Phase 4 (2016–2018)	Mild to moderate	Showing some symptomatic improvement [13]	02703636
Intepirdine (RVT-101)	The antagonist of the 5-HT6 receptor, CNS-specific	Phase 2 (2016–2017) Phase 3 (2016–2018)	Mild to moderate	Did not meet primary efficacy endpoints	02586909 02910102
BI 409306	Inhibitor of phosphodiesterase (PDE) 9A, increasing cGMP	Phase 2 (2015–2017)	Prodromal	No difference between drug and placebo groups on measures of efficacy	02240693 02337907
Neflamapimod (VX-745)	Inhibitor of p38 MAPK (mitogen-activated protein kinase) alpha	Phase 2 (2015–2016) Phase 2 (2017–2019)	Mild	Failed to meet the primary endpoint of improving episodic memory	02423122 03402659
BI 425809	Inhibitor of glycine transporter, keeping a higher level of glycine at the synapse promoting NMDA R activation	Phase 2 (2016–2019)	Mild to moderate	No improvement in the primary or secondary measures compared with the placebo [20]	02788513
Candesartan	Blocker of Angiotensin II	Phase 2 (2016–2020)	MCI	Superior in primary and secondary outcomes of executive function by TMT(B) and Hopkins Verbal Learning Test-Revised delayed recall [21]	02646982
Donepezil plus solifenacin (CPC-201)	Inhibitor of AchE and muscarinic receptor M3 treating overactive bladder, respectively	Phase 2 (2015–2017)	Moderate	Allowing the safe use of higher AchE inhibitors doses that may augment cognitive and global benefits [22]	02549196
Donepezil + memantine + masupirdine (SUVN-502)	Antagonists of the AChE, NMDA R, and 5-HT6 receptor	Phase 1–2 (2018)	Moderate	No additional benefit with the combination treatments	02580305
Memantine + bryostatin	NMDA R antagonist, macrolide lactones which increase the α-secretase activity and reduce Aβ accumulation	Phase 2 (2015–2017)	Moderate to severe	No additional benefit with the combination treatments	02431468

AD: Alzheimer's disease; 5-HT6: 5-hydroxytryptamine 6; MAOB: monoamine oxidase-B; MCI: mild cognitive impairment; TMT(B): Trail-Making Test-B; Aβ: amyloid-beta; NMDA R: N-methyl-D-aspartic acid receptor

Table 2. Status and rationale of selected compounds targeting various amyloid proteins tested in AD clinical trials

Invested agent name	Target and rationale	Status on clinical trials (start date–end date)	AD stage	Results	Clinical trial identifier (NCT number)
Posiphen tartrate (Buntanetap)	APP synthesis reduction	Phase 1–2 (2021)	Mild to moderate	Terminated due to business decision	04524351
Bryostatin	α-Secretase activity enhancer, reducing Aβproduction	Phase 2 (2019)	Moderate to severe	Ineffective	03560245
LY3202626	β-Secretase activity reduction [targeting BACE1 (β site APP cleaving enzyme 1)]	Phase 2 (2018)	Mild	Terminated due to low likelihood of identifying a statistically significant treatment effect	02791191
Lanabecestat (LY3314814)	β-Secretase activity reduction (targeting BACE1)	Phase 2/3 (2018)	Mild	Lack of efficacy or terminated due to unlikely to meet the primary endpoint and brain volume reduction	02245737 02783573
Verubecestat (MK-8931)	β-Secretase activity reduction (targeting BACE1)	Phase 2–3 (2017)	Mild to moderate	Terminated due to injuries and lack of efficacy	01739348
Umibecestat (CNP520)	β-Secretase activity reduction (targeting BACE1)	Phase 2/3 (2019 and 2021)	Mild, or at risk of AD with one allele of *APOE4* and elevated brain amyloid	Worsening cognition, and terminated due to safety reasons	03131453
Elenbecestat (E2609)	β-Secretase activity reduction (targeting BACE1)	Phase 3 (2020)	Mild/Early	Ended Due to an unfavorable risk-benefit ratio including lack of efficacy, and the adverse event being worse than the placebo with brain volume loss	02956486
Semagacestat	γ-Secretase inhibitor, preventing Aβ production (not selective)	Two phase 3 trials (2017–2020)	Mild to moderate	Significant deterioration of cognitive function, side effects (GI and skin cancer)	02423122 03402659
ELND005	Inhibiting Aβ formation	Phase 2 (2012–2015)	Moderate	Adverse effect (infection)	01735630
Exendin4	A glucagon-like peptide, binding to soluble Aβ fragments, lowering Aβ burden	Phase 2 (2016)	Prodromal/Mild	Adverse effect (infection), terminated due to lack of support	01255163
(Azeliragon) TPP488	RAGE (cell surface receptor linked to an increase in Aβ plaque formation) antagonist, increase Aβ clearance and targeting neuroinflammation	Phase 2 (2019–2021) Two phase 3 trials (2015–2018, 2016–2018)	Mild	Primary endpoints not met	03980730 02080364 02916056
Pioglitazone	Agonizing peroxisome proliferator-activated receptor (PPAR) to increase Aβ phagocytosis	Phase 3 (2015–2018)	MCI	Terminated due to lack of efficacy	02284906
Crenezumab (MABT5102A, RG7412)	Human monoclonal antibody (hmAB) targeting the clearance of Aβ oligomers and fibrillar species	Phase 3 (2016, 2017, 2018–2019)	Prodromal to mild	Discontinued by the sponsor due to lack of efficacy [23]	02670083 03114657 03491150
Solanezumab	hmAB targeting soluble Aβ peptide	Phase 3 (2013–2017)	Mild to moderate	Lack of efficacy	01900665
Gantenezumab	hmAB binds to insoluable Aβ plaques and removes them via phagocytosis	Phase 3 (2010–2020, 2014–2021)	Mild/Prodromal	Lack of efficacy, its primary endpoints not met	01224206 02051608
Aducanumab (BII3037)	hmAB targeting the clearance of Aβ plaques	Phase 2 (2018–2019) Phase 3	Mild/Early	Two identical trials (ENGAGE and EMERGE) were terminated due to futility analysis. Substudies for both trials showed a dose-dependent	03639987 02484547

