Review paper

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Treatment options for Alzheimer's Disease: An overview of the amyloid, tau, and alternate hypotheses

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Abstract
Alzheimer's disease (AD) tends to be more common in people sixty-five years of age and over. AD is a progressive brain disease that affects memory, thinking, and behavior. According to the World Health Organization (WHO), more than 50 million individuals globally suffer from AD. AD is the primary commonplace reason for dementia, a term used to explain cognitive function decline severe enough to warrant intervention on a day-to-day basis. The onset of AD is marked by gradual yet persistent challenges with language, memory loss, and confusion, which can hamper daily routines, often leaving patients increasingly reliant on continuous assistance in their personal lives. Despite concerted efforts made by scientists over years of research, a clear and definitive answer has remained elusive when isolating the exact causes of AD; it is thought that an interplay between genetic inheritance, environmental factors, and personal lifestyle choices increases susceptibility. Some individuals may carry inherited genes that heighten their vulnerability, whilst others develop AD for reasons not yet understood. The accumulation of β-amyloid proteins in the brain is posited to be a pivotal factor in AD progression, though the exact mechanisms remain to be elucidated. This article focuses on various aspects, including Neurotransmitter Dysfunction, Ca^{2+} Homeostasis Dysregulation, the Cholinergic System, Amyloid-Based Therapy, the Tau Hypothesis, Liquid-Liquid Phase Separation (LLPS), Microglia, Inflammation, CRISPR, the Lipid-Chaperone Hypothesis, Agonistic Autoantibodies, Human Mesenchymal Stem Cells, Low-Dose Ionizing Radiation, Heat Shock Proteins, Drug Repositioning, the Infection Hypothesis, Gut Microbiota, and Blood-Brain Barrier Dysfunction.

Keywords
Alzheimer’s disease, Dementia, Acetylcholinesterase, Plaque, Neurofibrillary tangles, Neurotransmitter dysfunction, BACE-1 inhibitor, Beta-amyloid, Microbiota, Neuroinflammation

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Introduction

When the world population is observed today, a significant increase in age is seen; hence there is a shift to an older population (1). This aging population is detrimentally affected by a neurodegenerative condition called Alzheimer's disease (AD), which leads to severe symptoms due to its effect on the central nervous system (1).

With over 55 million aging people, dementia is a growing global health concern (2). It is expected to double in rate until 2040, with an exponential growth rate (3). 10.7% of people older than 65 years of age and 33.2% of individuals older than 85 are affected by AD (4). The Turkish Statistical Institute (TÜİK) reported a significant 24% increase in the aging of the Turkish population over the past five years since 2021. According to TÜİK, in 2021, the Turkish elderly population will have increased to 8,245,124. The statistics on the causes of death in Turkey show that older adults who died from AD increased from 12,059 to 13,498 (5), an increase of 11% (5). This number is projected to increase with an increase in life expectancy (6). Cardiovascular disease can lead to AD both directly and indirectly (7).

AD is a ubiquitous form of dementia and neurogenerative disease. AD causes memory loss as brain cells deteriorate and eventually die. AD is classified as a psychiatric disorder as it gradually deteriorates memory and other cognitive abilities, leading to impaired independence in everyday life (1). It causes a gradual decline in remembering, thinking, and communicating. Over time, the effects become increasingly noticeable and more severe. Eventually, it can lead individuals to lose basic abilities such as those of eating and dressing. AD causes the deterioration of areas associated with memory, language, spatial perception, attention, executive functions, orientation, problem-solving abilities, and functionality, as reported by the AD and Related Disorders Association (ADRDA) and the National Institute of Neurological and Communicative Disorders and Stroke (8, 9). Apart from the cognitive challenges, AD also manifests with different neuropsychiatric and behavioral issues; depression being the most common. Alzheimer's patients typically have sleep disorders. Excessive daytime sleepiness may be observed during the early stages of AD, which leads to the quality of sleep being diminished at night.

AD is induced by plaque build-up in the brain. β-amyloid protein forms plaques in the brain. These plaques are associated with dysfunctional neurons. Another protein, called tau, forms tangled deposits around neurons, leading to the onset of AD. Some of the neuropathological changes in AD are positive and negative lesions (10). Positive lesions are distinguished by the build-up of neurofibrillary tangles, amyloid plaques, dystrophic neurites, and neuropil threads (10). Negative lesions are distinguished by atrophy (10). Overactivation of glial cells; which help protect neurons by maintaining immunological homeostatis, removing debris, and forming myelin, may also

contribute to the development of AD. The loss of glial cells can lead to memory loss which; in turn; may be related to Aβ and neurofibrillary tangles (11).

The buildup of beta-amyloid (Aβ) plaques and hyperphosphorylated tau causes inflammation in the brain, which can result in memory loss (12, 13). Hence, drugs and medications that target Aβ may be successful in treating AD. The brain's incapability to remove Aβ, rather than its accumulation, is thought to be responsible for most AD symptoms (12, 13). Since AD is more prominent in individuals over 65 years of age, aging has been assumed to be a contributing factor for AD. Aging people are thought to accrue tau tangles and Aβ plaques more than young persons (14). However, the association of tau tangles and Aβ plaques with the progression of AD remains uncertain (15, 16).

Although efforts to cure AD span decades, there are still no effective treatments to impede or restore the deterioration caused by AD. Unfortunately, there is no medicine or a treatment to cure or regress AD, as the the root cause(s) of AD still evade identification.

Discussion

Alzheimer's Disease and medication approaches

In the treatment of AD, major emphasis has been placed on amyloid and tau-targeting medicines. Some of the main factors thought to be important in the progression of AD are the accumulation of amyloid precursor protein (APP), APOE, a protein that is involved in the metabolism of lipids, and Presenilin-1, which is a protein involved in the processing of APP (17). The current research focuses on therapeutic approaches. The aim is to stop the progression of the disease, as there is currently no cure available to reverse it. Some therapeutic strategies are shown in Table 1.

Furthermore, ongoing clinical studies are exploring the use of new agents that may offer symptomatic relief. Only one new drug has been approved by the FDA for AD between 2003 and January 2023 (27-33). There are many clinical studies ongoing. The website http://clinicaltrials.gov was searched for the keywords "recruiting," "active but not recruiting," and clinical trials keywords; A total of 253 clinical studies were found (34). 52 of the studies were not yet recruiting, 201 were recruiting (34). Three; 21, 65, 31, and 119 were in early Phase I, Phase I, Phase II, Phase III, Phase 4 clinical studies and undefined respectively (34). Selected clinical studies are presented in Table 2.

Table 1. Therapeutic strategies (18-26)

Therapeutic Strategies	Mechanism	Targets	Example Treatment
Amyloid-Based Therapy	Reduction of Aβ production, Reduction of accumulation of Aβ peptides in the brain, Aβ aggregation inhibitors	Aβ peptides, amyloid fibril, α-secretase modulators, β-secretase inhibitors, anti-inflammatory agents, BACE1, γ-secretase, and APP	Aducanumab
Tau-Based	Tau phosphorylation inhibitors, tau-induced neurotoxicity	Preventing tau oligomerization, tau anti-aggregants	LMTM
Oxidative Stress	Reducing oxidative stress via antioxidant activity	Reactive Oxygen Species (ROS), Mitochondrial Dysfunction, Monoamine oxidase inhibitors	Coenzyme Q10 (CoQ10)
Modulation of Neurotransmission	Alteration of Aβ-induced neurotransmitter levels to support cognitive function	Neurotransmitters, AchE, NMDA receptor	Donepezil, Memantine

Table 2. Alzheimer's disease drug development (35-64)

Drug	Description	Phase
Verubecestat (MK- 8931)	BACE-1 inhibitor	2 and 3
Lanabecestat (AZD 3293/LY 3314814)	BACE-1 inhibitor	2 and 3
Atabecestat (JNJ-54861911)	BACE-1 inhibitor	2 and 3
Umibecestat (CNP520)	BACE-1 inhibitor	3
Elenbecestat (E2609)	BACE-1 inhibitor	3
LY3202626	BACE-1 inhibitor	2
LY2286721	BACE-1 inhibitor	1 and 2
CNP520	BACE-1 inhibitor	2
Semagacestat	γ-secretase inhibitor	3
Avagacestat (BMS-708163)	γ-secretase inhibitor	2
PBT2	Metal protein-attenuating compound (MPAC)	2 and 3
Scyllo-inositol (ELND005, AZD-103)	Aβ aggregation inhibitor	2
Acitretin	α-secretase enhancer	2
Epigallocatechin-Gallate (EGCG)	α-secretase enhancer	2 and 3
Etazolate (EHT-0202)	α-secretase enhancer	2
CT1812	sigma-2 (σ-2) receptor	Completed
Blarcamesine	sigma 1 (σ-1) receptor, M2 antagonist	2 and 3
SV2A modulator	Synaptic Vesicle Glycoprotein 2A (SV2A)	3

	modulator	
Mirtazapine	α-1 antagonist	3
Guanfacine	α-2 adrenergic agonist	3
VGL101	an agonist for TREM2	1
Relyvrio™	p-glycoprotein inhibitor	2
AAV2-BDNF	adeno-associated virus serotype 2 (AAV2) vector	1
Bryostatin 1	protein kinase C (PKC) agonist	2
Fosgonimeton (ATH-1017)	hepatocyte growth factor (HGF)/MET receptor system	2 and 3
Pioglitazone	peroxisome-proliferator activated receptor γ (PPARγ) agonists	3
Semaglutide	long-acting analog of glucagon-like peptide-1 (GLP-1)	3
ATLX-1088	targeting CD33, a cell surface protein	Pre-clinical
Docosahexaenoic acid (DHA)	Omega 3 fatty acid	4
Resveratrol	trans-3,4',5-trihydroxystilbene	3

Neurotransmitter dysfunction

Neurotransmitters are endogenous substances that facilitate communication between neurons with each other (64, 65). Neurotransmitters play a crucial role in the brain's ability to perform various functions with the process of chemical synaptic transmission (64, 65). Neurotransmitters are significant in early human development, encompassing neurotransmission, cellular differentiation, and neuronal growth (64, 65). They are stored in vesicles located in the cytoplasm of presynaptic neurons (66). They bind to receptors on the postsynaptic membrane, which allows them to transmit signals to adjoining neurons (66). Any alterations in the synthesis, storage, transportation, or breakdown of neurotransmitters can lead to neuronal dysfunction; some of which are related with AD (66).

Cognitive impairment has been linked to the death of cholinergic brain cells. Acetylcholine, which is a neurotransmitter, is found to be linked to the development of memories, and medications targeting acetylcholinesterase (AchE) can enhance acetylcholine levels (67, 68). It has been found that patients diagnosed with AD have lower levels of acetylcholine, which results from AchE inhibitors hindering the action of AchE and breaking down acetylcholine (67-69). Results suggest that AchE inhibitors increase the growth and connectivity of brain cells, as well as help to enhance the release of other neurotransmitters like dopamine and serotonin (70). The AchE breaks down acetylcholine and prevents its accumulation in the synapse (71, 72). Therefore, inhibiting the AchE enzyme is expected to lead to an accumulation of AchE in cholinergic synapses and increase cognitive function (71-73). In addition, research has

shown that administering AchE inhibitors to AD patients can improve their cognitive abilities.

