Innovative Research in Applied, Biological, and Chemical Sciences

ISSN: 3005-8449

INNOVATIVE RESEARCH JOURNALS

Review Article

IRABCS, vol. 3, issue 2, 14-23, 2025

Received: November 23, 2025
Revised: December 18, 2025
Accepted: December 26, 2025
https://doi.org/10.62497/irabcs.182

Repurposing Prescription Medications for Alzheimer's Disease Treatment: Mechanisms, Evidence, and Clinical Implications

Natasha Elaine Hastings
MD, MPH, St. George's University, School of Medicine

How to cite: Hastings NE. Repurposing Prescription Medications for Alzheimer's Disease Treatment: Mechanisms, Evidence, and Clinical Implications. IRABCS. 2025; 3(2):14-23. DOI: https://doi.org/10.62497/irabcs.182 Available from: https://irjpl.org/irabcs/article/view/182

Abstract

Alzheimer's disease (AD) is the most common cause of dementia worldwide, with prevalence growing alongside life expectancy. The burden of disease on healthcare systems globally is on the rise, as current treatments have failed to mitigate its morbidity, and this remains a dire public health concern. AD is characterized by the hallmarks of β-amyloid plaque deposition and neurofibrillary tangles of hyperphosphorylated tau proteins. Clinical diagnosis relies on clinical presentation and a series of testable criteria. Current treatments primarily focus on symptom management, while trials are underway to develop pharmaceuticals that may reduce the production of amyloid plaques and tau proteins. Alternatives include the repurposing of drugs already on market for treatment of other diseases such as diabetes, hypertension, inflammation, depression, epilepsy, and hypercholesterolemia. Due to their approved use in the management of other diseases, already licensed compounds proceed through trials in a faster and more cost-effective manner than un-licensed compounds. The aim of this paper is to draw attention to already-licensed compounds currently on the market that may prove effective in treating Alzheimer's disease.

Keywords: Alzheimer's, drug repurposing, amyloid plaques, tau proteins, management, therapeutics

1. Introduction

Dementia has been described in ancient texts over centuries, yet our understanding of it spans just over 100 years back when Alzheimer, himself, published a famous case study on the illness. Auguste Deter, the original patient, was a 51-year-old woman whose behavior "showed all the signs of complete helplessness" and autopsy revealed "plaques and tangles in the cerebral cortex" [1]. This disease of the mind is characterized by a buildup of β-amyloid plaque deposition and neurofibrillary tangles (NFTs) of hyperphosphorylated tau proteins. Plaque deposition occurs decades before the visible symptoms of cognitive impairment and the continuum of Alzheimer's disease (AD) is defined as asymptomatic, prodromal, mild, moderate, to severe [2].

Through this continuum, stages begin with physiologic evidence of neuronal injury and progress with behavioral and psychological changes followed by cognitive impairment and finally functional impairment. As patients progress to mild cognitive impairment (MCI) due to AD, their symptoms include short-term memory loss, struggling to find the right word, forgetting recent conversations, struggling with completing familiar tasks, or getting lost in familiar surroundings [2]. These each relate to deficits in language, episodic memory, executive and visuospatial function respectively.

Currently, therapeutics only exist to treat symptoms rather than mechanisms of disease. There are two FDA-approved classes of drugs used to treat AD: cholinesterase inhibitors and N-methyl d-aspartate (NMDA) antagonists [3]. The longstanding belief that β-amyloid (Aβ) plaques precipitate a deleterious cascade involving tau pathology and neurodegeneration has now steered pharmaceutical engineering to seek disease-altering therapy. This has encouraged repurposing of drugs to target disease mechanisms, such as abnormal tau protein metabolism, Aβ plaques, inflammatory response, and cholinergic and free radical damage [3].