Table 2. Status and rationale of selected compounds targeting various amyloid proteins tested in AD clinical trials (*continued*)

Invested agent name	Target and rationale	Status on clinical trials (start date–end date)	AD stage	Results	Clinical trial identifier (NCT number)
		(2015–2019, 2015–2019, 2020–2024, 2022–2024)		reduction of Aβ and CDR-SB. In the EMERGE trial (NCT 02484547), aducanemab at a high dose significantly reduced dementia rating score CDR-SB. The trial (NCT05310071) would be terminated due to the sponsor's decision	02477800 04241068 05310071
Donanemab (LY3002813)	hmAB targeting the clearance of Aβp3-42 plaques	Phase 1–3 (2017–2021, 2023, 2020–2024)	Mild/Early	Reduced Aβ plaques and tau, are under review for standard approval [14]	03367403 04437511 05108922 04640077
Lecanemab (BAN2401)	hmAB targeting the clearance of soluble Aβ aggregates	Phase 1–3 (2012–2023 2019–2027)	Mild	Reduced Aβ plaques and tau, with less decline of cognition and function. Received full FDA approval	02094729 03887455
UB-311 (AD vaccine)	Active immunotherapy with Aβ peptide (N-terminal amino acid 1-14), inhibiting Aβ aggregates	Phase 2 (2015–2018)	Mild	Robust immune response with adverse events such as microhaemorrages (14%), supporting phase 3 trials [24]	02551809

AD: Alzheimer's disease; Aβ: amyloid-beta; APP: Aβ precursor protein; MCI: mild cognitive impairment; CDR-SB: clinical dementia rating-sum of boxes; GI: gastrointestinal; APOE 4: apolipoprotein E 4

Table 3. Status and rationale of selected compounds targeting various tau proteins tested in AD clinical trials

Invested agent name	Target and Rationale	Status on clinical trial (start date–end date)	AD stage	Results	Clinical trial identifier (NCT number)
ABT-957 (Alicapistat)	Inhibition of calcium-dependent cysteine protease, calpain, which is linked to hyperphosphorylation of tau and its aggregation	Phase 1, (2014–2016)	Mild to moderate	Not reaching the effective level in CNS [25]	02220738
Semorinemab, RO7105705, RG6100	IgG4 antibodies targeting all 6 isoforms of extracellular tau (eTau)	Phase 2, (2021)	Mild/Prodromal	The primary endpoint not met didn't show benefit or modulation of the tau-PET signal	03289143
		Phase 2, (2023)	Probable AD and moderate	Promising results on cognition	03838747
BIIB092, Gosuranemab	hmAB against eTau	Phase 1/2, (2018–2021)	Mild	Lack of efficacy	03352557
Zagotenemab, LY3303560	hmAB against a conformational epitope of eTau	Phase 1/2, (2016–2021)	Mild or early symptomatic	Missed primary endpoints	03518073
RG7345, RO6426496	Rabbit monoclonal Ab targeting phosphorylated Tau (at serine 422)	Phase 1, (2015)	Healthy males	Terminated, unfavorable phamacokinetic profile	02281786
BIIB076, NI-105	Human recombinant monoclonal anti-tau Ab targeting mid-domain of Tau	Phase 1 (2017–2020)	Healthy and mild	Discontinued due to business reasons	03056729
AADvac1	Active vaccine using a synthetic tau peptide	Phase 1 (2013–2015) Phase 2 (2016–2019)	Mild to moderate	Safe [26] and promising, but lack efficacy [27]	01850238 02579252