Ligands have the ability to bind to a transition metal, in some cases metals, resulting in the formation of a coordination complex with the help of dative/coordinate bonds. AchE is a serine hydrolase enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine into choline and acetate (74). The active site of the enzyme is positioned in a canyon within the protein structure, lined with catalytic residues that play an integral role in enzyme activity. It is noteworthy that ligands or inhibitors can attach to either the active site or allosteric sites on the enzyme, without stearic hindrance.

Memantine, a type of N-methyl-D-aspartate (NMDA) receptor antagonist, treats dementia and AD in order to improve memory (75-78). It is effective because it prevents the release of glutamate, which is a neurotransmitter released by nerve cells (79). Hence, normal brain function is significantly dependent on normal glutamate levels. However, an excessive amount of glutamate is toxic to brain cells even contribute to death in AD patients (76, 80). By downregulating the action of glutamate, memantine has the potential to protect brain cells and improve cognitive function in AD patients (76, 80). Docetaxel, galantamine, donepezil, and rivastigmine, which are approved by FDA, are some examples of AChE inhibitors that help to increase acetylcholine levels.

Lower than normal levels of the neurotransmitter acetylcholine may exist in Alzheimer's patients. AChE inhibitors improve central cholinergic neurotransmission and alleviate the decline in cognition during the first year of treatment. The effect of AchE inhibitors is dependent on the stage of detection of disease. A lag time of six months between disease onset and administration significantly decreased drug efficacy (81). In randomized placebo-controlled trials lasting up to 52 weeks, all three AChE inhibitors demonstrated their effectiveness in stabilizing cognitive function and improving the quality of life (81, 82).

NMDA receptors facilitate nerve impulse transmission, but their hyperactivity has been associated with the death of brain cells (75). Memantine suppresses this hyperactivity, thus presenting an opportunity to shield nerve cells from deterioration while potentially enhancing cognitive abilities such as memory retention and learning improvement. There are many ongoing studies supporting the use of memantine as an agent which promotes neuroprotection (83).

An example of a memantine structure can be seen in Figure 1. Memantine, or 1-amino-5-(dimethylamino) adamantane, is a primary aliphatic amine that is derived from the 3,5-dimethyl form of adamantane (84). Memantine has 12 carbon atoms, 21 hydrogen atoms, and 1 nitrogen atom (84). Memantine is able to attach to certain receptors in the brain and affects brain function because of two key components:

the amine group and the methyl group (84). It has a three-ring structure with a primary aliphatic amine (85). An example of a memantine structure can be seen in Figures 1 and 2.

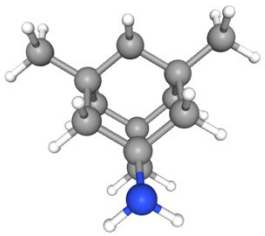

Figure 1. 3D Memantine Structure (84)

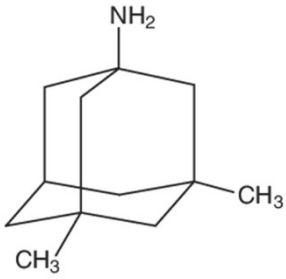

Figure 2. Memantine (73)

Memantine, which has been available since 1989, is available for moderate to severe AD in the United States, Canada, Europe, Germany, China, Japan, and many other countries (86). In the United States, memantine is offered in the form of extended-release capsules; 5 mg being the initial dose, which can be increased to 28 mg (86, 87). Each dose level is maintained for a minimum of one week (87).

BI-409306, which is also known as SUB-166499, is an inhibitor of phosphodiesterase 9A (PDE9A), which increases the brain levels of cyclic guanosine monophosphate (cGMP) (88). cGMP is formed from the neurotransmitters nitric oxide and glutamate. The pathway involved in modulating synaptic transmission and plasticity in the hippocampus and cerebral cortex is diminished in AD patients (88, 89). Two separate Phase 2 trials were initiated for a period of three months (90, 91). In one study, 288 individuals with mild to moderate AD who had not taken a cholinesterase inhibitor or memantine in the previous three months were divided into four groups receiving different doses of BI 409306, while another group received a placebo (90, 91). No significant changes were observed between the drug and placebo groups; hence, this compound was discontinued as an AD treatment (90, 91).

Another drug is Brexpiprazole, a dopamine receptor D2 partial agonist. It was approved for the treatment of Schizophrenia and AD in April 2023 (92). For AD, it is used for agitation and other behavioral symptoms. However, it has common adverse effects, such as insomnia. Phase 3 trials were conducted in 2018; a three-month trial commenced, evaluating the effects of daily doses of 2 and 3 mg of brexpiprazole compared to a placebo (93). The trial involved 345 patients with Alzheimer's disease and was conducted in both the United States and Europe

(93). Brexpiprazole has a favorable safety profile and was well-tolerated, as no noticeable rise in adverse events was observed in the treatment arm when compared with placebo (93). However, in Phase 3 studies, there were a higher number of deaths in the treatment groups compared to the placebo group, but none were related to the drug (93). Rexulti^{R} has been tested since 2019 in the treatment of Schizophrenia (94). The drug was tested in a group of 300 individuals in the Philippines who were diagnosed with Schizophrenia and major depressive disorder (94). The results will be published in 2024 (94).

Riluzole, Rilutek^{R}, is another drug that targets neurotransmitters. It is one of the first FDA-approved medications for amyotrophic lateral sclerosis (ALS) (95). Riluzole is a neuroprotective drug that acts by inhibiting glutamatergic neurotransmission; it blocks the release of glutamic acid from cultured neurons (96). It protects the motor neuron cells from excitotoxicity. In a Phase 2 study conducted by Rockefeller University, compared to individuals receiving a placebo, patients treated with Riluzole experienced a significantly lower decline in glucose metabolism within the posterior cingulate (95, 97).

Table 3. Neurotransmitter related drugs Phase 1 (94-99)

Drug	Company	Therapy Type
ALX-001	Allyx Therapeutics, Inc.	Small Molecule
SUVN-G3031	Suven Life Sciences Ltd	Small Molecule

Table 4. Neurotransmitter related drugs Phase 2 (99-110)

Drug	Company	Therapy Type
Vafidemstat	Oryzon Corporate	Small Molecule
SAGE-718	Sage Therapeutics, Inc.	Small Molecule
Rotigotine	UCB S.A.	Small Molecule
Riluzole/Rilutek^{R}	Sanofi	Small Molecule
Rasagiline	Teva	Small Molecule
Piromelatine	Neurim Pharmaceuticals Ltd.	Small Molecule
ORM-12741	Orion Pharma	Small Molecule
Dronabinol	AbbVie, Others	Small Molecule
Dexpramipexole	Biogen, Knopp Biosciences LLC, Virginia Commonwealth University	Small Molecule
Cannabidiol		Small Molecule
Atomoxetine	Eli Lilly & Co.	Small Molecule
Allopregnanolone		Small Molecule

Table 5. Neurotransmitter related drugs Phase 3 (99, 111-118)

Drug	Company	Therapy Type
Mirtazapine		Small Molecule
Masupirdine	Suven Life Sciences Ltd	Small Molecule
Lumateperone	Bristol-Myers Squibb, Intra-Cellular Therapies, Inc.	Small Molecule
Guanfacine		Small Molecule
Citalopram		Small Molecule
Aripiprazole	Bristol-Myers Squibb, Otsuka Pharmaceutical Co., Ltd.	Small Molecule
AVP-786	Avanir Pharmaceuticals, Concert Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd.	Combination, Small Molecule

Table 6. Neurotransmitter related drugs Discontinued (99, 119-124)

Drug	Company	Therapy Type
Xaliproden	Sanofi	Small Molecule
Troriluzole	Biohaven Pharmaceuticals	
Suritozole	Aventis Pharmaceuticals, Inc.	Small Molecule
Sembragiline	Evotech AG	Small Molecule
SGS-742	Novartis Pharmaceuticals Corporation	Small Molecule
SB 202026		Small Molecule
S47445	Cortex Pharmaceuticals, Inc., Servier	Small Molecule
S 38093	Servier	Small Molecule
PXT864	Pharnext	Combination, Small Molecule
PF-05212377	Pfizer	Small Molecule
Neramexane	Forest Laboratories, Inc., Merck	Small Molecule
NS2330	NeuroSearch A/S	Small Molecule
Intepirdine	Axovant Sciences Ltd	Small Molecule
Idalopirdine	Lundbeck, Otsuka Pharmaceutical Co., Ltd.	Small Molecule
Iclepertin	Boehringer Ingelheim	Small Molecule
ABT-288	AbbVie	Small Molecule
Besipirdine HCl	Aventis Pharmaceuticals, Inc.	Small Molecule
CX516	Cortex Pharmaceuticals, Inc.	Small Molecule

Ca^{2+} homeostasis dysregulation

Numerous studies have suggested a connection between modified Ca^{2+} homeostasis and the process of brain aging. Ca^{2+} is an essential controller of neuronal fate; thus, intracellular Ca^{2+} homeostasis must be carefully regulated in physiological conditions (203). Through plasma membrane channels, neuronal cells predominantly allow for the entry of calcium ions (Ca^{2+}). Upon successful internalization,

Ca^{2+} ions undergo regulation and buffering processes facilitated by crucial Ca^{2+} binding proteins as well as diverse organelles residing within the neuron (125). Several studies have demonstrated that disruptions in the Ca^{2+} balance are one of the initial steps in the series of changes that occur in neurons leading to the harmful effects caused by misshapen Aβ aggregates and hyperphosphorylated tau. The mechanisms responsible for neuronal Ca^{2+} dysregulation in AD are not completely understood. Recent studies suggest that the presence of mutated presenilin-2 (PS2) or APP may play a role in the calcium dysregulation and pathogenesis of AD. This is believed to occur through the over-activation of the ryanodine receptor (RYR37) (126-128). Overactivation of the RYR and dysregulated release of calcium from the endoplasmic reticulum may play pivotal roles in AD. It is worth noting that targeting the inhibition of ryanodine receptors' excessive activation could be a potential strategy in treating AD. Dantrolene, a well-known antagonist of the RYR, is widely utilized in the medical field to clinically address conditions such as malignant hyperthermia, muscle spasms, and neuroleptic malignant syndrome (129). Dantrolene has been shown to alleviate amyloid pathology, synaptic damage, and memory decline in different tissue cultures and animal models of AD. Thus, Dantrolene may hold promise as a potential medication to counteract calcium dysregulation and address cognitive dysfunction associated with AD. Dantrolene has the ability to modulate RyR-mediated Ca^{2+} release and also regulate the activities of β and γ secretases (130). Consequently, this modulation results in a decrease in Aβ production.

New therapeutic agents targeting Voltage-Gated Calcium Channels (VGCC) are potential AD treatment options in multi-targeted approaches (131). It was found that selective calcium influx through L-type calcium channels was linked with increased production of Reactive Oxygen Species (ROS) and neuron death (131). Recently, Michalska et al. developed a new class of 4,7-dihydro-2H-pyrazolo[3,4-b] pyridine compounds that selectively block L-type calcium channels, have anti-inflammatory properties, and inhibit GSK-3b (131). These compounds were tested on *in vitro* neurodegeneration models exposed to oxidative stress from rotenone, hyperphosphorylation from okadaic acid (OA), and heightened cytosolic calcium concentrations from potassium (131). All the variations of 4,7-dihydro-2H-pyrazolo[3,4-b] pyridine provided neuroprotection against calcium overload, enhancing survival rates (131). The most potent neuroprotective compound showed moderate VGCC-blocking ability and high antioxidant potential, highlighting the relationship between VGCC-driven calcium influx and increased ROS levels (131). Moreover, the compounds were examined in an *ex vivo* AD model, where one particular compound showed neuroprotective capabilities against oxidative stress and cytosolic calcium overload in OA-treated hippocampal slices (131).