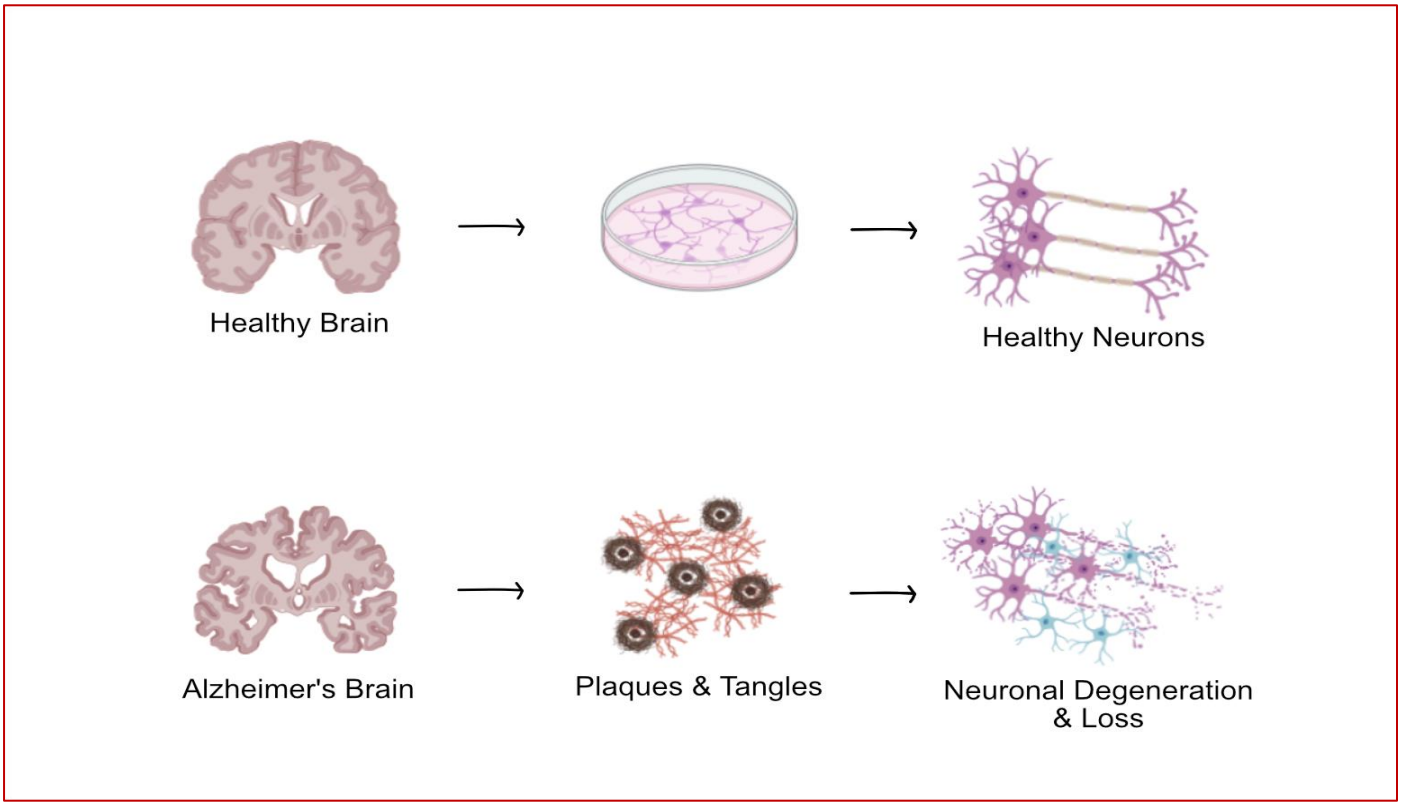

Figure 1: Comparing a healthy brain to a brain diseased with Alzheimer's.
The image depicts cortex shrinkage and ventricle enlargement, while comparing healthy neurons with those affected pathologically. Plaques and tangles contribute with their misfolded protein structure, eventually leading to neuronal destruction and loss. This neuronal loss is responsible for cognitive and functional impairment experienced by patients with AD.

Oxidative stress and mitochondrial dysfunction are also considered two primary role players in the pathological cascade that abates aggregation of Aβ plaques and neurofibrillary proteins [4]. Apolipoprotein E (APOE) is a protein that has been identified to predict risk in the development of AD and serves as another target for modulation. Off-label drug classes being evaluated for AD treatment - specifically to target neuroinflammation, abnormally folded protein processes, hippocampal excitability, etc. - include antidiabetic drugs, antihypertensives, cardiovascular agents, anti-inflammatory, immunomodulatory drugs, antidepressants, antiepileptics, lipid-modulating agents and neuroprotective agents. This paper serves to explore currently speculated agents and highlight the future pharmaceutical potential of these drugs.

2. Methods

A structured literature search was conducted to identify studies evaluating repurposed pharmacologic agents for the treatment of AD. 1,148 articles were procured from multiple sources, including Google Scholar, PubMed, and the Sage Journal of Alzheimer's Disease. From these articles, 212 were chosen for review and 23 articles were used in the writing of this paper. Search strategies incorporated a combination of Medical Subject Headings (MeSH) and keyword terms including: "Alzheimer Disease," "Disease Management," "Drug Repositioning," "Therapeutics," "Treatment," "Drugs", "Disease process," "Amyloid beta-Peptides/metabolism," "Tauopathies," "Neuroinflammation," "Mitochondria/metabolism," "Insulin Resistance," "GLP-1," "metabolic therapy," "neuroprotective antidiabetic drug," "Antihypertensive Agents," "Renin-Angiotensin System," "ARB Alzheimer's cognitive decline," "ACE inhibitor dementia progression," "Antidepressive Agents," "Serotonin Uptake Inhibitors," "Hydroxymethylglutaryl-CoA Reductase Inhibitors," "melatonin," and "ketamine."

Filters were applied to prioritize clinical trials, observational studies, and systematic reviews where available. Attention was predominantly focused on understanding the pharmaceuticals currently being repurposed to target disease mechanisms behind AD. Inclusion criteria included open-source full-text articles and focused on the pathophysiology as well as off-label intent in AD and papers that had been written in the most recent 10 years, between 2015 and 2025.

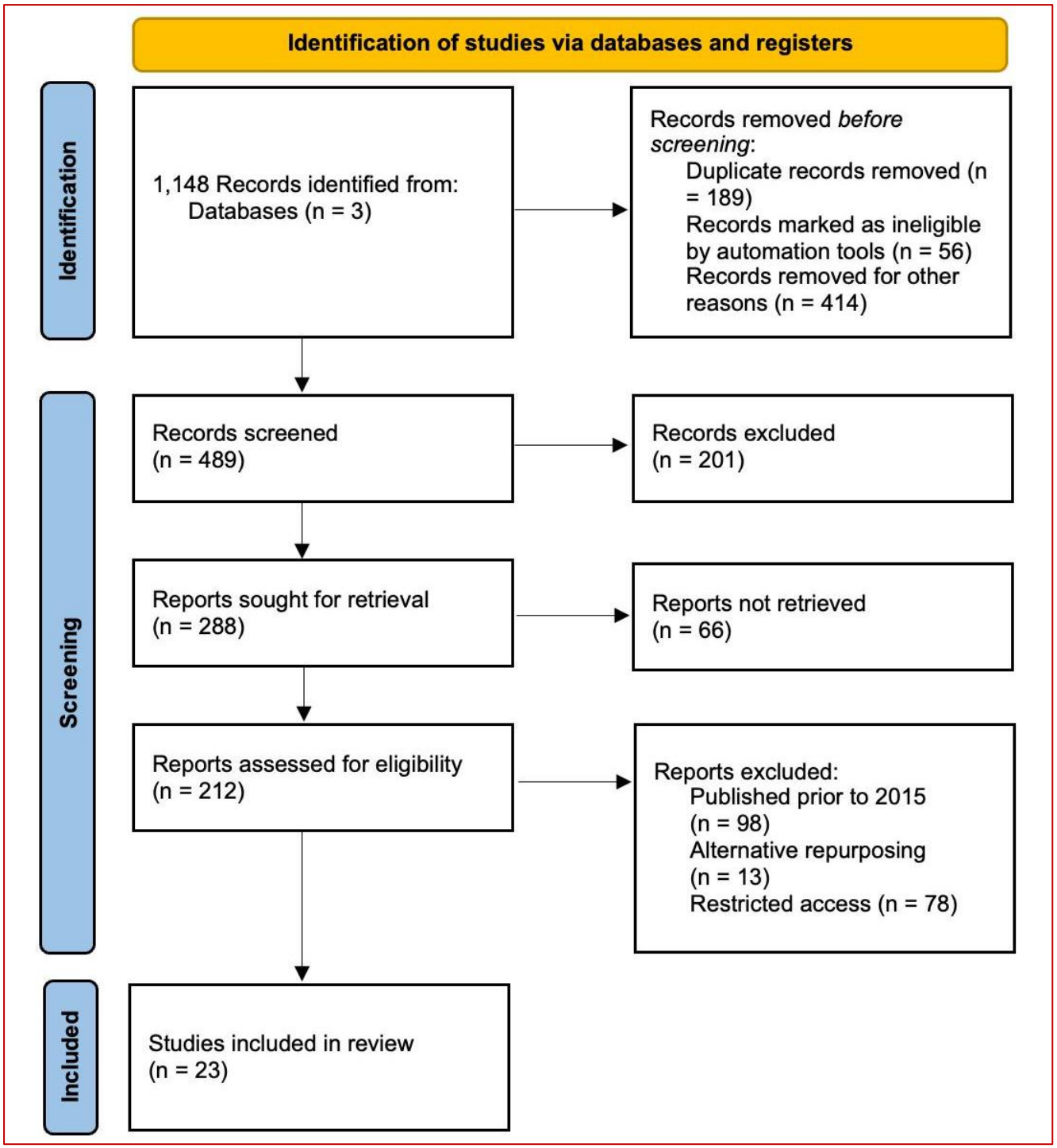

Figure 2. PRISMA Flow Diagram: How articles were chosen for this review?