AD: Alzheimer's disease; hmAB: human immunoglobulin monoclonal antibody

Further, combination therapy can combine both pharmacological approaches and/or combine non-pharmacological approaches. Combination therapy that improves symptoms plus disease-modifying

therapeutics (DMT) would modify and slow down the progression of AD as add-on treatments in combination with the current drugs. This combination therapy gives flexibility, gearing towards individual differences in regards to the drug target or multiple targets, more than one delivery method or delivery timing (sequential combinations), and the use of multifunctional molecules-single agents (multi-target drugs) that combine more than one activity or more than one target [28]. Combination therapy can also combine pharmacology and non-pharmacological intervention, such as gamma frequency neurostimulation (see the following section: non-pharmacological interventions and [28]).

Multi-target drugs acting on different targets

To improve efficacy, single molecule drugs have been designed to incorporate two or more pharmacological structural features of different bioactive drugs acting on different targets. The different structural components can be connected through a tether/linker or merged together [9]. Examples include ANAVAX 2-73 (blarcamesine), lumateperone, idolopiridine, ladostigil, and J-147.

Blarcamesine, combining agonist activities at the muscarinic M1 receptor, the NMDA receptor, and the sigma-1 receptor, targets protein tau and reduces AD neurodegeneration [29]. Two consecutive multicenter phase 2a trials, randomized and open-label, show it improves cognition, dose-dependently, in mini-mental status examination (MMSE) and AD Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) in subjects with mild-to-moderate AD [30]. The ongoing ATTENTION-AD trial (NCT04314934) is a phase 2b/3 open-label extension study to evaluate the effects of blarcamesine on the safety and efficacy of daily treatment with an enrollment of 450 participants globally who have completed the previous ANAVEX2-73-AD-004 double-blind study (clinicaltrials.gov). Lumateperone and iolopiridine targeted both 5-hydroxytryptamine 6 (5-HT6) and AchE, though both were discontinued due to lack of efficacy. Ladostigil is a hybrid molecule combining the carbamate group of rivastigmine and the N-propargyl group of monoamine oxidase (MAO) inhibitors, though it failed to meet the primary endpoint of delaying cognitive impairment in phase 2. J-147 under phase 1 is a multi-target drug including targets like MAO. MAOB activity is increased in AD at reactive astrocytes near amyloid plaques.

Clinical trials targeting Aβ protein

The rationales of these early AD drug trials from 2011 to 2020 are based on the Aβ hypothesis. Trials targeting degradation and production from Aβ precursor protein (APP) include those designed to: (1) decrease APP production, for example, posiphen (buntanetap); (2) increase α-secretase (stimulating non-amyloidogenic pathway), such as bryostatin; (3) inhibition of β-secretase to reduce Aβ production, in amyloidogenic pathway) [9], such as atabecestat and lanabecestat [31]; (4) inhibition of gamma-secretase (to reduce Aβ production, in the amyloidogenic pathway), such as LY3202626; (5) target Aβ solubility and aggregation such as Alzhemed (discontinued) and its pro-drug ALZ-801(for its potential efficacy in patients with the *APOE4/4* genotype or its carriers), as soluble Aβ aggregates are considered to be the relevant cytotoxic form of the protein [32]; (6) target Aβ clearance by antagonizing RAGE (cell surface receptor linked to an increase in Aβ plaque formation), which primarily targeting neuroinflammation. These trials resulted in failure due to lack of efficacy and/or side effects of toxicity, for example [31] (Table 2).