Cholinergic system

The Cholinergic system is a vital branch of the nervous system, playing an essential role in memory, digestion, regulation of heart rate, blood pressure, movement, and other functions (132). The system includes acetylcholine (ACh), cholinergic receptors (AChRs), choline acetyltransferase (ChAT) enzyme, and acetylcholinesterase (AChE) enzyme (133). These neurotransmitters play a crucial role in immune response and in maintaining homeostasis (133).

Indirect and direct are two categories of cholinergic drugs. Direct-acting cholinergic agonists function by directly binding to and stimulating the muscarinic receptors (134). Direct-acting cholinergic agents are choline esters and alkaloids (291). Indirect cholinergic agents increase drug receptor engagement at the cholinergic receptors; these include reversible and irreversible agents (134).

Donepezil, an acetyl cholinesterase inhibitor, is approved in the United States for all the stages of AD; however, in the EU and Japan, the medication is approved for mild-to-severe AD patients (135, 136). It increases the availability of the acetylcholine in cholinergic synapses, which improve cholinergic transmission. A sustained-release tablet version weighing 23 mg has been authorized for the management of moderate to severe AD; this tablet is given to patients who have already been taking a 10 mg dose for a minimum of three months, and it is administered once (137).

Galantamine, an alkaloid isolated from Galanthus nivalis, is approved in the United States for mild-to-moderate AD; for the EU, it is mild-to-moderately severe AD; and in Japan, mild-to-moderate AD (138, 139). Rivastigmine has been approved for use in 60 countries (140). The oral formulation is suitable for patients with mild to moderate AD, and the patch can be used for all stages of AD (141). It is also used for Parkinson's disease. Some of the side effects are diarrhea, vomiting, and nausea.

The alpha-7 nicotinic acetylcholine receptor is a new drug class for the treatment of symptomatic AD (142). These receptors, which are connected to cognitive processes, are now crucial drug targets in managing symptomatic Alzheimer's. Aβ peptides have a high affinity for these receptors (143). Activating alpha-7 nicotinic acetylcholine receptors, the structure can be seen in Figure 3, have lowered the number of amyloid plaques in the brain (144, 145).

Encenicline is a pro-cognitive oral active agent (Figure 3) that has been tested in clinical trials and shown to work at nanomolar concentrations (149). It is an alpha-7 nicotinic acetylcholine receptor (α7 nAChRs) agonist (150). Encenicline presents a promising solution for addressing the various ailments that stem from cognitive impairment, which span from AD to schizophrenia and Parkinson's disease (150). While research has validated its efficacy in improving memory function,

clinical trials have been discontinued due to gastrointestinal toxicity (150).

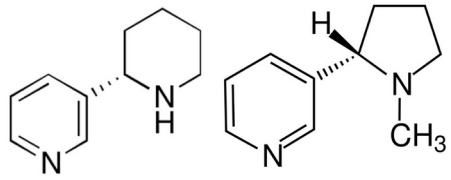

Figure 3. alpha-7 nicotinic acetylcholine (145-148)

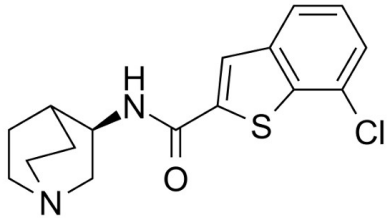

Figure 4. Encenicline (EVP-6124) (151)

Table 7. Cholinergic System related drugs (99, 144, 152-158)

Drug	Company	Therapy Type	Phase
BPN14770	Shionogi Pharma, Tetra Therapeutics	Small Molecule	2
Memogain ALPHA-1062	Alpha Cognition, Galantos Pharma	Small Molecule	3
KarXT	Karuna Therapeutics	Combination, Small Molecule	3
Donepezil	Corium, Inc., Eisai Co., Ltd., Pfizer	Small Molecule	Approved
Galantamine	Janssen, Ortho-McNeil Pharmaceutical, Sanochemia Pharmazeutika, Shire, Takeda Pharmaceutical Company	Small Molecule	Approved
Rivastigmine	Pfizer, Shionogi Pharma	Small Molecule	Approved
Varenicline	Pfizer	Small Molecule	Discontinued
S 38093	Servier	Small Molecule	Discontinued
Physostigmine Salicylate	Forest Laboratories, Inc.	Small Molecule	Discontinued
PF-06852231	Pfizer	Small Molecule	Discontinued
Nelonicline	AbbVie	Small Molecule	Discontinued
Nefiracetam	Daiichi Sankyo Pharmaceuticals	Small Molecule	Discontinued

Milameline	Aventis Pharmaceuticals	Small Molecule	Discontinued
Metrifonate		Small Molecule	Discontinued
Ladostigil	Avraham Pharmaceuticals Ltd	Small Molecule	Discontinued
Eptastigmine	Mediolanum	Small Molecule	Discontinued
Encenicline	FORUM Pharmaceuticals Inc	Small Molecule	Discontinued

Amyloid based therapy

Two enzymes called β-secretase and γ-secretase break down a protein in the brain called amyloid precursor protein into fragments termed as Aβ peptides. AD has been linked to these Aβ peptides. Consequently, these enzymes have been identified by researchers as potential targets for AD curative drugs.

Initial trials of β-secretase-targeting drugs have ceased due to their incapability of penetrating the blood-brain barrier and causing liver toxicity (150, 159). Despite these challenges, researchers still hold out hope for developing a more effective cure that exclusively targets this specific enzyme.

The drug Verubecestat hinders the function of β secretase 1 (BACE1), an enzyme which is responsible for synthesizing amyloid beta peptides that may lead to plaque buildup in the brain and contribute to AD (14, 36). During preclinical trials, it demonstrated potent inhibitory efficacy against BACE1 by effectively decreasing its activity (160). It was also able to stop the development of amyloid plaques in mice and primates, implying that it could slow or protect against the progression of AD in humans (160). However, it did not show efficacy in clinical trials (14). As a result, the development of Verubecestat as a treatment for AD was stopped.

The inhibition of γ-secretase is a secondary target. Inhibitors developed against this target have many undesirable side effects due to their ability to disrupt notch signaling, which is vital for cells (161). The most interesting of these is that these inhibitors can inhibit learning as a side effect in Alzheimer's patients (162). Therefore, more selective inhibitors of γ-secretase are being developed that are less disruptive to notch signaling, which would reduce these undesirable side effects while still targeting the enzyme. Figures 5 and 6 show the structure of some of these selective inhibitors.

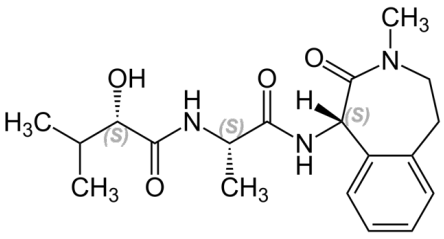

Figure 5. Semagacestat (163)

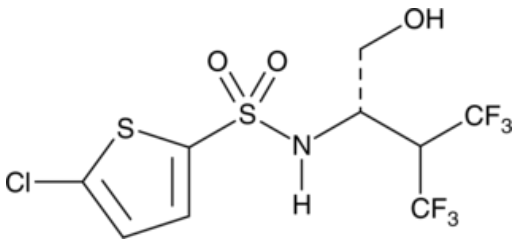

Figure 6. Begacestat (164)

The motivation to develop these specific inhibitors is to block the activity of the γ-secretase enzyme in specific signaling pathways. However, because the γ-secretase enzyme performs multiple functions in the body, inhibiting it may have unintended consequences on other systems and processes.

The liver is an important organ that performs several critial functions, including that of detoxification. However, utilizing γ-secretase inhibitors may interfere with liver function and potentially cause off-target effects (164). These inhibitors also cause a range of side effects like headaches or digestive disturbances, including nausea, vomiting, or stomach burns (164). Additionally, they also interact unfavorably with other drugs.

Tarenflurbil is one of the most well-known γ secretase modulators and is the R isomer of flurbiprofen, which is a nonsteroidal anti-inflammatory drug (NSAID) (165). Tarenflurbil lacks cyclooxygenase inhibitor activity, which means that it does not inhibit the enzyme cyclooxygenase, which is involved in the production of prostaglandins (165). While Tarenflurbil has not been authorized as an AD treatment option yet, researchers have studied its potential for this application with interest (166). Preliminary research suggests that Tarenflurbil could successfully reduce β-amyloid plaque build-up inside the brain.

BAN2401 is a humanized version of the mAb158 mouse antibody that selectively targets large, soluble Aβ protofibrils. This treatment was developed following the discovery of the “arctic” mutation in the APP gene, which causes a form of AD characterized by high levels of Aβ protofibrils and few amyloid plaques (167).

The U.S. FDA granted accelerated approval for Leqembi^{R} (lecanemab-irmb) for the treatment of AD, a significant step forward in combatting the debilitating condition (168, 169). As a result, Leqembi^{R} is the second medicine designed to combat AD from a new perspective, seeking to take on the root of the disorder (58, 84). Researchers evaluated Leqembi^{R}'s efficacy in a double-blind, placebo-controlled, parallel-group, dose-finding phase III study of 856 patients with AD (168). Patients with early-stage cognitive impairment and dementia, along with Aβ pathology, were given treatment (168, 170). Those receiving treatment showed a clear relationship between the dose of lecanemab and the rate of decrease in Aβ plaque (170). Patients on the accepted dosage regimen (10 milligrams per kilogram every two weeks) demonstrated a decrease in amyloid plaque in the brain from the start to week 79, contrasted with the placebo arm, which experienced no reduction (170). Treatment with lecanemab caused a decrease in Aβ in the brain and a consistent improvement in cognitive function, assessed using various clinical and biomarker measures (170). The evidence indicated that even after the disappearance of Aβ in the brain, continuous dosing was still needed (170). Additionally, biomarkers from blood tests could help monitor the effects of lecanemab treatment.

The Phase 3 trial results suggest that the drug has the potential to prevent the progression of AD, yet it is connected with some severe adverse reactions, such as brain swelling and bleeding (171). The results demonstrate that roughly 6.9% of participants in the lecanemab trial, who were given an intravenous infusion, discontinued the trial as a result of adverse effects; this was compared to 2.9% of those given a placebo (171). However, a similar number of patients experienced serious adverse events in the lecanemab and placebo groups (171).

Individuals taking lecanemab should not receive acute thrombolytic treatment but may continue to take common antiplatelet medications, such as aspirin or clopidogrel. APOE genotyping should be performed before treatment so that doctors can discuss risks with patients, but treatment is still permitted for individuals with two copies of the APOE4 gene (171).