3. Discussion

3.1 Pathophysiology and Rationale for Drug Repurposing

AD is considered a neurodegenerative disease. Its pathogenesis has been proven to be due to extracellular aggregates of Aβ plaques and intracellular buildup of neurofibrillary tau tangles. Amyloid precursor protein (APP) processes anomalously with β-secretases, producing Aβ monomers that further oligomerize and aggregate into senile plaques [5]. High concentrations of extracellular Aβ peptides in the central nervous system (CNS) initiates microglial infiltration, and NFTs accumulate intracellularly. Aβ plaques initially form in basal, temporal, and orbitofrontal regions, before spreading to widespread cortical and subcortical structures [5]. Aβ accumulation triggers tau tangle formation in the locus coeruleus and entorhinal regions, later spreading to the hippocampus and neocortex [5]. Buildup of plaques is followed by microglial activation and local inflammatory response, diffusing these misfolded proteins into synaptic clefts and interfering with synaptic signaling. The effects of plaques and NFTs are neurotoxic.

Variation in the apolipoprotein E (APOE) gene is recognized as the strongest genetic determinant of late-onset AD [6]. APOE*ε-2 demonstrates an odds ratio of 0.621 (95% CI 0.456-0.85) compared with individuals

homozygous for APOE*ε-3, and APOE*ε-4 with an odds ratio of 3.68 (95% CI 3.30-4.11) [6]. Comparing allelic variants, carrying one APOE*ε-2 allele is associated with a decreased risk of late-onset AD 3-4 fold, and carrying two alleles increases the risk 9-15 fold [6]. Among patients suffering from AD, APOE*ε-4 is associated with lower age of disease onset [6].

Pharmaceutical efforts have been directed at symptom alleviation, until recently. There has been a push to disease-modifying drugs, but risks associated have been too great for the industry to successfully adopt this approach. As of 2021, only 29 pharmacologic or biologic agents were identified in phase II or phase III trials for the disease modification of AD [7]. Because of this, increasing efforts are focusing on repositioning drugs to aid in the treatment of AD. Drug repositioning describes the process of developing existing therapeutic agents for new clinical indications. This provides a research pathway that extends beyond pharmaceutical companies to include academic institutions, government agencies, and non-profit organizations. A major benefit to this approach is the ability to bypass timely pre-clinical phase II trials, enhancing efficiency and cost-effectiveness. Efforts to modify the course of AD remain out of reach, but finding new ways to mitigate the effects of this disease are ongoing and may provide more accessible avenues to larger populations. Many successful treatments for common comorbidities like diabetes, hypertension, and cardiovascular disease are being investigated as potential treatments. The longevity of these treatments minimizes adverse effect profiles, an issue often seen with current treatments for AD.

3.2 Current Drug Targets & Purposes Drug Development Pipeline

As of January 1, 2025, there are currently 182 ongoing trials assessing 138 drugs, with disease-targeted therapies (DTTs) consisting of only 30% of this pipeline, small-molecule DTTs making up 43%, enhancing cognitive impairment taking 14%, and agents that target neuropsychiatric symptoms in AD patients contributing 11% of the pipeline [8]. Each year, the pipeline grows and currently biomarkers are playing a key role in determining trial eligibility criteria and outcome measures. Approximately one-third of the 2025 AD drug development pipeline consists of repurposed agents, representing 33% (46) of active drugs and 37% (68) of ongoing trials [8].