Aβ clearance by immunotherapy was first demonstrated in an ischemic mouse model showing amyloid plaques can disappear with injections of human β-amyloid-(1-42)-peptide for some months [33]. Aiming for elimination of Aβ aggregation has two approaches: passive immunization and active immunization. Passive immunotherapies with monoclonal antibodies against Aβ in clinical trials went through three generations of development [11, 34], with FDA approval of two drugs for MCI to early stage of AD. First-generation antibody against N-terminus aggregated amyloid plaque, bapineuzumab, has no efficacy, due to low potency [35]. Second-generation anti-amyloid antibody against soluble monomeric Aβ (solanezumab), insoluble monomeric Aβ (gantenezumab), and monoclonal antibody against multiple Aβ forms (crenezumab) failed to have efficacy in improving cognitive functions for mild and moderate AD in several clinical trials (Table 2, for example [36]). The third generation of human immunoglobulin monoclonal antibody (hmAB; aducanumab, donanemab, and lecanemab) directed against insoluble, modified, N-

terminal truncated form of Aβ, targeting Aβ plaque clearance, seems to benefit MCI or AD with mild dementia patients [34, 37]. Aducanumab and lecanemab are the first agents in two decades to demonstrate efficacy in clinical studies.

Aducanemab's benefits are controversial [38, 39]. Four aducanumab phase 3 trials against Aβ fibrils were carried out; two were terminated due to futility analysis, and two trials (ENGAGE and EMERGE) showed benefit by reducing AD biomarkers, Aβ and tau proteins, in early-onset AD in certain patients [9]. Sub-studies for the two trials showed a dose-dependent reduction of Aβ and clinical dementia rating-sum of boxes (CDR-SB) a global measure of both cognition and function. In the EMERGE trial (NCT 02484547), aducanumab at a high dose significantly reduced dementia rating score CDR-SB (clinicaltrials.org, for a review see [14]). In 2024, the marketing of aducanumab was discontinued by the manufacture. Donanemab (under FDA review) can effectively reduce the cerebral spinal fluid (CSF) level of amyloid protein and plasma P-tau and T-tau [40, 41], provides a benefit of slowing down cognitive declines and improving function, and meet the primary endpoint, the integrated AD Rating Scale (IADRS), for those who are at the earliest stage of AD with a low level of tau proteins, and to a lesser extent those who carry *APOE4* [42]. Lecanemab, directed against amyloid protofibrils, is approved for MCI/mild AD dementia based on the clarity AD trial (NCT03887455). This is an 18-month, multicenter, double-blind, phase 3 trial with early AD (MCI or mild dementia due to AD) with evidence of amyloid on PET or CSF testing. The administration of this antibody manifested significant (27%) slower progress in cognitive decline in the patients based on the primary end points, the change from baseline at 19 months in the score on the CDR-SB (with higher scores being greater impairment), and secondary endpoints, the change in the 14-item cognitive subscale of the AD assessment scale (ADAS-cog 14; higher scores being greater impairment), the AD composite score (ADCOMS; higher being worse) and the score on the ADCS-ADL for MCI (ADCS-MCL-ADL; lower scores being greater impairment). Overall, lecanemab significantly reduced amyloid burden with modestly less decline in measures of cognition and function in early-stage AD patients [34, 39, 43].

For cognitively normal individuals who are at high risk carrying AD genes, clinical trials were also started to prevent AD from onset or delay its onset. In one AD trial, crenezumab was tested for its preventative effect. The benefits of crenezumab on cognitively unimpaired autosomal dominant AD participants wait to be understood based on the recently closed phase 2 clinical trial (NCT 01998841) [44, 45].

Finally, trials on active immunotherapies targeting Aβ are limited. The first active immunization in humans, with the AN 1792 vaccine, was terminated due to its ineffectiveness in removing Aβ deposits from the brain or slowing cognitive decline, and adverse effects [46]. Later vaccine development resulted in improvement of cognition and reduction of Aβ accumulation; for example, active AD vaccine UB-311 has shown promising results for mild AD patients, able to generate a high response rate (100%) of antibody production in a phase 2 trial, with plans for a clinical phase 3 trial (Table 2) [9, 47].

Clinical trials targeting tau proteins

Although amyloid remains the most common pharmaceutical target, targeting the tau protein, which is downstream to Aβ oligomers and contributes to intracellular neurofibrillary tangles, has received attention in recent years (Table 3; Clinicaltrials.org) [14, 48]. A tau imaging study showed tau accumulates slowly in large neocortical areas, taking approximately 15–20 years, with the highest rates of tau accumulation at the temporal, parietal, and lateral occipital cortex [49]. Currently, there is more evidence that hyperphosphorylated tau plays an important role in AD pathogenesis, reducing synaptic transmission at the nerve terminals and leading to tangle formation [37].