Gantenerumab targets both the N-terminal and central amino acids of Aβ. The drug works by breaking down and removing amyloid plaques by attracting microglia and activating their ability to engulf and destroy the plaques. Brainshuttle, known as RO7126209, was developed by Roche to treat AD (172). It is a fully human antibody that binds to a specific structure on Aβ fibrils with high affinity. It was designed to increase the delivery of therapeutic antibodies across the blood-brain barrier by using a receptor-mediated transcytosis mechanism (173). Brainshuttle also targets and removes Aβ plaques (173). The compound RO7126209 circulating in the blood binds to the transferrin receptor found on the endothelial cells forming the blood-brain barrier (BBB) (174). As a result, it undergoes endocytosis and is subsequently released into the brain parenchyma. The target of the medicine is amyloid-related. A study was completed in July 2020 with an actual enrollment of 34 (173, 174). Doses ranging from 0.1 to 7.2 mg/kg demonstrated a direct correlation between the concentrations of RO7126209 in the blood plasma and cerebrospinal fluid (CSF) (174). The compound exhibited a plasma half-life of three to six days. Notably, RO7126209 had a CSF/plasma ratio of 0.8 percent, which was eight times greater than that of gantenerumab. No anemia or hematology-related safety issues were observed (173, 174). A phase 1 trial commenced to assess various doses of the treatment in a group of 120 individuals diagnosed with prodromal or mild to moderate AD, all of whom had a positive amyloid PET scan (173, 174). The trial is expected to continue until January 2025 (173, 174).

GV-971, or sodium oligomannate, is a combination of oligosaccharides derived from the marine algae *Ecklonia kurome* is utilized in China as a therapeutic approach for AD, developed by Shanghai Green Valley Pharmaceuticals and approved in 2019 in China in order to enhance cognitive function (175, 176). The target type of GV-971 is amyloid-related. The predominant binding mechanism of GV-971 to Aβ is likely

attributed to the multisite electrostatic interactions between the carboxylic groups of GV-971 and the three histidine residues present in Aβ40/Aβ42. GV-971's impact on Aβ aggregation is primarily influenced by factors other than dynamic alterations (177). A clinical trial was registered to compare the effectiveness of GV-971 with donepezil in 150 patients diagnosed with mild to moderate AD; the trial is expected to last until 2024 (178).

Donanemab is another biological drug that is developed from mouse mE8-IgG2a. It is an IgG1 monoclonal antibody that targets amyloid (179, 180). Donanemab is based on directly targeting deposited plaque, but other strategies have had a low affinity to sediment amyloid plaques (179). In 2014, studies demonstrated that donanemab diminished both cored and diffuse plaques (181). In the Phase 1 study, the administration of the 10 mg/kg dose resulted in a reduction of amyloid deposits (179). However, in this trial, most patients developed antibodies against the drug (179). A Phase 2 study, which focused on the evaluation of safety, tolerability, and efficacy was conducted (179). The outcome was the change observed in the Integrated Alzheimer's Disease Rating Scale (iADRS), cognitive and functional evaluations designed for early-stage AD (182). In 2021, this clinical trial, termed TRAILBLAZER-ALZ successfully achieved its primary goals. Donanemab showed a 32 percent decrease in the decline in the iADRS compared to placebo (179). Mintun et al. reported that donanemab prolonged the rate of build-up of tau neurofibrillary tangles (183). In early 2023, donanemab's accelerated approval application was rejected by FDA due to inadequate safety data (184). The company Eli Lilly revealed that initial outcomes for Trailblazer-ALZ2 are promising (185). During the Phase 3 trial, the treatment showed a 40 percent reduction in the rate of decline on the primary measure of iADRS (179). AD patients receive donanemab through an IV infusion once a month (185). It was found that donanemab not only decreases tau concentrations in the blood, but it is more effective at removing Aβ compared to Leqembi^{R} and Aduhelm^{R} (186). Tables 8, 9 and 10 list various amlyoid related drugs in Phase 1, 2, and 3 clinical trials respectively. Tables 11 and 12 list approved and discontinued drugs.

Table 8. Amlyoid related drugs Phase 1 (99, 172, 187-197)

Drug	Company	Therapy Type
Trontinemab/ Brain Shuttle Gantenerumab	Hoffmann-La Roche	Immunotherapy (passive)
PRX012	Prothena	Immunotherapy (passive)
MemorEM Transcranial Electromagnetic Treatment	NeuroEM Therapeutics, Inc.	Procedural Intervention
MEDI1814	AstraZeneca, Eli Lilly & Co.	Immunotherapy (passive)
LX1001	Lexeo Therapeutics	DNA/RNA-based

IBC-Ab002	ImmunoBrain Checkpoint	Immunotherapy (passive)
DNL919	Takeda Pharmaceutical Company	Immunotherapy (passive)
CpG 1018^{R}	Dynavax Technologies	Immunotherapy (active), DNA/RNA-based
Contraloid	Priavoid GmbH	Small Molecule
AV-1959D		Immunotherapy (active)
ALZ-101	Alzinova AB	Immunotherapy (active)
ALX-001	Allyx Therapeutics, Inc.	Small Molecule
ALN-APP	Alnylam Pharmaceuticals, Inc.	DNA/RNA-based
ACU193	Acumen Pharmaceuticals, Inc.	Immunotherapy (passive)

Table 9. Amlyoid related drugs Phase 2 (53, 99, 198-209)

Drug	Company	Therapy Type
Varoglutamstat	Probiodrug AG, Vivoryon Therapeutics N.V.	Small Molecule
UB-311	United Neuroscience, Vaxxinity	Immunotherapy (active)
PBT2	Prana Biotechnology Limited	Small Molecule
Nasal Insulin		Small Molecule
NIC5-15	Humanetics Pharmaceuticals Corporation	Small Molecule, Supplement, Dietary
Levetiracetam	UCB S.A.	Small Molecule
Lenalidomide	Celgene Corporation	Small Molecule
CT1812	Cognition Therapeutics Inc.	Small Molecule
Buntanetap	Annovis Bio	Small Molecule
Bexarotene/ Targretin^{R}	Ligand Pharmaceuticals, Inc., ReXceptor Inc.	Small Molecule
Acitretin	Actavis, Allergan plc	Small Molecule
ACI-24	AC Immune SA	Immunotherapy (active)
ABvac 40	Araclon Biotech	Immunotherapy (active)
ABBV-916		Immunotherapy (passive)

Table 10. Amlyoid related drugs Phase 3 (99, 210-214)

Drug	Company	Therapy Type
Solanezumab	Eli Lilly & Co.	Immunotherapy (passive)
Simufilam	Cassava Sciences	Small Molecule
Sensory Stimulation Systems	Cognito Therapeutics, Inc.	Combination, Procedural Intervention
Remternetug	Eli Lilly & Co.	Immunotherapy (passive)
Donanemab	Eli Lilly & Co.	Immunotherapy (passive)

ALZT-OP1	AZTherapies, Inc.	Combination, Small Molecule
ALZ-801	Alzheon Inc.	Small Molecule

Table 11. Amlyoid related drugs Approved (168, 169, 215)

Drug	Company	Therapy Type
Aduhelm[R]	Biogen, Neurimmune	Immunotherapy (passive)
Leqembi[R]	BioArctic AB, Biogen, Eisai Co., Ltd.	Immunotherapy (passive)

Table 12. Amlyoid related drugs Discontinued (37, 42, 99, 216-226)

Drug	Company	Therapy Type
Verubecestat	Merck	Small Molecule
Vanutide cridificar	Janssen	Immunotherapy (active)
Umibecestat	Amgen, Inc., Novartis Pharmaceuticals Corporation	Small Molecule
Thalidomide/Thalomid[R]	Celgene Corporation	Small Molecule
Semagacestat	Eli Lilly & Co.	Small Molecule
SAR228810	Sanofi	Immunotherapy (passive)
RG7129	Roche	Small Molecule
Ponezumab	Pfizer	Immunotherapy (passive)
PF-06751979	Pfizer	Small Molecule
PF-06648671	Pfizer	Small Molecule
Lu AF20513	Lundbeck, Otsuka Pharmaceutical Co., Ltd.	Immunotherapy (active)
Lanabecestat	AstraZeneca, Eli Lilly & Co.	Small Molecule
LY3202626	Eli Lilly & Co.	Small Molecule
LY2886721	Eli Lilly & Co.	Small Molecule
LY2599666	Eli Lilly & Co.	Immunotherapy (passive)
Gantenerumab	Chugai Pharmaceutical Co., Ltd., Hoffmann-La Roche	Immunotherapy (passive)
Gammagard[R]	Baxter Healthcare	Immunotherapy (passive)
Flurizan[TM]	Myriad Genetics & Laboratories	Small Molecule

Tau Hypothesis

The tau hypothesis is a theory that states that abnormalities in tau proteins are a significant root cause of AD (227). According to this theory, neurofibrillary tangles, a characteristic of AD, are produced due to the accumulation of tau protein in the brain (227). By recognizing how tau proteins operate in the brain, researchers hope to target the unusual accumulation of tau proteins, which might assist in delaying or perhaps stopping the start of AD. As a result, some researchers have concentrated on developing medications that target tau protein in order to treat AD.

Medications targeting Aβ formation are more complex than medicines based on the tau hypothesis. Tau is bound to microtubules and facilitates neuronal transport; it detaches from microtubules and aggregates into knots in AD. The separation of microtubules and tau is the cause of the decrease of neuronal transportation (228). AD progression involves significant changes within proteins like tau - one such transformation being phosphorylation (or addition of phosphate ions) (229). During this process, there is an increase in the number of inserted phosphates (hyperphosphorylated). This condition is thought to result in damaging effects such as decreased neuron function or continuous deficiency due to the build-up of tau tangles (229).

Anti-tau therapies are in development concentrating on enzymes involved in the hyperphosphorylation and dephosphorylation of tau (229). Protein kinases are among the candidate enzymes that may modify the phosphorylated state of tau protein and interrupt or reverse its formation into tangles (229). By selectively targeting these enzymes' activity levels, may be disrupted (229). In particular, scientists have highlighted how crucial an event is related to tau phosphorylation during the onset of this disease. Certain enzymes, either acted upon by phosphatases or kinases, can phosphorylate or de-phosphorylate tau. One of these enzymes is glycogen synthase kinase 3β; a tau-kinase (150). The drug Tideglusib (Figure 7) acts by blocking the action of this enzyme, hence reducing the excessive phosphorylation of tau protein.

Clinical research on tideglusib indicates its utility as a glycogen synthase kinase three inhibitor (150). Nevertheless, there has been no evidence of its potential to treat AD or related conditions (150).

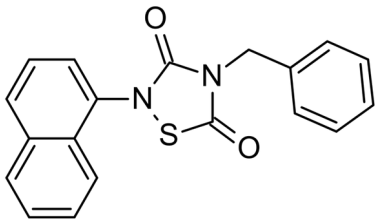

Figure 7. Tideglusib (230)

Microtubule-stabilizing agents may also provide clinical benefits in the treatment of AD. Paclitaxel, a medicine that is used to treat different cancers, cannot be used due to its side effects, but clinical trials have been initiated for TPI 287, a taxane derivative with good BBB penetration, for AD. A Phase 1 study of TPI 287 was initiated by UCSF, involving 66 patients with a primary four-repeat tauopathy. Due to the challenge of finding patients with these uncommon tauopathies, the enrollment target was reduced to 44 (231, 232). This group

of patients did not experience any allergic reactions (232). However, TPI 287 caused an increase in falls among corticobasal degeneration and progressive supranuclear palsy patients, and there was a dose-related worsening in the Clinical Dementia Rating-sum of boxes after three months (232).