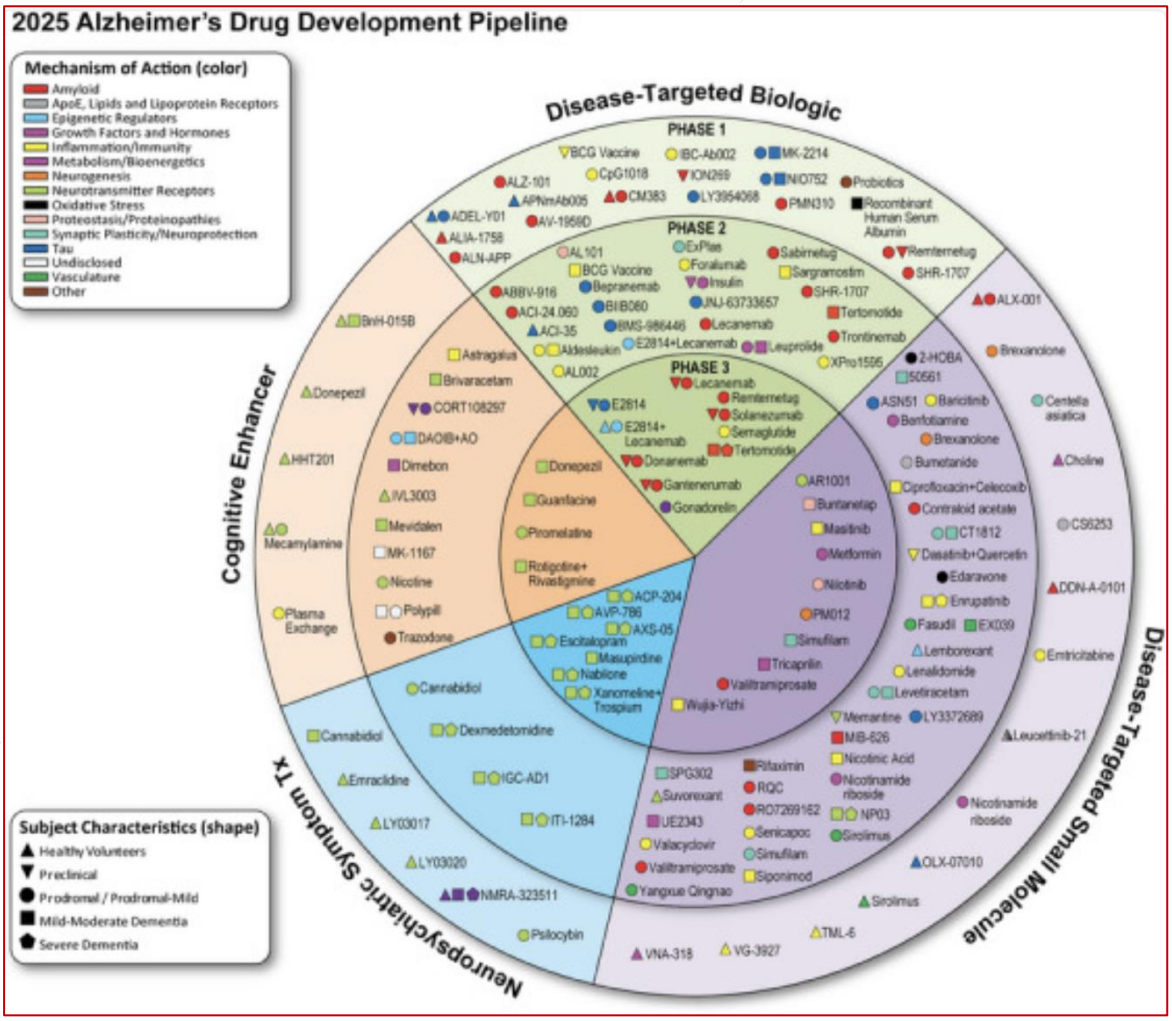

Figure 3. This figure depicts agents in clinical trials for treatment of Alzheimer's disease as of January 1, 2025, as recorded on clinicaltrials.gov. Phase 3 agents are seen in the inner-most ring, Phase 2 agents in the middle ring, and Phase 1 agents

are in the outermost ring. Green agents are the biologics, purple agents are disease modifying small molecules, orange agents address the symptoms of cognitive impairment, and blue agents target behavioral neuropsychiatric symptoms. Populations are depicted by shape and the Common Alzheimer's Disease Research Ontology (CARDO) class is depicted by color [8].

The drugs that this paper will focus on include Metformin, Semaglutide, Captopril, Losartan, Sertraline, Citalopram, Atrovastatin, Simvastatin, Melatonin, and Ketamine. These drugs were chosen as examples from each of the classes in the 2025 pipeline because of their familiarity among potential readers and because of widespread understanding of their current uses.

3.3 Antidiabetic Agents (Metformin & Semaglutide)

Metformin is well-known as an insulin sensitizer and is used in the treatment of diabetes. Increasing evidence elucidates Metformin's neuroprotective effects against AD by improving memory in experimentally induced AD rat models. Specifically, Metformin displays a therapeutic effect by inactivating AMP-activated protein kinase (AMPK) which activates mammalian target of ripamycin (mTOR), opposing cellular pathways that regulate cell growth and survival [9]. AMPK promotes cell maturity by sensing energy levels and activating mTOR, a growth promoter. Metformin inhibits mTOR signaling, reducing age-related pathologies and improving metabolic regulation [9]. Conversely, chronic mTOR activation has been linked with aging-associated neurodegenerative disorder, including AD. Contraindications do exist for the use of this treatment modality. Kuhla et al. report that Metformin has been reported to exacerbate tau pathology and neurodegeneration, yet other studies indicate that Metformin prevents the decay of memory caused by hyperbaric hypoxia with novel object recognition memory and Morris Water Maze (MWM) tasks [10, 11].

Glucagon-like peptide-1 (GLP-1) agonists have gained immense attention in recent times, but due to their beneficial weight-loss effects. Much less attention has been given to the anti-inflammatory and immunological properties of these drugs, enhancing vascular function [12]. Due to these beneficial effects on known risk factors, it can be hypothesized that these drugs are effective in preventing the onset of AD. Preclinical studies have demonstrated efficacy of Semaglutide in producing neuroprotective and anti-inflammatory effects [12]. In real-world trials with type 2 diabetes mellitus (T2DM) patients, Semaglutide was associated with a significant 40-70% reduction in AD risk [12]. It remains unknown whether this drug is associated with reduced risk of other forms of dementia.

3.4 Antihypertensive Agents (Captopril & Losartan)

The renin-angiotensinogen system (RAS), target of antihypertensive medications, is known for its effects on the vascular system, but all components of RAS are also found in the brain. Key mediators in the RAS cascade include Renin and Angiotensin (AT). AT exists in two forms, AT1 and AT2, primarily found in the lungs, liver, and blood vessels. These hormones act on Angiotensin Converting Enzyme (ACE) to mediate blood pressure in response to levels in the blood. Elevated AT2 and ACE levels have been observed in AD, and ACE overexpression in monocytes was shown to mitigate AD-related cognitive decline [13]. ACE inhibitors, like Captopril, have been studied for their effects on inflammatory mediators released by lipopolysaccharide (LPS)-treated microglia.

Captopril has shown successful results in its mediation of oxidative stress. Specifically, Captopril reduces LPS-induced nitric oxide (NO) release in primary mixed glial cell cultures and modulates (iNOS) expression, NO production, and interleukin-10 (IL-10) levels [13]. Interleukins are key mediators in immune response, cell differentiation, activation, and movement. Captopril's stunting of IL-10 release helps to mitigate cell growth and decay. The effects of Captopril on microglia are neuroprotective in patients with AD. We have also seen decreases in Aβ plaques in mice treated with Captopril [13].

Losartan acts through angiotensin targeting and is specifically known as an angiotensin receptor blocker (ARB). This fulfills another class of antihypertensive medications. ARBs exhibit neuroprotective effects in AD models, though outcomes related to memory, cholinergic activity, neurogenesis, and Aβ clearance vary substantially between studies. Route of administration affects both delivery and targeting in therapeutic efficacy of ARBs, with intranasal and intraperitoneal administration proving most effective in decreasing Aβ plaques and inflammatory cytokines [14]. Losartan promotes neurogenesis and astrocyte migration in transgenic AD models, regardless of administration route [14]. This drug, and the antihypertensive class as a whole, demonstrate great promise in expanding treatment options for AD.