So far, three generations of anti-tau non-immunotherapy drugs failed clinical trials. First-generation anti-tau drugs target reversing post-translation hyperphosphorylation modifications that induce tau aggregation or inhibit tau aggregation directly, for example, nicotinamide and curcumin [50]. However, the tau aggregation inhibitor leuco-methylthioninium bis (hydromethanesulphonate), (LMTM, TRX 0237) trial, treating mild and moderate AD and frontotemporal dementia (2018), was terminated and failed at both primary endpoints (Alzforum.org). Second-generation anti-tau, Saracatinib (AZD0530), is a dual kinase

inhibitor of Src and Ab1 family kinases and a repurposed drug originally treating cancer. Third-generation anti-tau drug Atuzagnstat (COR 388), for mild to moderate AD (2019–2022), failed due to adverse gastrointestinal (GI) effects and subject withdrawal.

On the other hand, the anti-tau immunotherapeutic approach is more complicated due to the various isoforms of tau protein, with at least six monoclonal antibodies against tau now in phase 2 and phase 3 clinical trials [11, 51]. Earlier phase 1 clinical trials targeting tau failed due to lack of recruitment; these agents reduce tau build-up via histamine H3 receptor antagonists and calcium-dependent cysteine protease inhibitors for mild to moderate AD. Later anti-tau therapeutic design includes antibody against different forms of tau proteins, mostly targeting the N-terminus such as semorinemab and gonsuranemab, or microtubule-binding regions such as AADvac1 and zagotenemab which are shown to reduce CSF P-tau level [50] (Table 3). Semorinemab and R07105705 are active against all six isoforms of tau, whereas, RG7345 is only active against phosphorylated-tau. Semorinemab was ineffective and did not slow the decline in a primary cognitive outcome for early AD in the phase 2 trial [52].

Active vaccine AADvac1, a synthetic tau peptide, reduces tau deposit by attacking the conformational epitope of tau for mild to moderate AD and has been well tolerated in clinical trial phase 1–2. A subgroup analysis of younger AD patients (participants 67 years or younger) showed significant beneficial changes in biomarker plasma neurofilament light chain (NfL) and cortical atrophy [51]. A post hoc subgroup analysis of the participants positive for amyloid and tau from phase 2 trial (NCT02579252) found the vaccine slowed AD-related decline on the CDR-SB and ADL scores in an antibody-dependent manner, and brain volume was preserved with treatment compared with control [48]. Phase 3 trial of active vaccine against tau protein is anticipated for treating mild AD [51].

Moreover, the antibody against tau protein can recognize extracellular tau (in most cases) or intracellular tau, or both. Antibody recognizing extracellular tau is thought to block the spread of tau across synapses [53], though it may not be perfect, for example, BIIB092, CN2-8E12, tilavonemab, and LY3303560 that recognize extracellular tau protein lack efficacy (Table 3). To target production and degradation of the intracellular tau, antisense oligonucleotides and small interfering ribonucleic acids (siRNAs) treatment is used to reduce tau production. In addition, proteolysis-targeting chimeras are used to enhance tau proteasomal degradation in early AD [50]. A current phase 2 clinical trial is investigating whether upstream gene activation, triggering receptor expressed on myeloid cells 2 (TREM-2) dependent microglia activation, can halt tau accumulation inside the cells (NCT04592874). One might assume that an antibody recognizing both extracellular and intracellular tau protein will be the most efficacious. However, this is not the case; for example, RG7345 that can bind to both intracellular and extracellular tau proteins has an unfavorable pharmacokinetic profile (Table 3).

Repurposing pharmacological agents

Repurposing pharmacological agents has advantages from a drug development standpoint. Based on FDA regulation, an application that contains reports of safety and effectiveness in at which at least some of the information required for approval comes from studies conducted for a previously approved product receives much shortened review, leading to a speedy approval compared to a new drug. There are numerous repurposed drug trials that had encouraging results. Masitinib targets (inhibiting) tyrosine kinase and modulated neuroinflammation in 2012–2020 phase 2/3 trials for mild to moderate AD [9]. Minocyclin is a repurposed drug on trial for mild AD. Riluzole, a D2 receptor agonist approved for ALS, completed its phase 2 trial for mild AD as well and showed promise in improving glucose metabolism [54]. Rasagiline, an MAOB inhibitor approved for Parkinson's disease, showed a favorable effect on neuroimaging biomarker tau and some benefit in quality of life in patients with mild to moderate AD [55]. Nabilone, an antiemetic and synthetic cannabinoid completed a phase 3 trial in 2019 and showed its promise in controlling agitation, a challenging and the most prevalent neuropsychiatric symptom, through anti-inflammatory effects in moderate-to-severe AD patients [56, 57].