Methylthioninium is another treatment that precludes tau protein tangles from forming in the brain. It has two distinctive chemical states: an oxidized state, as well as a minimized/reduced state. The even more stable oxidized methylene blue is likewise referred to as the chloride salt of the color (233). The oxidized type of methylene blue is considered to be the active type of medicine and is believed to engage with tau proteins preventing them from forming tangles in the brain (233). However, methylthioninium's insolubility has thus far prevented its use as a tau inhibitor. Consequently, an additional medicine called TRx0237 was developed as a second-generation inhibitor; however this was discontinued (234). TRx0237 was not effective in individuals with mild-to-moderate Alzheimer's conditions (234). TauRx initiated a Phase 3 trial with the goal of enrolling 180 individuals with all-cause dementia and AD. The trial was conducted in 55 North America, Belgium, Poland, and the United Kingdom sites (235). The study's primary outcomes were 18F-FDG-PET imaging and safety, while secondary outcomes included structural MRI, as well as assessments of cognition and daily living activities (235).

Another study evaluated the safety and effectiveness of TRx0237 at doses of 16 mg/day and 8 mg/day in treating patients with AD, in comparison to a placebo (236). There are 598 participants in the study. The primary outcome measure will be evaluated in the group receiving TRx0237 at a dose of 16 mg/day, in comparison to the group receiving a placebo (236). The scores on this scale range from 0 to 78 (236). On this scale, scores range from 0 to 78, with higher numbers indicating a more favorable outcome, meaning lower levels of impairment. However, no results have been announced yet (236). Tables 14, 15 and 16 list Tau related drugs in phase I, II and III clinical trials respectively. Table 17 is a list of discontinued drugs.

Table 14. Tau related drugs Phase 1 (99, 237-243)

Drug	Company	Target Type
APNmAb005	Aprinoia Therapeutics	Immunotherapy (passive)
ASN51	Asceneuron SA	Small Molecule
BIIB080	Biogen, IONIS Pharmaceuticals	DNA/RNA-based
BIIB113	Biogen	Small Molecule
Lu AF87908	Lundbeck	Immunotherapy (passive)
MK-2214	Merck	Immunotherapy (passive)
NIO752	Novartis Pharmaceuticals Corporation	DNA/RNA-based

OLX-07010	Oligomerix, Inc.	Small Molecule
PRX005	Bristol-Myers Squibb, Prothena	Immunotherapy (passive)

Table 15. Tau related drugs Phase 2 (244-249)

Drug	Company	Target Type
Semorinemab	AC Immune SA, Genentech, Hoffmann-La Roche	Immunotherapy (passive)
LY3372689	Eli Lilly & Co.	Small Molecule
Bepranemab	Hoffmann-La Roche, UCB S.A.	Immunotherapy (passive)
ACI-35	AC Immune SA, Janssen	Immunotherapy (active)
AADvac1	Axon Neuroscience SE	Immunotherapy (active)

Table 16. Tau related drugs Phase 3 (236)

Drug	Company	Target Type
LMTM/ TRx0237	TauRx Therapeutics Ltd	Small Molecule

Table 17. Tau related drugs Discontinued (250-256)

Drug	Company	Target Type
BIIB076	Biogen, Eisai Co., Ltd., Neurimmune	Immunotherapy (passive)
Epothilone D	Bristol-Myers Squibb	Small Molecule
Tideglusib	Zeltia Group	Small Molecule
Rember^{R}	TauRx Therapeutics Ltd	Small Molecule
Gosuranemab	Biogen, Bristol-Myers Squibb	Immunotherapy (passive)
Tilavonemab	AbbVie, C2N Diagnostics, LLC	Immunotherapy (passive)
Zagotenemab	Eli Lilly & Co.	Immunotherapy (passive)

Liquid-liquid phase separation (LLPS)

Liquid-liquid phase separation (LLPS) is a phenomenon that is observed in the formation of membraneless organelles in eukaryotic cells (257). LLPS occurs when there are weak intermolecular interactions (258). Any disruption in LLPS, can result in irreversible solidification. Infectious diseases, cancers, and neurodegenerative diseases are related with biocondensation through anomalous LLPS (257, 259-261). These disorders are typified by the pathological accumulation of certain proteins, such as tau protein, which have been verified to undergo the LLPS process (257, 259). Tau protein, under normal conditions, has been demonstrated to undergo in the LLPS process (262). Tau transforms from a gel-like state into abnormal protein tangles, in the event of abnormal LLPS. The substance then tests positive for thioflavin-S, a methylation of dehydrothiotoluidine with sulfonic acid produces a homogenous mixture used in

protein aggregation biophysical studies, indicating that the β-pleated sheet structure found in tau is formed in the body (263, 264). Protein aggregation can occur through LLPS, hence leading to the development of neurogenerative disease. Furthermore, tau droplet have been shown to biocondense into insoluble aggregates, which may cause AD (257). According to Boyko and Surewicz, the tau proteins form biocondensates *via* the mechanism of LLPS (265). RNAs undergo phase separation in order to form liquid-like compartments (257). Awry LLPS processes can cause plaque formation, which is commonly seen in AD (257, 263).

Tau proteins are different from other phase-separated proteins such as FUS and TDP-43, which contain a typical Low Complexity Domain (LCD) (257, 259). Instead of having a typical LCD, tau protein is an intrinsically disordered protein (IDP), displaying a heterogeneous charge distribution along its sequence (257, 259, 266, 267). Tau protein has a highly flexible structure; the absence of a clear tertiary structure enables tau protein to engage in a multitude of interactions with other molecules, thereby facilitating tau phase separation (257, 259). This flexibility originates from high glycine and proline content (257, 259). The phase separation of tau is increased by the electrostatic interactions occurring among its diverse regions (257, 259, 262, 268, 269). LLPS process of various proteins is modulated by Post-Translational Modifications (PTMs) (257, 259). This modulation occurs by interactions of proteins with other cellular components. PTMs take place by phosphorylation, ubiquitination, and acetylation (270). These protein modifications ultimately lead to aggregation (270). It has been shown that PTMs influence the tendency of tau protein to undergo phase separation (271).

Phase separation and its associated changes can cause neurotoxicity. There is a relationship between RNAs and tau phase separation and oligomerization (272, 273). Tau may result from changes in RNA metabolism (257, 259). MicroRNAs and antisense oligonucleotides (ASO), genes coding proteins such as T-cell intracellular antigen-1 (TIA1) and Alpha-Synuclein (α-Syn) may be helpful in preventing tau toxicity (274-276). Targeting cations such as Zn^{2+} and Fe^{3+} may be beneficial as these metals are found in increased concentrations in patients with AD. Hence, targeting regulators or elements may have a beneficial impact on abnormal tau LLPS. Pharmacological approaches may be used in order to decrease abberant tau phase separation. Dai et al. showed that myricetin, a flavonoid compound, may be used in the modulation of tau LLPS (277). Another natural compound, Shikonin, extracted from various medicinal plant species belonging to the Boraginaceae family, has been demonstrated that reduce tau aggregation (257, 259, 278). Further research is needed in order to explore the full spectrum of therapeutic possibilities and strategies effective for modulating abnormal LLPS driven tau phase separation.

Microglia

Microglia are immune cells present in the brain and central nervous system that protect neuron health by removing damaged or unnecessary cells *via* phagocytosis (279). With regard to AD, microglia play an integral role in the performance of a variety of functions. For instance, at first, these cells detect Aβ and then move quickly to eliminate it before it develops itself into protein plaques that then leads to more significant damage (279, 280). Therefore, this function is vital as it mitigates any further damage. The buildup of Aβ plaques and tau tangles in AD triggers an activation response from microglia (279). This activation can result in substances that are harmful being released by these cells, which damage or even destroy neurons (279). This contributes further to the degeneration of brain tissue (279). Microglia, on the other hand, might also play a protective role in the early stages of AD. In fact, studies conducted on animals have suggested that reducing their numbers or preventing their activation worsens (increases) both tau tangles and Aβ plaque development (280). The function of microglia in AD is still not fully understood, despite being the focus of ongoing research. A complex relationship between microglia and the disease may have both beneficial and detrimental effects, depending on the stage of the disease (279).

There are two phenotypes of microglia: M1 (proinflammatory) and M2 (anti-inflammatory) (281). M1 and M2 are different states or phenotypes that microglia can adopt in response to different stimuli. M1 microglia are in a state called activated or proinflammatory, which means they synthesize molecules that cause inflammation and damage to tissues (281). Chronic inflammation and autoimmune diseases are frequently linked to this phenotype. The alternatively activated or anti-inflammatory state of M2 microglia, in contrast, is characterized by the production of molecules that support tissue repair and the resolution of inflammation (281). Individuals that display this phenotype often experience a correlation between the process of repairing tissue damage and the resolution of inflammation. PPAR-γ agonists are drugs that stimulate the PPAR-γ receptor, a protein found in all cells of the body (282). These drugs have a variety of effects, including reducing inflammation and regulating the metabolism of lipids and sugar. In mice, treatment with the PPAR-γ agonist pioglitazone increased M1-M2 conversion while decreasing Aβ levels (284).

Nicotinamide adenine dinucleotide phosphate (NADP) has been demonstrated to be involved in the control of oxidative stress and inflammation in the context of AD (284). It is assumed that inflammation and oxidative stress play a role in the onset and progression of AD. Reactive oxygen species (ROS), which are highly reactive molecules that can harm cells and tissues, are produced by NADP as well as by its reduced form, NADPH (285). The buildup of Aβ and tau tangles, which are signs of AD, has been linked with how NADP-dependent pathways work. The NADPH oxidase family of enzymes oxidizes intracellular NADPH and NADH, leading to

the production of superoxide; this makes the inhibition of oxidases a potential therapeutic target in neurodegenerative diseases such as AD (286).

Recent discoveries suggest that these plaques are not formed spontaneously but rather constructed by microglia (287). Granulomas are structured clusters of white blood cells, mainly macrophages, that can form a persistent infection, becoming impossible to eliminate from the body (288-290). A granuloma can create a favorable environment that allows bacteria to proliferate with binary fission (291). Lemke et al. suggested that Aβ dense-core plaques are granulomas (287). Studies have demonstrated that the removal of microglia does not impact the stability of dense-core plaques once they have formed (292, 293). According to Lemke et al., the majority of evidence suggests that dense-core plaques do not form without the presence of microglia (287). According to the granuloma hypothesis, agents that dissolve dense-core plaques without simultaneously reducing the production and accumulation of Aβ peptides, oligomers, and proto-fibrils may not be effective (287). The hypothesis suggests that if dense-core plaques are a type of granuloma, and macrophages construct all granulomas, then dense-core plaques should not form without microglia (287). According to research, microglia and other tissue macrophages require continuous signaling *via* the Colony stimulating factor 1 receptor (CSF1R) to survive (292, 294, 295). Blocking this receptor with small-molecule CSF1R kinase inhibitors can cause the death and depletion of almost all microglia in the mouse brain (292, 294, 295). The limited number of plaques observed post-treatment exhibited a clear correlation with microglia that had survived elimination, providing evidence in favor of the granulomas hypothesis. (292).

Promising new strategies for reducing Aβ peptide levels may involve compounds that modulate the activity of γ-secretase through allosteric mechanisms, rather than simply inhibiting it. Additionally, next-generation therapeutic options could include Mer-selective and brain-penetrant substances that stimulate microglial Mer expression or enhance its kinase activity. (287).