3.5 Antidepressant Agents (Citalopram & Sertraline)

Antidepressants have already been used to assist in ameliorating the behavioral complications of AD. However, now they have been studied and shown to target disease mechanisms such as Aβ plaque buildup in patients and transgenic mice models [15]. After 4 weeks of treatment, citalopram use displayed a reduction in short-term memory loss and depression, with an increase in sociability [15]. Prolonged citalopram use significantly reduced Aβ plaque deposition and microglial activation [15]. This drug shows great promise in being used in disease-targeting because it directly delays the processes that predispose patients to AD. This previous study identifies citalopram's usefulness in treating early stages of AD, and there is also evidence to support use in moderate AD. Used synergistically with memantine, one of the already FDA-approved drugs for AD treatment, citalopram has

been shown to alleviate aggression, agitation, irritability, emotional lability, behavioral disturbances, distress in caregivers, and neuropsychiatric scores [16]. Cardiotoxicity has been identified as a potential side effect of citalopram use at doses higher than 30 mg/day, and its purpose in this later trial serves more as symptom management than disease modification [16].

Dysregulation of enzymes involved in neurotransmission, inflammation, and apoptosis, including glycogen synthase kinase 3β (GSK-3β), acetylcholinesterase (AChE), β-site amyloid precursor protein cleaving enzyme 1 (BACE-1), caspase-3, and cyclooxygenase-2 (COX-2), has been implicated in AD pathology. Sertraline, used in treatment of depression in patients with AD, has been identified as a dual AChE and COX-2 inhibitor with further docking studies revealing strong binding affinities between sertraline and AChE and COX-2 binding sites [17]. As in previous studies, LPS-induced rat models were used to demonstrate the effects of sertraline on AChE, COX-2, GSK-3β, and BACE-1. Significant reductions in the levels of each of these enzymes was found, and downstream effects demonstrated significant decreased caspase -3 ($p<0.05$) and malondialdehyde levels ($p<0.001$) [17]. Sertraline effectively mitigated both enzymatic activity pathological changes. These molecular interactions are evidence that antidepressants are capable of more than treating neuropsychiatric symptoms in AD patients.

3.6 Lipid-Lowering Agents (Simvastatin & Atorvastatin)

Disordered lipid metabolism is a risk factor for the development of AD. Emerging evidence suggests that disturbances in lipid metabolism and neuroinflammatory pathways contribute to the development of mild cognitive impairment and AD [18]. 3-Hydroxyl 3-methylglutaryl CoA reductase (HMGCR) is the rate-limiting enzyme in cholesterol synthesis. Drugs known as statins primarily target this enzyme and have recently been studied for their neuroprotective qualities, due to their ability to lower lipid levels and inflammation. HMGCR-related pathways in AD pathogenesis involve lipid metabolism, oxidative stress, inflammation, microglial proliferation, and Aβ plaque deposition [18]. Oxysterols derived from cholesterol increase neuroinflammatory cytokine expression and contribute to neuropathology [18].

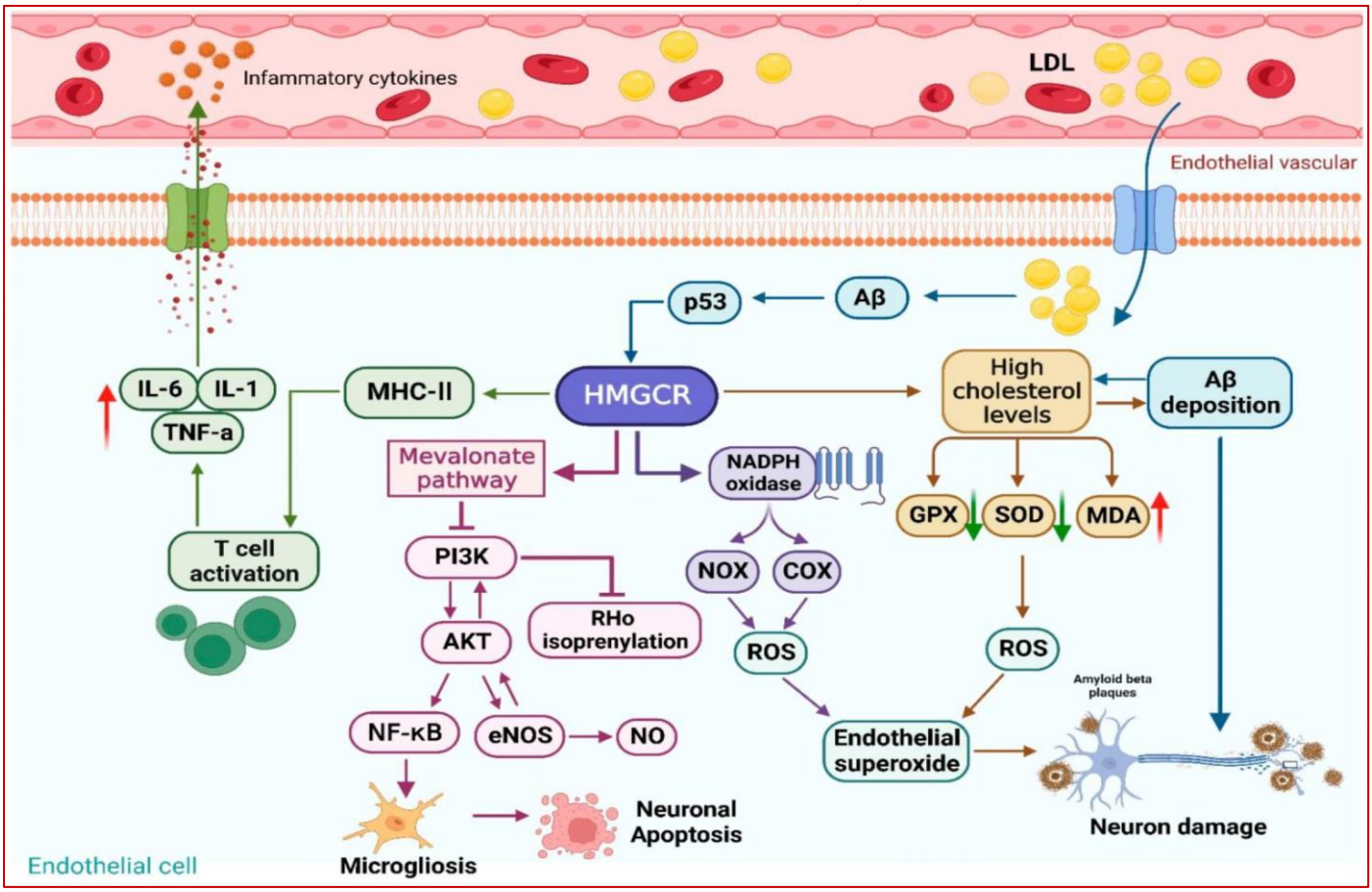

Figure 4. Oxidative stress, neuroinflammatory mediators, microglial proliferation, and Aβ deposition are the main causes of the HMGCR-mediated inflammatory response.