Table 4. Status and rationale of ongoing AD clinical trials

Invested agent name	Target and rationale	Status on clinical trial (phase, start date–end date in year)	AD stage	Clinical trial identifier (NCT number)
ANAVAX 2-73 (Blarcamesine)	Sigma 1 receptor agonist, modulating muscarinic receptors to decrease the APP synthesis, restoring homeostasis	Phase 2/3 (2019–2024 July)	Early	04314934
ALZ-801 (a prodrug version of Alzhemed)	Binding to soluble Aβ fragments, inhibiting Aβ aggregation	Phase 2 (2020–2024)	MCI-moderate	04693520
		Two phase 3 trials (2021–2024, 2024–2026)	Early AD with the *APOE4* carriers, or *APOE4/4* genotype	04770220 06304883
Aducanumab	Human anti Aβ monoclonal Ab targeting the clearance of Aβ plaques	Phase 3 (2020–2025)	Mild	04241068
Donanemab	Human anti Aβ monoclonal Ab targeting the clearance of Aβp3-42 plaques	Phase 3 (2021–2027)	Preclinical	05026866
			Early	04437511
		Phase 3 (2020–2025, 2023–2025, 2022–2027)		05738486 05508789
Lecanemab (BAN2401)	Human anti Aβ monoclonal Ab targeting the clearance of soluble Aβ aggregates	Phase 2–3 (2012–2027)	Preclinical/Early	01767311 03887455 04468659
		Phase 2–3 (2012–2027)	Mild or cognitive normal EOAD	05269394 01760005
AL002	Halting intracellular tau accumulation via TREM-2 dependent microglia activation	Phase 2 (2021–2024 September, 2023–2025)	Early AD	04592874 05744401
JNJ-63733657	Human IgG1 monoclonal Ab recognizes the microtubule binding region of phosphorylated tau (p217+), interferes with spread of pathogenic tau	Phase 2 (2021–2025)	Early AD	04619420
UCB0107 Bepranemab	Human IgG4 monoclonal Ab recognizing the mid-region of tau (aa. 235-250), near the microtubule-binding domain, interferes with the spread of tau, more potent than N-terminally targeted antibodies	Phase 2 (2021–2025)	Mild or prodromal	04867616
Lecanemab with and w/o E2814	Anti-Ab and Tau antibody therapy to reduce the burden of both	Phase 2–3 (2021–2027)	Cognitively normal or MCI, with dominantly inherited genetically AD mutation	05269395

AD: Alzheimer's disease; Aβ: amyloid-beta; APP: Aβ precursor protein; MCI: mild cognitive; EOAD: early-onset AD; TREM-2: triggering receptor expressed on myeloid cell 2

Pharmacological combination therapy and ongoing clinical trials

Considering the complexity of AD pathogenesis, using combination drug therapy on two or more different targets presents the potential for improved efficacy and outcomes, as targeting multiple pathways or mechanisms might have a synergistic effect on therapeutic outcomes. For example, Namzaric, a fixed dose-combination of donepezil and memantine, is used for the treatment of AD patients with moderate to severe AD dementia [9]. However, adding the 5-HT6 receptor antagonist, masupirdine (SUVN-502), as adjuvant to donepezil and memantine, demonstrated no additional palliative benefits in a phase 2 clinical trial (NCT02580305) [58, 59]. It was suggested that memantine interferes with the effect of 5-HT6 antagonist masupirdine.

Other pharmacological combination therapy includes targeting both neuroinflammation and Aβ clearance as in t-octhylphenol 1 (T-OP1), combining a mast cell stabilizer and an Aβ aggregation inhibitor (cromolyn) with a nonsteroidal anti-inflammatory drug (NSAID) [60], and targeting tau (with antibody or a microtubule stabilizer) and acetylcholinesterase inhibitors (AChEI) therapy, the latter of which worked better when targeting mild to moderate stage AD in clinical trial. However, most of these trials failed to

meet each trial's specific cognitive endpoints, for example, clinical trials of Aβ clearance agent Rosiglitazone as an add-on therapy for patients with AD on donepezil or other AChEIs [37].