Inflammation

Neuroinflammation is the inflammation that occurs in the nervous tissues. Neuroinflammation occurs when the nervous system is infected with pathogens, suffers traumatic brain injury, accumulates toxic metabolites, or when the immune system goes rogue and turns on its own. Microglia and astrocytes play a crucial role in the health of neurons. However, when they become activated in an inflammatory response, they can contribute to damage in the brain. Chronic neuroinflammation, noticeable by the activation of microglia and astrocytes, could lead to a cycle of inflammation. Neuroinflammation is important in the pathogenesis of AD. Disarranging of brain waste clearance systems, such as the glymphatic system, due to inflammation may lead to the buildup of harmful proteins. Three

clinical trials were found on clinicaltrials.gov about Sargramostim. Sargramostim is a recombinant form of GM-CSF (296). It is produced by recombinant DNA technology (yeast-derived rhu GM CSF/Leukine) (296). It targets the innate immune system and ameliorates AD symptoms. Sargramostim modulates the activation of microglia and the reduction of amyloid plaques in the brain (297). It increases phagocytosis of pathogenic protein deposits by bone-marrow-derived macrophages and brain-resident microglia; it also stimulates other neuroprotective innate immunity processes (297). According to CU Alzheimer's and Cognition Center, Sargramostim is the first drug to show significant improvement in AD in a phase II clinical trial. Sargramostim has been used for over 30 years as it is an FDA-approved safe medication that is used for other disorders (298).

Table 18. Inflammation related drugs Phase 1 (99, 299-310)

Drug	Company	Target Type
TB006	TrueBinding, Inc.	Immunotherapy (passive)
Protollin	Jiangsu Nhwa Pharmaceutical Co., Ltd	Immunotherapy (active)
MW151	ImmunoChem Therapeutics	Small Molecule
Inzomelid	Inflazome Ltd.	Small Molecule
IBC-Ab002	ImmunoBrain Checkpoint	Immunotherapy (passive)
GC021109	GliaCure	Small Molecule
Edicotinib	Janssen	Small Molecule
DNL919	Takeda Pharmaceutical Company	Immunotherapy (passive)
CpG 1018^{R}	Dynavax Technologies	Immunotherapy (active), DNA/RNA-based
AZP2006	AlzProtect	Small Molecule
AL044	Alector	Immunotherapy (passive)

Table 19. Inflammation related drugs Phase 2 (99, 311-319)

Drug	Company	Target Type
XPro1595	INmune Bio Inc.	
Neflamapimod	EIP Pharma	Small Molecule
Montelukast	Intelgenx	Small Molecule
MW150	Neurokine Therapeutics	Small Molecule
Lomecel-B	Longeveron	
Etanercept	Pfizer	Immunotherapy (passive)
CY6463	Cyclerion	Small Molecule
AL002	Alector	Immunotherapy (passive)

Table 20. Inflammation related drugs Phase 3 (99, 213, 320-322)

Drug	Company	Target Type
Sensory Stimulation Systems	Cognito Therapeutics	Procedural Intervention
NE3107	BioVie Pharma	Small Molecule
ALZT-OP1	AZTherapies Inc.	Combination, Small Molecule

Table 21. Inflammation related drugs Discontinued (99, 218, 323-330)

Drug	Company	Target Type
Thalidomide	Celgene Corporation	Small Molecule
Rofecoxib	Merck	Small Molecule
Prednisone		Small Molecule
Naproxen	Procter & Gamble	Small Molecule
Lornoxicam	JSW Lifesciences	Small Molecule
HF0220	Newron	Small Molecule
Celecoxib	Pfizer	Small Molecule
Azeliragon	Pfizer	Small Molecule
AL003	AbbVie, Alector	Immunotherapy (passive)

CRISPR

CRISPR technology allows for the accurate evaluation of individual genes and their influence on trait expression and disease progression, allowing researchers to quantify the effect each gene has on downstream biomarkers. Identifying correct predictive biomarkers for causation can speed up the process of finding drugs for AD. Through the use of CRISPR, it is possible to identify genes linked to cognitive decline that may not be directly responsible for the formation of Aβ and neurofibrillary tangles. CRISPR technology is highly beneficial in helping to differentiate between observational bias and clinical symptoms. Most of the research in this area concentrates on how this technology can be used to create AD models, identify genes that cause the disease, and use specific target genes to treat it. Table 22 lists select studies utilizing and/or studying CRISPR-targeted genes and proteins.

Table 22. Select studies related to CRISPR-targeted genes and proteins (331-336)

Studies	Work Area	Results	Focus: Gene or Protein
Arnaud et al.	Human induced pluripotent stem cell lines	Brain samples from patients often have low levels of TAGLN3 with AD. Adding TAGLN3 to APOE4 astrocytes reduces the inflammatory responses.	hiPSC, TAGLN3

Sanchez et al.	SH-SY5Y, cell line was established from a bone marrow biopsy of a 4-year-old female with neuroblastoma, neuroblastoma cell line produced in vitro	A genome-wide investigation utilizing CRISPR technology was used to determine regulators of the tau protein.	BRD2, FUS, TRIM28, and PHOX2A
Ma et al.	SH-SY5Ye, iPSC-MN cells	The loss of TDP-43 causes a cryptic exon to be included in the UNC13A, is expressed in neuronal tissue and is involved in maintaining synaptic active zones, mRNA and reduced expression of UNC13A.	TDP-43
Polanco et al.	Tau biosensor cells	In order to mitigate the adverse effects associated with neurodegenerative disorders, it is essential to limit the accumulation of tau proteins that is prompted by both exosome-associated and free-floating tau seeds	EIF1AD, NUSAP1, VPS18, BANF1
Drager et al.	A human-induced pluripotent stem cell (iPSC) line has been engineered to express transcription factors, thus generating cells that resemble microglia in their behavior and functionality.	They have devised an approach centered around the direct alteration of cell fate through the amplified expression of transcription factors. They have manipulated an iPSC line, integrating two cassettes that, upon doxycycline stimulation, trigger the expression of three transcription factors each within the Citrate Lyase Beta Like.	INPP5D, PFN1

Lipid-chaperone hypothesis

The lipid-chaperone hypothesis is a broader molecular model that suggests that the lipid-protein complex in solution is the primary agent responsible for membrane damage (337). The lipid-chaperone hypothesis posits that free lipids found in the aqueous phase can create a stable complex with the amyloid structures; this complex is subsequently transported into the bilayer (338). This hypothesis is supported by *in vitro* experiments (337). Cellular defense mechanisms prevent any adverse consequences arising from protein aggregation (338). Exposed hydrophobic patches of oligomers can be shielded by chaperones. Moreover, as people age, chaperone levels decrease (338). Abnormal lipid metabolism is visible in AD patients, which may manifest in the development of AD (338, 339). Bioenergetic dysfunction is caused due to increased levels of fatty acids, acyl-carnitines, and acyl-CoA (340). Alterations in the amount of unsaturated fatty acids have been associated with AD development. Patients have lower levels of unsaturated fatty acids in their blood (341). Also, patients have lower levels of

docosahexaenoic acid (DHA) in the brain's hippocampus region compared to healthy subjects. Lipids can also play a significant role in the onset of AD. When intrinsically disordered proteins interact with lipid membranes, they can misfold into abnormal shapes and form amyloid aggregates (337).

More research is required in this area, but free phospholipids may play a crucial role in the development in AD (337, 339, 342). The lipid-chaperone hypothesis has the potential to introduce effective drugs.

Agonistic Autoantibodies (agAAb)

Agonistic autoantibodies (agAAb) can activate certain receptors. Naturally occurring agAABs are substances that can remove autoantibodies by plasmapheresis or immunoadsorption (343). AgAAB have been shown to cause macrovascular and microvascular impairments in the vessels of the brain, resulting in a decrease in blood flow and vessel density (344). In AD and dementia patients, agAABs and G protein-coupled receptors (GPCR) opposed to the α1-adrenoceptor (α1AR) and ß2-adrenoceptor (ß2AR) were found at a prevalence of 50% (345). β2-agAAb can be found in sera of patients with ocular hypertension; β2-agAAb targets the trabecular meshwork (346). One of the ongoing trials is investigating whether the removal of α1AR-AABs by a 5-day immunoadsorption procedure has a positive effect on changes in hemodynamic and cognitive parameters in AD patients (345). The IMAD trial is designed as an exploratory monocentric interventional trial (345). This trial offers insights regarding the impact of decreasing or eliminating α1AR-agAABs as a potential cause of cerebrovascular impairment associated with AD and dementia; this study can introduce a new treatment strategy for individuals with AD who test positive for α1AR-agAABs, at various stages of AD progression (345).

Human Mesenchymal Stem Cells (hMSCs)

Human Mesenchymal Stem Cell therapy for AD represents a unique approach. MSC treatment mitigates brain inflammation by eradicating amyloid-β and neurofibrillary tangles, as well as abnormal protein degradation (347). This therapy also enhances the recuperation of the blood-brain barrier and autophagy-related processes, controls the concentrations of acetylcholine, and augments cognitive function in the brain. Human mesenchymal stem cells (MSCs) are cells derived from the bone marrow, umbilical cord blood, and donor tissues (348). One of the clinical trials is assessing the safety and tolerability of ischemia-tolerant allogeneic human mesenchymal stem cells (hMSCs) versus a placebo administered intravenously to subjects with mild to moderate AD who are amyloid-positive based on an amyloid PET scan using the radiotracer florbetapir (349). This phase II study started in 2016 and will be completed in 2024. Another trial is investigating the safety and efficacy of allogeneic hMSC infusion versus placebo in patients with AD, which is also in Phase II (350). Clinical trials are focusing more on the

safety and efficacy of this treatment option. Table 23 lists select trials on MSCs.

Table 23. Some Trials on MSCs (349, 351-354)

Agents	Sponsors	Phase	Intervention/Treatment
Allogeneic human MSCs	Bernard (Barry) Baumel, University of Miami	1	Approximately 100 million cells allogeneic hMSC
Allogeneic human MSCs	Stemedica Cell Technologies, Inc.	2	Human Mesenchymal Stem Cells and Lactated Riunger's Solution
Human Umbilical Cord blood-derived MSCs	Medipost Co Ltd.	1	Human umbilical cord blood derived mesenchymal stem cells
Placenta Derived MSCs	CHABiotech CO., Ltd	1	CB-AC-02

Low-dose Ionizing Radiation (LDIR)

Low-dose ionizing radiation (LDIR) is a technique that uses a relatively low level of radiation for treatment. However, this technique has sufficient energy to remove tightly bound electrons from atoms, resulting in the formation of ions. Immediate acute effects are observed with this technique. LDIR has been used to decrease oxidative damage in the brain. A case study reported a patient diagnosed with severe AD who underwent a series of CT scans, during which ionizing radiation was applied to the patient's brain. Following the treatment, the patient's cognitive abilities, speech, and mobility improved (355). A pilot study was conducted by Baycrest in order to investigate the effect of (LDIR) on severe AD (355). According to Cuttler et al., LDIR is a potential albeit controversial therapy for AD (355). Hwang et al. highlighted that LDIR has positive impacts on human Aβ42 expressing *Drosophila Melanogaster* models for AD (356, 357). Ionizing radiation at a dosage of 50 milligray (mGy) alleviated AD-associated symptoms such as locomotive dysfunctions (356, 357). Furthermore, when using the same dose of gamma irradiation, it decreased cell death induced by Aβ42 by suppressing the Wrinkled gene, which encodes a protein that activates caspases (356, 357).

In order to assess the advantages of LDIR, it is necessary to conduct double-blind, placebo-controlled trials, specifically focusing on milder forms of AD (355). Also, a larger group of patients are needed. Quantitative measures, including the use of biomarkers associated with oxidative stress, are necessary to capture the significant changes caused by LDIR (355).