Upregulation of MHC-II expression leads to T-cell activation, increasing the release of proinflammatory cytokines Interleukin-1 (IL-1) and Interleukin-6 (IL-6) as well as tumor necrosis factor (TNF-α). Cholesterol dysregulation promotes oxidative stress by decreasing GPx and SOD activity and increasing MDA levels in the brain. Red arrows demonstrate stimulation or an increase, with green arrows displaying inhibition or a decrease. Created from https://app.biorender.com (accessed on 28 November 2022) [18].

Simvastatin has demonstrated promising results in influencing the turnover of Aβ proteins in yeast models

[19]. Yeast cells carrying Aβ proteins fused with green fluorescent protein (GFP) were treated with simvastatin, atorvastatin and lovastatin followed by analysis using flow cytometry, to study the rates of clearance. Simvastatin proportionately cleared Aβ proteins in a dose-dependent manner, highlighting its potential [19]. It can be hypothesized that statin-induced reduction of Aβ proteins can be a consequence of targeting a protein clearance pathway, likely that of autophagy. Inhibiting cholesterol synthesis with statins was associated with a decrease in the activation of the main autophagy suppressor, mTOR [20].

Atorvastatin has also been studied for its neuroprotective effects in modulating oxidative stress and lowering lipid levels, exemplifying potential benefit to patients with AD. Rather than in yeast models, this was studied in dogs, beagles specifically [21]. Main enzyme targets of these preclinical trials were isoforms of haem oxygenase (HO-1 and HO-2), enzymes with significant neuroprotective activity. Inverse correlations between HO-1 expression and oxidative stress markers in the parietal cortex were found, as well as a significant correlation with up-regulation of HO-1 and lower discrimination learning error scores amongst beagle subjects [21]. Translation of outcomes from animals to humans remains elusive, as the comparative dose is between 200-400 times higher in animals than it would be in humans. Nonetheless, these discoveries underscore the mechanistic ability for lipid-lowering agents to be manipulated in effort to mitigate AD symptoms and pathology.

3.7 Miscellaneous Neuroprotective Agents (Melatonin & Ketamine)

Aβ plaque formation is one of the most important pathogenic factors in the etiology of AD. Imbalance of accumulation and clearance leads to neurotoxic deposition as oligomers form. Melatonin has been studied for its ability to inhibit Aβ peptide formation, promote Aβ clearance, and ameliorate Aβ oligomers [22]. Melatonin has also been shown to sustain the blood brain barrier (BBB) in APOE*ε-4 knockout mice, carriers of the protein that can cause degeneration of brain capillaries and accelerated BBB breakdown [22]. Early diagnosis of MCI can be achieved via the study of volumes in brain matter, particularly the hippocampus. As cognitive function declines, the hippocampus atrophies. Neuroprotective effects of melatonin have been seen in mice with prolonged extended-release exposure, with the drug effectively increasing hippocampal volume and improving cognitive performance [22]. Theoretically, neurotransmission should be improved in patients with AD with the use of melatonin - due to its effects on Aβ plaque metabolism, BBB integrity, and brain matter volume.

Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist, is another candidate for treatment of AD. Preclinical studies indicate that ketamine exerts neuroprotective effects through attenuation of inflammation and oxidative stress as well as by enhancing cognitive function [23]. Specific actions of the drug include reducing the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and decreasing microglial activation, suggesting a therapeutic role for ketamine in modulating immune dysregulation associated with AD [23]. A metabolite of ketamine known as (2R, 6R)-hydrocynorketamine (HNK) has been shown to restore hippocampal synaptic plasticity and improve memory in AD mouse models [23]. HNK activates key signaling cascades supporting memory formation, neuronal repair, and NMSA receptor-independent neuroprotection [23].

These findings indicate that ketamine's neuroprotective effects may be mediated by intracellular mechanisms independent of its psychoactive profile.

Table 1. Dosing ranges of Repurposed Drugs Evaluated in Alzheimer's Disease-Related Studies

Drug	Study Type	Dosing Range Used	Model / Population	Reference(s)
Metformin	Preclinical (animal)	100–300 mg/kg/day (oral)	Rat AD models	[9,11]
	Preclinical (genetic model)	~300 mg/kg/day	ApoE$^{-/-}$ mice	[10]
Semaglutide	Human (observational / target trial emulation)	Standard T2DM dosing (0.25–1.0 mg weekly, SC)	Adults with T2DM; AD-related dementia outcomes	[12]
Captopril	Preclinical (animal)	10–50 mg/kg/day	LPS-induced neuroinflammation and AD mouse models	[13]
Losartan	Preclinical (animal)	10–30 mg/kg/day (oral, intranasal, or IP)	Transgenic AD mouse models	[14]
Citalopram	Preclinical (animal)	~10 mg/kg/day	APP/PS1 transgenic mice	[15]
	Human (clinical trial)	20–30 mg/day (oral)	Patients with moderate AD and BPSD	[16]
Sertraline	Preclinical (animal)	10–20 mg/kg/day	Rodent neuroinflammation and AD models	[17]
Atorvastatin	Preclinical (large animal)	80 mg/day (oral)	Canine preclinical AD model	[21]
Simvastatin	Preclinical (cellular / yeast models)	Dose-dependent exposure (concentration-based; mg/kg not applicable)	Yeast and cellular Aβ models	[19,20]

Melatonin	Preclinical (animal)	10–50 mg/kg/day	Rodent AD and Aβ toxicity models	[22]
Ketamine	Human (reviewed clinical / experimental use)	0.3–0.5 mg/kg IV (subanesthetic)	Older adults; cognitive & neuropsychiatric outcomes	[23]

Metformin, Semaglutide, Captopril, Losartan, Sertraline, Citalopram, Atrovastatin, Simvastatin, Melatonin, and Ketamine have individually been studied for their alternative uses in AD pathology management. The table above lists the types of studies as well as dosage range involved in each, with a majority having been in animal models. The three studies in humans, those done for Semaglutide, Citalopram, and Ketamine hold the most weight as their results are translational to the population we are trying to find treatment alternatives for.