Current research suggests that amyloid and tau have a synergistic interaction and effect in promoting neurodegeneration and cognitive decline [61], and therefore, clinical trials that target both removing Aβ protein and tau burden with lecanemab are ongoing with the results yet to be released (Table 4). Other ongoing clinical trials aim to remove Aβ plaques with hmAB such as aducanumab, donanemab, gantenezumab, and lecanemab, and continuously monitor their safety and efficacy. Lastly, with the hope that tau is a promising candidate, ongoing clinical trials target intracellular tau and different regions of extracellular tau to block the spread of prion-like tau, for example, JNJ63733657 and UCB0107 (Bepranemab) targeting microtubule binding and tau mid-region, respectively (Table 4).

Non-pharmacological interventions

These interventions include exercise, diet, cognitive training, sleep-related intervention, neurostimulation (with devices), combination therapy, and others (such as environmental enrichment) based on Common Alzheimer's Disease Research Ontology (CADRO).

Exercise, diet, cognitive training, and other

Aerobic exercise for 26 weeks increased glucose metabolism and improved executive function (NCT 02384993) [62]. Social dance movement and exercise with treadmill walking for people with MCI or early stage of AD and other dementia significantly improved multiple brain network characteristics, global efficiency, modularity, quality of life, and balance (NCT 03333837) [63].

Effects of intermittent calorie restriction on CSF biomarkers related to AD were studied in women with insulin resistance. The result showed a significant reduction of the CSF Aβ42/Aβ40 ratio and reduction of tau (NCT 02460783). Alternative diet therapy includes the nutraceutical huperzine A, vitamin D, omega-3 fatty acids, and probiotics, and has shown benefit in cognitive functions [11, 64]. Nutraceutical huperzine A has shown benefits in improving cognitive function, memory function, and daily living activities by reducing oxidative stress [65]. Clinical trials with omega-3 fatty acids supplements have shown benefits in improving memory probably in link to its cardiovascular benefits in subjects with MCI [11, 66]. Randomized double-blind controlled clinical trials and their meta-analysis showed that probiotics improved cognitive performance and metabolic profiles in AD possibly by reducing intestinal inflammation and oxidative stress [64, 67]. The current early phase 1 triple-masked clinical trial (NCT06181513) is underway to investigate whether giving probiotics (20 million CFU of Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus helveticus, Bifidobacterium breve) to patients with mild AD reduces neuroinflammation, improves cognitive function and modify neurophysiological measures compared to placebo group.

Brain stimulation with a computer program showed a trend to increase cognitive function and reduce depression in mild to moderate AD in a terminated trial (due to COVID-19) (NCT 03656107) [68]. Behaviorally, play intervention to meet the unmet needs of belonging, esteem, and self-actualization seemed to increase cognitive assessment and memory score in AD (NCT 02846415). Finally, physical and social environmental modification such as ecological therapy with gardening helped to reduce behavioral disorders in moderate to severe AD (NCT 04555616, NCT 02462291).

Neurostimulation devices

AD progression from the hippocampus to other parts of the brain disrupts circuitry-level connection (e.g., [69]); that finding led to early clinical trials for inducing gamma-frequency or brain training to promote the connection among brain areas, and cognitive functions. Gamma oscillations using transcranial alternating current stimulation (tACS) at 40 Hz increased blood perfusion in bilateral temporal lobes in mild to moderate AD patients based on an arterial spin labeling study using MRI ([70]; NCT03290326, and NCT 03412604). Similarly, investigators sought to replicate the finding from the AD mouse model study that gamma stimulation with light flicker (gamma entrainment using sensory stimulus or GENUS) reduced

phosphorylated tau and amyloid with combined visual and auditory GENUS in the medial prefrontal cortex [71]. A clinical trial (NCT03543878) was designed to entrain human brain activities by exposure to the same gamma oscillation frequency with Flicker devices, licensed by Cognito Therapeutics, in the MCI stage of AD patients; however, the results on AD biomarkers and cognitive behavior scores are not available. On the other hand, transcranial direct current stimulation (tDCS) improved cognition and behavior, with a significant interaction between default mode network (DMN) and salient network and functional connectivity changes in a polarity-dependent effect [72].