Heat Shock Proteins (HSPs)

Heat shock proteins (HSPs) are common in prokaryotic and eukaryotic organisms and respond to exposure to stressful environments/conditions in order to protect cells (358). Within cells, HSPs function as molecular chaperones and operate as a cohesive network. HSPs also have an integral role in cell signaling transduction, cell cycle, and apoptosis regulation (358). HSPs prevent the aggregation and misfolding of other proteins; HSPs can play an important role in

impeding Aβ plaques and neurofibrillary tangles (359). Magrane et al. found that the diminished functioning of HSPs may contribute to the advancement of AD (359). There have been many studies that targeted HSPs, determining the relationship between HSPs and HSPs for AD. One study found that HSP co-inducer BGP-15 could improve cognition and reduce Aβ plaque formation in a mouse model of AD (360). Extensive evidence supports the involvement of Hsp60 in tumor progression (361). Several studies have highlighted the potential of Hsp60 inhibition as a promising therapeutic strategy, but only a limited number of compounds have been thoroughly characterized, and the mechanisms of action for most of these inhibitors remain undisclosed (362, 363). The field of drug design that targets Hsp60 has promising prospects, but potential therapy for AD has not been thoroughly explored (362). The activation of HSP70 is responsible for promoting the clearance of Aβ by increasing the expression levels of insulin-degrading enzymes and TGF-β1 (364). HSP70 has a potential therapeutic role in the regulation of tau homeostasis; hence, researchers have started to focus on this protein (364). Results suggest that HSP70 can prevent taupathy as it is crucial in inhibiting tau aggregation and facilitating its degradation (364). HSP70 directly hinders the aggregation of tau by mechanism, including preferential associations with soluble, monomeric, and prefibrillar oligomeric tau species (364).

Table 24. HPSs associations, functions, and pharmacological targeting (362, 365-371)

HSPs	Association	Functions	Pharmacological targeting
Hsp60	Aβ and APP	The interplay between immune cells and other body tissues. Folding of proteins within the mitochondria.	Restriction of the process of protein folding. Preventing the separation of the co-chaperonin Hsp10. Focusing on cysteine residues.
Hsp70	Tau and APP	The process of client proteins being folded Immuno-modulatory effects. Prevention the aggregation of proteins that haven't been folded.	Modulation of Hsp70 expression levels. The interaction of misfolded Tau with Hsp70's various allosteric sites through its modulation.
Hsp90	Aβ	The process of folding a large number of proteins. Signal transduction Activation of microglial phagocytosis.	Modulation of Hsp90 functions through co-chaperones. Interaction with the nucleotide-binding pocket.

Drug repositioning

Drug repositioning is the procedure of determining new therapeutic uses for existing medications. Drug repurposing may accelerate traditional drug development efforts. Newly discovered gene expression patterns obtained from cells extracted during the initial phases of AD could serve as a tool to identify additional

candidate drugs (372). Alternatively, existing substances that share structural similarities with compounds involved in the metabolism of L-tryptophan or L-arginine could potentially be repurposed as therapeutic options (373). When conducting Phase II trials to evaluate repurposed drugs, both the optimal target population for a particular therapy and the mechanism of action of the treatment should be considered (372). Fasudil, antiviral drugs, and phenserine were identified as the top three priority candidates for repurposing in AD (372). Bayraktar et al. identified eight drugs for the repositioning, including mitoxantrone, bortezomib, parbendazole, crizotinib, withaferin-a, SA-25547, and two unstudied compounds (374). These identified drugs have the ability to inhibit glutaminase and decrease the production of glutamate through multiple neurodegeneration-associated mechanisms (374). Another study showed 27 potential drugs for AD, including Irsogladine (PDE4 inhibitor), Tasquinimod (HDAC4 selective inhibitor), and Suprofen (dual COX-1/COX-2 inhibitor) (375). Irsogladine was also demonstrated as the most potent drug for AD treatment (376). According to Das et al., Allopurinol, Bromocriptine, Bupropion, Raloxifene, Thalidomide, and Zidovudine may have a potential to treat AD (377). Table 25 lists select repurposed agents.

Table 25. Repurposed agents, therapeutic field, drug class, and agent mechanism (adopted and re-organized from (378))

Drug	Therapeutic field	Drug Class	Agent mechanism
Benfotiamine	Antidiabetic	Synthetic thiamine	Metabolic
Candesartan	Cardiovascular	Angiotensin II Receptor Blocker	neuroprotective, metabolic
Cilostazol	Hematologiconcologic	Antiplatelet	Neuroprotective
Dapagliflozin	Antidiabetic	Sodium-glucose co-transporter 2 inhibitor	Metabolic
Daratumumab	Hematologiconcologic	Human antibody targeting CD38	Anti-inflammatory
Liraglutide	Antidiabetic	Glucagon-like peptide-1 agonist	Metabolic
Leuprolide depot	Hormonal	Gonadotropinreleasing hormone agonist	Metabolic
Sagramostim	Hematologiconcologic	Human granulocytemacrophage colonystimulating factor	Neuroprotective
Tacrolimus	Immunologic	Calcineurin inhibitor	Neuroprotective
Telmisartan	Cardiovascular	Angiotensin II	Neuroprotective

		Receptor Blocker	
Amlodipine	Cardiovascular	Calcium channel blocker	Anti-inflammatory
Atorvastatin	Cardiovascular	Statin	Anti-inflammatory
Losartan	Cardiovascular	Angiotensin II receptor blocker	Anti-inflammatory
Metformin	Antidiabetic	Insulin sensitizer	Metabolic

Infection hypothesis

Infection hypotheses suggest that a pathogen may induce the development of AD. The role of infectious agents in the development of AD should be given more consideration among the many factors (379). There are three different hypotheses: The first one suggests that infectious agents may play a role in triggering the development of AD; the second one suggests that infectious processes may not necessarily initiate a disease, but they may accelerate the development of AD that has already begun; the third one suggests that previous associations described in the literature may be explained by reverse causation and residual confounding (379). HIV has been linked to cognitive impairments, particularly in HIV-associated neurocognitive disorder (HAND); however, epidemiological studies have not yet established a definitive connection between HIV infection and an increased risk for AD (379). It is known that HIV is associated with Aß plaque presence (380). Results suggest that *C. pneumoniae*, bacterial specie contributes to the development of both bronchial asthma and chronic obstructive pulmonary disease (COPD) and is responsible for approximately 20% of lower respiratory tract infections (381). Also, *C. pneumoniae* is a possible factor that can trigger AD (382). *T. pallidum* infection causes cortical atrophy, amyloid deposition, and dementia (379). One possible approach to treat AD is by using specific agents that are designed to control or eliminate microorganisms. These agents include antivirals, antibacterials, and antifungal products. When considering viruses, the antiviral drugs that can cross the blood-brain barrier (BBB) are particularly important. Among these drugs, Valacyclovir has proven to be highly effective in treating herpes viral encephalitis (383-385). Several antibiotics have been met with hopeful anticipation to hinder the potential effects of AD. Amongst them are doxycycline, minocycline, and rifampin, which prevail as extensively studied antibiotics within clinical trials devoted to this cause (386). Based on conclusive trial results observed without any major adverse occurrences, possible therapeutic effects were identified in administering doxycycline and rifampin for individuals with mild to moderate AD (386). Even so, attributing these effects solely to *C. pneumoniae* seems improbable since establishing a definitive mechanism could not be achieved through this study. A clinical study conducted by Howard et al. found that minocycline did not demonstrate any ability to delay the progression of cognitive or functional impairment in individuals with mild AD over a

period of two years (387). The employment of peptoid has demonstrated considerable effectiveness as antimicrobial substances both in vitro and in mice (388). Antimicrobial peptides like LL-37 can be used as an AD treatment (389). Also, one antimicrobial agent may not be enough to treat AD but can be used as a supplement. An epidemiological study recently uncovered evidence demonstrating diminished representation of Bacteroides species in patients diagnosed with AD (390). As a result, these findings strongly indicate that manipulating the microbiota could prove advantageous for individuals suffering from AD. The macrolide antibiotic azithromycin, which is known for its potency against *P. gingivalis*, has also been found to possess mTOR-modulating properties (391, 392). Additionally, it has shown senolytic effects suggesting its potential usefulness in the treatment of AD (391, 392). Infectious burden can be divided into single-taxon and multi-taxon infections. Figure 8 shows the single-taxon and multi-taxon infections.

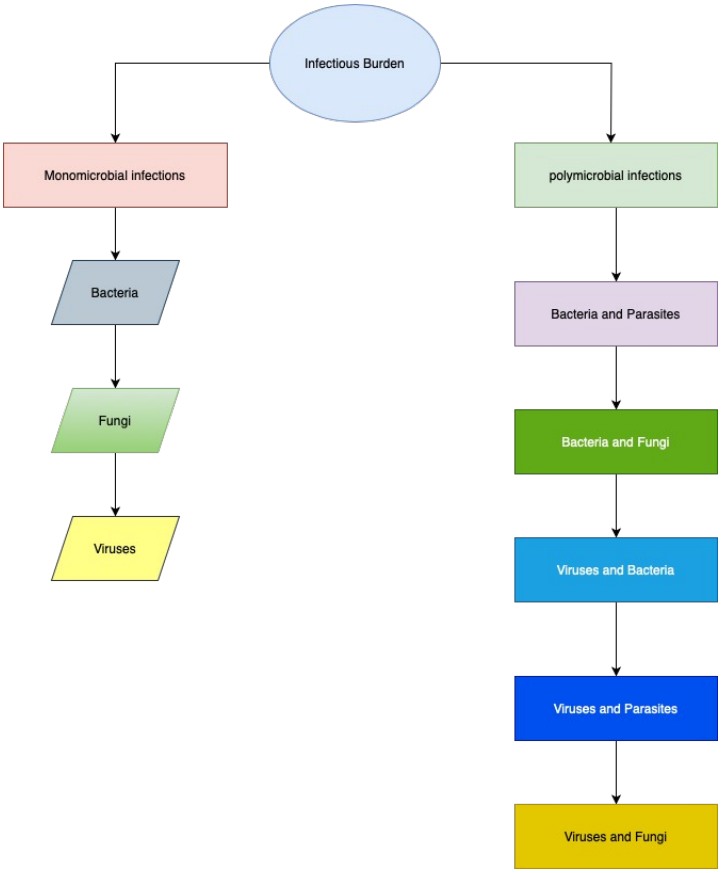

Figure 8: Single-taxon and multi-taxon infections (Adapted from 393)

Table 26 lists studies identifying single and multi-taxon pathogens taken from AD patients.