4. Safety, Ethics, and Regulatory Considerations

Safety is a major concern for most of the drugs studied for repurposing, as doses animal models were treated with are not easily transferred into human-appropriate amounts. Concerns for each mentioned drug are as follows: Metformin - gastrointestinal (GI) intolerance and mitochondrial stress; Semaglutide - GI intolerance, a common side effect of GLP-1 receptor agonists; Captopril - none quantified, studies were in vivo or in vitro; Losartan - variability across routes of administration but no toxicity described; Citalopram - QT-interval prolongation and cardiotoxicity; Sertraline - side-effect profile limited by pre-clinical study design; Atorvastatin - side-effect profile limited by pre-clinical study design; Simvastatin - side-effect profile limited by pre-clinical study design; Melatonin - side-effect profile limited by pre-clinical study design; Ketamine - neuropsychiatric effects [9-17, 19, 20-23]. Across the reviewed literature, adverse effects were inconsistently reported due to the predominance of preclinical and mechanistic studies included. When discussed, safety concerns reflect class-specific adverse-effect profiles rather than Alzheimer's disease-specific toxicity.

Safety is a major concern for most of the drugs studied for repurposing, as doses animal models were treated with are not easily transferred into human-appropriate amounts. Concerns for each mentioned drug are as follows: Metformin - gastrointestinal (GI) intolerance and mitochondrial stress; Semaglutide - GI intolerance, a common side effect of GLP-1 receptor agonists; Captopril - none quantified, studies were in vivo or in vitro; Losartan - variability across routes of administration but no toxicity described; Citalopram - QT-interval prolongation and cardiotoxicity; Sertraline - side-effect profile limited by pre-clinical study design; Atorvastatin - side-effect profile limited by pre-clinical study design; Simvastatin - side-effect profile limited by pre-clinical study design; Melatonin - side-effect profile limited by pre-clinical study design; Ketamine - neuropsychiatric effects [9-17, 19, 20-23]. Across the reviewed literature, adverse effects were inconsistently reported due to the predominance of preclinical and mechanistic studies included. When discussed, safety concerns reflect class-specific adverse-effect profiles rather than Alzheimer's disease-specific toxicity.

5. Future Directions

Going forward, the definitive evaluation of the repurposed pharmacologic agents for the treatment of AD will require continued investigation in well-designed clinical trials involving human populations. Randomized controlled trials (RCTs) represent the most effective method for identifying the clinical utility of off-label drug usage in AD, particularly with respect to ethics, safety, and dosage. While many of the studies highlighted here provide endpoints of cognition and biomarkers, future studies should incorporate the effects of the drugs per stage of disease, duration of use, and look for enrichment strategies. Comorbid conditions commonly associated with AD, including diabetes, hypertension, and depression, must also be considered in future studies. For these populations, combination therapy has potential to mitigate adverse effect profiles while maximising therapeutic efficacy. Precision medicine can tailor the most appropriate usage of these FDA-approved therapies, and benefits can be identified between disease modification and delay of onset. These are only a handful of appropriate medications that are already FDA-approved for other uses that may prove beneficial in the treatment of AD. Therefore, large-scale efforts are required to identify all potential candidates for this use and to expand the landscape of viable treatment strategies for AD.

6. Conclusion

Current treatments for AD are extremely limited, and focus is on symptom management not disease modification. If we are going to cure this disease, this approach will not suffice. Repurposing medications has the potential to modify the course of AD, as well as provide more equitable access to treatment. Abundant drugs exist that wield potential in mitigating the pathological processes by which AD occurs. The disease itself remains somewhat elusive, with Aβ plaques forming decades before symptom onset. This poses an extensive barrier to the identification of diseased individuals, limiting our true ability to prevent disease onset. Because of this, focus on screening is imperative, especially in those with a family history of the disease. Screening is a powerful tool, but it is not a reliable one. It also depends on patients to be willing to screen and for appropriate populations to be educated about this process. Ultimately, combatting AD is multi-faceted and the true cure to the disease lies in finding cost-effective available therapeutics that can reverse the disease process. Pharmaceutically, we are a long way from achieving this goal, but repurposing medications gets us one step closer.

Repurposing medications is a powerful tool in expanding frontiers of treatment for AD. Irony lies in the applicable uses of drugs for comorbidities that are commonly suffered by AD patients, as they already hold the chemical tools to combat much of the disease process. This overlap between AD pathology and common comorbid conditions suggests that treating the systemic disease may influence neurodegeneration itself. Because these medications are already FDA-approved for other uses, their safety is one less concern when introducing them to the population. Repurposing medications leverages decades of pharmaceutical knowledge and offers a time- and cost-efficient alternative to de novo drug development. This is especially relevant given the high attrition rates in AD trials.

The long preclinical phase of AD underscores the importance of early intervention, where repurposed agents may be most effective. Therapeutic efforts may be more realistic when aiming to delay onset rather than reverse the disease process. Because of this, earlier-stage populations represent optimal timing for evaluating the repurposing of therapies. While repurposed agents are unlikely to represent a definitive cure, they may be able to meaningfully alter disease trajectories and offer patients a longer life of better quality.

Combatting AD will require the integration of many sectors, including public health, pharmacology, genetics and ethics. Drug repurposing offers a pragmatic and scientifically grounded approach forward. Although challenges remain, repurposing FDA-approved medications brings the medical field closer to accessible, scalable and patient-centered solutions for AD.