Clinical trials for the neuropsychiatric symptoms of dementia

Among the few clinical trials targeting non-cognitive symptoms, there are several drugs that show improvement or are FDA-approved (Table 5). Methylphenidate, a dopamine transporter blocker that increases dopamine levels, seems to show mild improvement in apathy, the most prevalent disorder among the neuropsychiatric symptoms of AD [73]. Pimavanserin (Nuplazid), an inverse agonist and antagonist of 5-HT2A in serotonin neurotransmission, shows promising reduction of psychosis. Lastly, lamborexant (Dayvigo) and suvorexant (Belsomra, MK-4305) antagonizing the orexin receptor are approved for insomnia in mild to moderate AD.

Table 5. Drugs targeting non-cognitive symptoms of Alzheimer's disease

Drug name	Target and rationale	Status on clinical trial (start date–end date)	AD stage	Results	Clinical trial identifier (NCT number)
Methylphenidate	Block DAT. And increase the dopamine level	Completed phase 3, (2016–2020)	Apathy in AD	Mild improvement of apathy, measured at 6 months compared to placebo	02346201
Prazosin	Antagonist of alpha1-adrenergic receptor	Completed (2018–2022)	Moderate to severe disruptive behavior	Non-significant improvement of agitation	03710642
Pimavanserin (Nuplazid)	Inverse agonist and antagonist of 5-HT2A in neurotransmission	Completed phase 2 (2017–2019)	Probable AD who has symptoms of agitation and aggression	(1) Promising reduction of psychosis score in AD, also see [74] and (2) delay in psychosis relapse ($p < 0.05$) and a lower risk of relapse with the continuation of the drug [75]	03118947 03325556
ITI-007 (Lumateperone)	5-HT2A serotonin receptor antagonist	Terminated phase 3 (2019) due to pre-specified interim analysis indicating futility	Probably AD	Terminated	02817906
Lemborexant (Dayvigo)	Orexin receptor antagonist	Completed (2016–2020)	Mild-moderate	Approved for insomnia, lower nighttime activity, and improved circadian rhythmicity	03001557
Suvorexant (Belsomra, MK-4305)	Orexin receptor antagonist	Completed (2016–2018)	Mild-moderate	Approved for insomnia in AD, lengthened total night sleep time	02750306

AD: Alzheimer's disease; DAT: dopamine transporter; 5-HT2A: 5-hydroxytryptamine 2A

Conclusions

Considering that tau proteins correlate with AD more closely than amyloid proteins and participate in the spreading of the disease [51], current multiple ongoing anti-tau immunotherapies are working on improving safety and efficacy and might provide a cheaper affordable, and more efficacious approach in the future, compared to currently approved anti-amyloid therapy against AD. Further, the interplay between Aβ and tau pathology remains to be known, and targeting both pathways could be promising for development of effective therapeutic interventions.

Future approaches will be first, to improve the drug delivery efficiency through the blood-brain barrier, which will help to reduce the therapeutic dose and reduce side effects (e.g., [10]), and second, to discover therapeutic agents to slow down the decline of several cognitive domains including memory [11]. Further, a precision medicine approach will allow different biomarkers to target the heterogeneity in the pattern of cognitive deficits and presentation in any individual [76]. An equipotential model of AD beyond the amyloid model will warrant specific "precision" treatment to AD, targeting pathology other than amyloid or interacting with tau and amyloid pathology.

It takes 10–20 years for AD to manifest itself (e.g., [5, 69]). The best approach and current focus of attention would be to predict AD onset as early as possible through the discovery of biomarkers, and then to prevent AD from happening early on or delay the progression of AD, for example, through good diet, aerobic exercise, cognitive stimulation, and enough good quality of sleep and reduction of inflammation (e.g., reviews [10, 28]). For example, various forms of P-tau provide non-invasive cost-effective prediction as biomarkers [50].

Further, disease-modifying treatment for AD targeting tau, neuroinflammation and neuroprotective mechanisms, immunotherapies, and repurposing existing drugs are under investigation. Combination therapies targeting multiple pathways or multiple aspects of the same pathway may be the key to effective AD treatment and "precision" individualized medicine.

Abbreviations

5-HT6: 5-hydroxytryptamine 6

AD: Alzheimer's disease

APOE: apolipoprotein E

Aβ: amyloid-beta

CDR-SB: clinical dementia rating-sum of boxes

CSF: cerebral spinal fluid

MAO: monoamine oxidase

MCI: mild cognitive impairment

NMDA: N-methyl-D-aspartic acid

Declarations

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Author contributions

DX: Conceptualization, Funding acquisition, Investigation, Writing—original draft, Writing—review & editing. CZ: Conceptualization, Funding acquisition, Writing—review & editing. All authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

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Consent to participate

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