Table 26: Pathogens in samples taken from individuals diagnosed with AD (393-407)

Infectious Burden	Pathogens	Methodology	Studies
Single-Taxon	Cytomegalovirus (CMV), HSV-1	Enzyme-Linked Immunosorbent Assay (ELISA)	Lövheim et al.
Sinfle-Taxon	Helicobacter pylori, periodontal bacteria	Immunochemical analysis,	Beydoun et al.
Single-Taxon	Gingivitis bacteria Periodontal bacteria	16S rDNA sequencing	Siddiqui et al.
Single-Taxon	Human Herpesvirus 6 (HHV-6) and HHV-7	RNA sequencing, statistical analysis	Redhead et al.
Single-Taxon	Firmicutes, Proteobacteria	16S rRNA sequencing	Emery et al., 2017
Single-Taxon	Candida albicans, Cladosporium cryptococcus, Malasezzia globosa	Next-Generation Sequencing	Alonso et al., 2017
Single-Taxon	Malassezia restricta, Neosartorya hiratsukae, Saccharomyces cerevisiae, Sclerotina borealis	Immunochemical analysis	Pisa et al., 2015
Single-Taxon	Periodontal bacteria	ELISA	Sparks Stein et al., 2012
Single-Taxon	CMV, Epstein-Barr virus (EBV), HHV-6	PCR-based analysis, ELISA	Carbone et al., 2014
Single-Taxon	Varicella-Zoster Virus (VZV), HSV-1, HHV-6, V	PCR-based analysis	Hemling et al., 2003
Multi-Taxon	Several bacterial and fungal species	PCR-based analysis	Alonso et al., 2018
Multi-Taxon	CMV, HSV-1, HSV-2 Toxocaris, Toxoplasmosis	Immunochemical analysis	Gale et al., 2016
Multi-Taxon	HSV-1, HSV-2, CMV, Toxoplasma gondii	Immunochemical analysis	Nimgaonkar et al., 2016
Multi-Taxon	Helicobacter pylori, Toxoplasma gondii	Immunochemical analysis	Gale et al., 2015
Multi-Taxon	HSV-1, CMV, Borrelia burgdorferi, Chlamydia pneumoniae	ELISA	Bu et al., 2014
Multi-Taxon	HSV-1, HSV-2, CMV, Chlamydia pneumoniae	ELISA	Katan et al., 2013

Antiviral, antibacterial, antifungal, and anti-biofilm agents may be effective in AD treatment. (393). Some of the antiviral agents are Valacycloir and Valganciclovir; some of the antibacterial agents are rifampicin, minocycline, and doxycycline; some of the antifungal agents are voriconazole, and flucytosine; and some of the anti-biofilm agents are myriocin and parthenolide (393). Therapeutic strategies that target infectious agents can be beneficial for AD, but further research is required to specify the specific impact of infectious agents in treating AD at various stages.

Gut Microbiota

The gut is an important part of humans and is also termed as the second brain (408). The gut microbiota is a community of microorganisms living in the gastrointestinal tract, and dysfunctional complex communities can influence both gut and central nervous system disorders, including AD (409). Probiotic commensal bacteria, play a vital role in providing the body with substances to prevent inflammation (278, 410). A wide range of diseases, such as colorectal cancer, obesity, inflammatory bowel disease, and heart failure, are linked to changes in the gut microbiota (410). Furthermore, there is a connection between gut microbiota and the central nervous system *via* the gut–brain axis; the nervous system facilitates communication and interaction between the intestine and the brain (410). The messages transmitted by the brain in the form of neurotransmitters are received by the gut bacteria. The research focused on gut microbiota and the brain suggests that gut microbiota modulates the immune, nervous, and endocrine systems (410, 411). Microbiota gut-brain axis may be impacted by microbiota through direct natural mechanisms (410, 412). Hence, this can cause cognitive dysfunction (413). More than 85% of the individuals diagnosed with AD were reported to have changes in gut microbiota compositions compared to AD-free healthy individuals (414). Correlations were observed between the levels of certain bacterial species and the biomarkers of AD pathology found in the cerebrospinal fluid (415). The gut microbiota can communicate with the central nervous system *via* the microbiota-gut-brain axis, with various mechanisms, including metabolic influences and neural stimulation (416). Research has shown that gut microbial metabolites have an impact on the pathogenesis of AD. The gut microbes are involved in AD, as it relates to Aβ deposit, tau phosphorylation, neuroinflammation, metabolic dysfunction, and oxidative stress (415). Furthermore, the progression of AD is reinforced by mechanisms related to the imbalance in the gut microbiota (408). One study showed that administering a combination of probiotic bacteria improved cognitive function and reduced inflammation in AD patients (417).

Many studies have demonstrated that antibiotic treatments in the long-run may affect intestinal microbiota in humans (418). The usage of antibiotics can have both positive and negative impacts on gut microbiota. For instance, Streptozotocin and ampicillin disrupt the

balance of gut bacteria (410). Also, cefepime has the ability to cross BBB and lead to cognitive dysfunctions (410). However, positive outcomes for cognitive function were observed when pathogenic bacteria like *Helicobacter pylori* were eradicated with antibiotics (410). Minocycline and rapamycin have demonstrated a positive impact as they reduced Aβ and microglia (419, 420). Antibiotics can have antiaging properties and cure AD-like pathology in animal models (420). Hence, antiaging properties of these compounds can be investigated for potential therapeutic use.

Probiotics may be used in the treatment of AD as they have clinically measurable effects on cognitive function (421). In comparison to untreated AD mice, transgenic AD mice that received probiotics showed improved cognitive performance and a decrease in the number of Aβ plaques in the hippocampus (410).

Blood-Brain Barrier dysfunction

Regardless of changes in Aβ and/or tau biomarkers, individuals exhibiting early cognitive dysfunction show signs of brain capillary damage and a breakdown in the blood-brain barrier (BBB), specifically within the hippocampus (422, 423). Concerning the brain and the BBB, normal aging can be outlined as a decline in bodily activities with no associated cognitive ailment. A recent study found that the breakdown of the (BBB) may be considered an important indicator of the natural aging process (424). Results suggest that aged individuals with prior cognitive impairment exhibit increased vulnerability towards disruptions in the BBB compared to those without any cognitive dysfunction at the same stage of life. Therefore, there is merit in considering BBB disruption as an early biomarker associated with the decline in human cognition. The findings of a study utilizing cerebrospinal fluid biomarkers and the DCE-MRI technique demonstrated that aged individuals with prior cognitive impairment displayed heightened permeability of the BBB, surpassing that observed in healthy individuals (425). Some of the BBB elements that change with AD are basal lamina, pericytes, astrocytes, microglia, neurons, transporter dysfunctions, tight junction proteins, and extracellular components (423). In AD, the accumulation of extracellular components increases, the thickness of basal lamina increases, pericytes number decrease, Vascular coverage reduces, microglia changes to amoeboid morphology, synaptic plasticity decreases, BBB integrity decreases, and BBB permeability increases (423). The breakdown of the BBB hampers the clearance of Aβ and APP, ultimately accumulating Aβ in the brain. Pericytes have an integral role in the formation of BBB (426, 427). Results suggest a significant decrease in both the number and density of these cells within the cortex and hippocampus of patients with AD. This decrease consequently results in an increase in the expression of Aβ and phosphorylated tau proteins (426, 427). The primary event leading to BBB disruption occurs through the activation of inflammatory and oxidative stress signaling pathways (428-430).

Aquaporin 4 (AQP4) serves as the main water channel in the central nervous system; it is predominantly found in astrocytes, which are essential for maintaining the balance and stability of the brain (431). Consequently, AQP4 plays a crucial role in regulating normal brain functions and is also involved in several neurological disorders (431). AQP4 has been found to contribute to the deposition of Aβ and inflammation in the human brain (432). In individuals with AD and animal models, there were changes in the expression and distribution of AQP4, which resulted in the accumulation of Aβ (432). Hence, therapeutic strategies that focus on AQP4 may prevent the progression of AD.

Apolipoprotein E (ApoE), a protein associated with APOE, plays a crucial role in preserving the integrity of the BBB (433). The APOE4 isoform has been identified by researchers as a prominent risk factor for AD. When Aβ binds with ApoE4, it disrupts the efficient clearance of soluble Aβ40/42 (434). The presence of APOE4 in the body has been found to contribute to a decrease in the integrity of the BBB. This is primarily due to its promotion of pericyte degeneration. The absence of LRP1 in endothelial cells triggers the activation of the CypA-MMP9 pathway within the endothelium (423). As a result, this leads to the breakdown of BBB. In the quest to find effective treatments for AD, exploring the targeting of ApoE4 or inhibition of the CypA–MMP9 pathway appears promising. Such interventions have shown the potential to reduce AD symptoms. Despite abundant evidence suggesting a considerable vascular role in the disease, this particular aspect has received inadequate attention. Neurovascular dysfunction is commonly found in AD patients' brains. This has led to the development of a "vascular hypothesis" of AD, which is based on the observation of cerebral perfusion and metabolic deficits in patients with AD (435, 436). Numerous investigations have presented different correlates that are associated with vascular cell dysfunction (437). Such correlates encompass Aβ mediated cytotoxicity, deficits in Aβ clearance, as well as weakening of the BBB. Vascular changes are an early sign of AD pathology, and changes in blood flow to the brain can start prior to symptoms appearing. There is an increasing amount of evidence supporting a connection between vascular dysfunction and Aβ pathology. Thomas et al. conducted a study that offered the initial evidence suggesting that Aβ is related to vasoactive properties (438). They found that when Aβ was applied to segments of rat aorta, it led to the constriction of the vessels (438). The study found that Aβ interacts with the cells lining blood vessels, leading to an overproduction of free radicals that cause changes in the blood vessels. There appears to be significant interplay among the advancement of AD pathology, systemic vascular risk factors, and genetic risk factors. The connection between Aβ and vascular changes is even stronger when there are already existing chronic risk factors (439). There is increasing evidence that AD could be related to a dysfunctional BBB, but not much effort has been made to target the cells in blood vessels as

a way to treat AD (440). Therapeutic targeting of vascular dysfunction can involve Aβ degrading enzymes, anti-angiogenic treatments, anti-inflammatory agents, and ameliorating neurotransmitter dysfunction.

Conclusion

Efforts to create drugs for AD are continuing rapidly; researchers are working relentlessly to develop therapies that can assist patients, either by reducing the illness's progression or by curing it completely. A variety of strategies are being pursued consisting of new ways to target Aβ a protein that has been linked to the illness. The intricate nature of AD has thus far prevented the discovery of a conclusive cure. Along with medication, as well as vaccine development scientists are exploring other therapies that may give symptomatic alleviation or target the underlying cause of the illness.

The amyloid and tau hypotheses of AD propose that the accumulation of amyloid protein in the brain and the formation of tau tangles are key drivers of the disease. Hence, many researchers have focused on developing drugs that can target these abnormalities to slow or halt the progression of the disease. Many drugs that have been developed to treat AD have been based on these hypotheses, with the aim of reducing the accumulation of Aβ or tau in the brain. Nonetheless, these drugs have failed to meet clinical endpoints in multiple trials leading scientists to examine whether these hypotheses actually pinpoint the underlying reason for the disease. To answer this question, researchers have looked beyond the amyloid and also tau hypotheses concentrating on other factors such as inflammation (including that of the blood brain barrier), oxidative stress, anxiety, gut microbiota, biocondensates and mitochondrial dysfunction that might have an effect on the development and progression of AD. Factors such as these have driven researchers to investigate the intricate relationships between them, striving to create more efficient treatments and medicine which target multiple aspects of the illness.

Progress has been slow due to the complexity and scope of the disease's underlying mechanisms, a propensity to focus exclusively on the beta-amyloid hypothesis at the expense of equally plausible alternative hypotheses. Current proposed compounds, hypotheses, and therapies have not resulted in breakthroughs in treating the condition. To effectively fight this disease, it is essential that scientists continue to invest in understanding the root causes of AD. Recent studies have started focusing on the role of neuroinflammation and alternative hypotheses in AD. Greater attention to the immunology behind the disorder could result in more effective and all-encompassing treatments.

There is also a need to streamline trials to be more efficient, compact, and cost-effective to speed up the creation of critical medication. The adoption of biomarkers, focused clinical outcomes, and enhancements in the performance of trial locations will play key roles in realizing this aim. Once regulatory

bodies approve new treatments, it could draw for AD research.
interest from and draw more financial support

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