References

1. Rainulf A. Stelzmann, H. Norman Schnitzlein PhD., F. Reed Murtagh. 1995. “An english translation of alzheimer's 1907 paper, “über eine eigenartige erkankung der hirnrinde” Clinical Anatomy 8, issue 6, pages 429-431.
2. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. J Prev Alzheimers Dis. 2021;8(3):371-386. doi: 10.14283/jpad.2021.23. PMID: 34101796; PMCID: PMC12280795.
3. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24):5789. doi: 10.3390/molecules25245789. PMID: 33302541; PMCID: PMC7764106.
4. Stone JG, Casadesus G, Gustaw-Rothenberg K, Siedlak SL, Wang X, Zhu X, Perry G, Castellani RJ, Smith MA. Frontiers in Alzheimer's disease therapeutics. Ther Adv Chronic Dis. 2011 Jan 1;2(1):9-23. doi: 10.1177/2040622310382817. PMID: 21743833; PMCID: PMC3129861.
5. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine. 2019 Jul 19;14:5541-5554. doi: 10.2147/IJN.S200490. PMID: 31410002; PMCID: PMC6650620.
6. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol. 2019 Sep;15(9):501-518. doi: 10.1038/s41582-019-0228-7. Epub 2019 Jul 31. PMID: 31367008; PMCID: PMC7055192.
7. Ballard C & Murphy C Clinical trial pipelines for Alzheimer’s disease pose challenges for future effective treatment and therapies [abstract P4–017]. Alzheimers Dement. 14, P1439 (2018).
8. Cummings JL, Zhou Y, Lee G, Zhong K, Fonseca J, Leisgang-Osse AM, Cheng F. Alzheimer's disease drug development pipeline: 2025. Alzheimers Dement (N Y). 2025 Jun 3;11(2):e70098. doi: 10.1002/trc2.70098. PMID: 40463637; PMCID: PMC12131090.
9. Ale Mahmoud Mehraban R, Babaei P, Rohampour K, Jafari A, Golipoor Z. Metformin improves memory via AMPK/mTOR-dependent route in a rat model of Alzheimer's disease. Iran J Basic Med Sci. 2024;27(3):360-365. doi: 10.22038/IJBMS.2023.73075.15879. PMID: 38333746; PMCID: PMC10849203.
10. Kuhla A, Brichmann E, Ruhlmann C, Thiele R, Meuth L, Vollmar B. Metformin therapy aggravates neurodegenerative processes in ApoE-/- mice. J Alzheimers Dis. 2019;68:1415–1427. doi: 10.3233/JAD-181017.
11. Zhao M, Cheng X, Lin X, Han Y, Zhou Y, Zhao T, et al. Metformin administration prevents memory impairment induced by hypobaric hypoxia in rats. Behav Brain Res. 2019;363:30–37. doi: 10.1016/j.bbr.2019.01.048.
12. Wang W, Davis PB, Qi X, Gurney M, Perry G, Volkow ND, Kaelber DC, Xu R. Associations of semaglutide with Alzheimer's disease-related dementias in patients with type 2 diabetes: A real-world target trial emulation study. J Alzheimers Dis. 2025 Aug;106(4):1509-1522. doi: 10.1177/13872877251351329. Epub 2025 Jun 24. PMID: 40552638; PMCID: PMC12262134.
13. Asraf K, Torika N, Apte RN, Fleisher-Berkovich S. Microglial Activation Is Modulated by Captopril: in Vitro and in Vivo Studies. Front Cell Neurosci. 2018 May 1;12:116. doi: 10.3389/fncel.2018.00116. PMID: 29765306; PMCID: PMC5938337.
14. Drews HJ, Klein R, Lourhmati A, Buadze M, Schaeffeler E, Lang T, Seferyan T, Hanson LR, Frey Ii WH, de Vries TCGM, Thijssen-van Loosdregt IAEW, Gleiter CH, Schwab M, Danielyan L. Losartan Improves Memory, Neurogenesis and Cell Motility in Transgenic Alzheimer's Mice. Pharmaceuticals (Basel). 2021 Feb 20;14(2):166. doi: 10.3390/ph14020166. PMID: 33672482; PMCID: PMC7923419.
15. Zhang Q, Yang C, Liu T, Liu L, Li F, Cai Y, Lv K, Li X, Gao J, Sun D, Xu H, Yang Q, Fan X. Citalopram restores short-term memory deficit and non-cognitive behaviors in APP/PS1 mice while halting the advance of

Alzheimer's disease-like pathology. Neuropharmacology. 2018 Mar 15;131:475-486. doi: 10.1016/j.neuropharm.2017.12.021. Epub 2017 Dec 11. PMID: 29241655.
16. Zhou T, Wang J, Xin C, Kong L, Wang C. Effect of memantine combined with citalopram on cognition of BPSD and moderate Alzheimer's disease: A clinical trial. Exp Ther Med. 2019 Mar;17(3):1625-1630. doi: 10.3892/etm.2018.7124. Epub 2018 Dec 21. PMID: 30783429; PMCID: PMC6364245.
17. Arfeen M, Mani V. Sertraline as a Multi-Target Modulator of AChE, COX-2, BACE-1, and GSK-3β: Computational and In Vivo Studies. Molecules. 2024 Nov 14;29(22):5354. doi: 10.3390/molecules29225354. PMID: 39598743; PMCID: PMC11596569.
18. Zhou X, Wu X, Wang R, Han L, Li H, Zhao W. Mechanisms of 3-Hydroxyl 3-Methylglutaryl CoA Reductase in Alzheimer's Disease. Int J Mol Sci. 2023 Dec 22;25(1):170. doi: 10.3390/ijms25010170. PMID: 38203341; PMCID: PMC10778631.
19. Dhakal S, Subhan M, Fraser JM, Gardiner K, Macreadie I. Simvastatin Efficiently Reduces Levels of Alzheimer's Amyloid Beta in Yeast. Int J Mol Sci. 2019 Jul 19;20(14):3531. doi: 10.3390/ijms20143531. PMID: 31330953; PMCID: PMC6678968.
20. Vilimanovich U, Bosnjak M, Bogdanovic A, Markovic I, Isakovic A, Kravic-Stevovic T, Mircic A, Trajkovic V, Bumbasirevic V. Statin-mediated inhibition of cholesterol synthesis induces cytoprotective autophagy in human leukemic cells. Eur J Pharmacol. 2015 Oct 15;765:415-28. doi: 10.1016/j.ejphar.2015.09.004. Epub 2015 Sep 8. PMID: 26358205.
21. Butterfield DA, Barone E, Di Domenico F, Cenini G, Sultana R, Murphy MP, Mancuso C, Head E. Atorvastatin treatment in a dog preclinical model of Alzheimer's disease leads to up-regulation of haem oxygenase-1 and is associated with reduced oxidative stress in brain. Int J Neuropsychopharmacol. 2012 Aug;15(7):981-7. doi: 10.1017/S1461145711001118. Epub 2011 Jul 18. PMID: 21767440.
22. Li Y, Zhang J, Wan J, Liu A, Sun J. Melatonin regulates Aβ production/clearance balance and Aβ neurotoxicity: A potential therapeutic molecule for Alzheimer's disease. Biomed Pharmacother. 2020 Dec;132:110887. doi: 10.1016/j.biopha.2020.110887. Epub 2020 Nov 2. PMID: 33254429.
23. Avakian A, Merhavy ZI. Exploring the Neuroprotective and Neuropsychiatric Symptom Management Potential of Ketamine in Alzheimer's Disease. Cureus. 2025 Jun 27;17(6):e86855. doi: 10.7759/cureus.86855. PMID: 40718268; PMCID: PMC12296335.